2010 Dietary Guidelines Advisory Committee:

Systematic Reviews of the Protein Subcommittee

USDA's Nutrition Evidence Library supported the 2010 Dietary Guidelines Advisory Committee as it conducted systematic reviews on diet and health. This document includes archives from www.NEL.gov of the complete evidence portfolios for all NEL systematic reviews conducted by the Protein Subcommittee. The *Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 2010* summarizes these systematic review findings and provides interpretations and implications related to these reviews.

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ACKNOWLEDGEMENTS

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CHAPTER 1. OVERVIEW AND NEEDS FOR FUTURE RESEARCH

OVERVIEW

For the first time, the 2010 Dietary Guidelines Advisory Committee (DGAC) included a chapter focusing solely on the relationship between protein and health. Most of the questions addressed in this section are new topics not previously addressed by a DGAC. Recent literature has begun to examine the relationship between protein source and health outcomes. The Committee addressed this topic in three separate questions:

- Animal protein products
- Vegetable protein
- Vegetarian vs. animal-based diets.

Protein-related food groups were also considered:

- Milk and milk products
- Cooked dry beans and peas.

These food groups are significant protein sources in the American diet, and they also are important sources of other nutrients.

For each question considered in this section, the following general criteria applied. With minor exceptions noted in the review of each question, all study designs were originally included in the searches, but cross-sectional studies were later excluded from the review if there was sufficient evidence from studies with stronger designs. Also original research articles included in systematic reviews or meta-analyses were not included as individual articles in the review, so as not to count the study twice.

Finally, the Committee excluded studies that considered only participants diagnosed with chronic disease, hyperlipidemia, hypertension (HTN) and related health conditions. The Committee reviewed evidence from January 2000 to 2009. Because the 2005 DGAC reviewed the topic of milk and milk products, the 2010 Committee agreed with those recommendations and provided here only an updated review of evidence from June 2004 to 2009.

NEEDS FOR FUTURE RESEARCH

1. Develop standardized definitions for vegetable proteins and improve assessment methods for quantifying vegetable protein intake to help clarify outcomes in epidemiologic studies in this area.
   - Rationale: Assessing vegetarian eating patterns and their protein content is complex and current methodologies do not capture critical variations. Therefore, investigators' ability to quantify any possible association with health benefits is limited. Better standardized definitions and improved assessment methods will improve the ability to quantify health benefits associated with consumption of vegetable protein.
2. Develop better methods of conducting cohort studies of populations consuming plant-based diets compared to animal-based diets, including defined classifications of vegetarian and "near vegetarian" eating patterns and more specific impacts of

dried beans and peas on health.

- Rationale: Large US cohorts do not include enough vegetarians and vegans to make comparisons on health outcomes including weight control and blood pressure (BP). Widespread public interest and possible public health impacts of this dietary pattern raise the priority for this research.

3. Conduct studies of potential limitations of plant-based diet for key nutrients, including calcium, iron, vitamin B_{12}, and protein quality, especially in children and the elderly.
   - Rationale: These data are needed to determine whether vegan children require dietary supplements to attain adequate nutrient status and growth.
4. Examine the role of dairy products in lipid profiles, especially through intervention trials in which all types of dairy products, both low- and high-fat, are fed. Bioactive components that alter serum lipid levels may be contained in milk fat.
   - Rationale: Consumption of milk products may not have predictable effect on serum lipids, weight control and metabolic syndrome. The ability of dairy consumption to increase HDL levels and their effect on weight gain or weight loss and metabolic syndrome is also of widespread public health interest and worthy of additional study.
5. Develop and investigate potential biomarkers for objective assessment of vegetable protein intake.
   - Rationale: Few measures of protein status exist in healthy subjects, so it is difficult to compare protein status of participants in cohort studies with diverse protein intakes.
6. Develop better assessment tools to classify vegetarian patterns in epidemiologic studies.
   - Rationale: No assessment methods are currently available to classify participants into the wide range of vegetarian eating patterns.
7. Conduct randomized controlled trials (RCTs) to answer the question whether intake of dairy products alters BP.
   - Rationale: Results from prospective studies are inconsistent and suggest that many other variables that affect BP, such as weight loss and other nutrients, will make associations difficult to determine.
8. Ensure that prospective cohort studies continue to track the association between intake of dairy products and metabolic syndrome.
   - Rationale: Evidence to date does not suggest that high-fat dairy products are more likely than low-fat dairy products to induce metabolic syndrome. Whether there are other protective compounds in milk products, such as calcium, protein, fatty acids, and so on, that provide protection requires further research.

CHAPTER 2. ANIMAL PROTEIN PRODUCTS – CARDIOVASCULAR DISEASE

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF ANIMAL PROTEIN PRODUCTS AND CARDIOVASCULAR DISEASE?

Conclusion statement

Limited evidence from prospective cohort studies show inconsistent relationships between intake of animal protein products and cardiovascular disease (CVD), with somewhat more positive evidence for processed meats and coronary heart disease (CHD).

Grade

Limited

Evidence summary overview

The evidence review for this question included seven articles (Djousse, 2008; Halton, 2006; Keleman, 2005; Nakamura, 2004; Nakamura, 2006; Qureshi, 2007; Sinha, 2009), which represented prospective cohorts from the US and Japan published since 2000.

Regarding the relationship between the intake of total animal protein and coronary heart disease (CHD), no relationship was observed in the Nurses' Health Study (Halton, 2006) or Iowa Women's Health Study (Keleman, 2005). However, a positive association between red meat and processed meat and cardiovascular disease (CVD) mortality was observed in the National Institutes of Health-American Association for Retired Persons (NIH-AARP) Diet and Health Study (Sinha, 2009), and substituting red or processed meat (combined) for carbohydrate-dense foods was positively associated with CHD mortality in the Iowa Women's Health Study (Keleman, 2005).

Studies found no association between egg intake and CVD (Djousse, 2008; Nakamura, 2006; Nakamura, 2004; Qureshi, 2007). Thus, limited information is available on this relationship and risk may depend on type of meat or meat products consumed and the type of CVD.

Evidence summary paragraphs

Sinha et al, 2009 (positive quality) examined the relations of red, white and processed meat intakes to risk for total and cause-specific mortality among 545,653 adults (59% men; age 50 to 71 years) in the NIH-AARP Diet and Health Study (US). Deaths were determined by linkage to the Social Security Administration Death Master File and cause of death was determined by follow-up searches of the National Death Index. Meat intake was estimated from a 124-item food frequency questionnaire (FFQ) at baseline. Red meat included all types of beef and pork and included bacon, beef, cold cuts, ham, hamburger, hot dogs, liver, pork, sausage, steak and meats in foods such as pizza and chili. White meat included chicken, turkey and fish and included poultry, cold cuts, chicken mixtures, canned tuna and low-fat sausages and low-fat hot dogs made from poultry. Processed meat included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham,

regular hot dogs and low-fat hot dogs made from poultry. The components constituting red or white and processed meats can overlap because both can include meats such as bacon, sausage, and ham, while processed meat can also included smoked turkey and chicken. However, these meat groups are not used in the same models; thus, they are not duplicated in any one analysis. During 10 years of follow-up, there were 47,976 male deaths and 23,276 female deaths of all causes. There was an increased risk of CVD mortality in both men (HR=1.27; 95% CI: 1.20, 1.35; P for trend<0.001) and women (HR=1.50; 95% CI: 1.37, 1.65; P for trend<0.001) in the highest compared with the lowest quintile of red meat intake in the fully adjusted model. There was an increased risk of CVD mortality in both men (HR=1.09; 95% CI: 1.03, 1.15; P for trend<0.001) and women (HR=1.38; 95% CI: 1.26, 1.51; P for trend<0.001) in the highest compared with the lowest quintile of processed meat intake. There was a small increase in risk for CVD mortality in men (HR=1.05; 95% CI: 1.00, 1.11; P for trend=0.009) but not women (HR=1.04; 95% CI: 0.96, 1.14; P for trend=0.19) with higher intake of white meat. For CVD mortality, there was an 11% decrease in men and a 21% decrease in women if red meat consumption was decreased to the amount consumed by individuals in the first quintile. The median red meat consumption based on men and women in the first quintile was 9.8g per 1,000kcal per day compared with 62.5g per 1,000kcal per day in the fifth quintile. For women eating processed meat at the first quintile level, the decrease in CVD mortality was approximately 20%. The median processed meat consumption based on men and women in the first quintile was 1.6g per 1,000kcal per day compared with 22.6g per 1,000kcal per day in the fifth quintile. The authors concluded that red and processed meat intakes were associated with modest increases in CVD mortality.

Halton et al, 2006 (positive quality) examined the association between the low-carbohydrate (CHO) diet score and risk of CHD in 82,802 women (age 30 to 55 years) from the Nurses' Health Study cohort in the US. Secondary analyses examined the association between animal protein intake and CHD risk. Non-fatal MI was self-reported with follow-up confirmation, and fatal coronary events were identified from state vital records and National Death Index or reported by next of kin or the US Postal Service. Diet was assessed using a semi-quantitative food frequency questionnaire (FFQ) in 1980, 1984, 1986, 1990, 1994 and 1998. During 20 years of follow-up, 1,994 cases of CHD were identified. Animal protein was not significantly associated with the risk of CHD in multivariate analyses (RR between extreme deciles=1.13; 95% CI: 0.91, 1.41; P for trend=0.65).

Keleman et al, 2005 (neutral quality) investigated the associations of different protein sources with chronic disease mortality in 29,017 postmenopausal women (age 55 to 69 years) in the Iowa Women’s Health Study (United States). Mortality was ascertained through linkage with the National Death Index. Diet over the previous year was assessed with a semi-quantitative FFQ at baseline. During 15 years of follow-up, 739 CHD deaths were identified. There was no significant association for CHD mortality from substituting an isoenergetic quantity of animal protein (protein from meat, poultry, dairy, fish and eggs) for the same amount of energy from CHO (P for trend=0.29). When substituting vegetable protein for animal protein while simultaneously controlling for CHO, there was a 30% decreased risk of CHD mortality among women in the highest compared with lowest category of vegetable-for-animal protein intake (risk ratio between extreme quintiles=0.70; 95% CI: 0.51, 0.98; P for

trend=0.02). A daily substitution of 0.9 servings of red or processed meat per 1,000kcal in place of a similar number of servings of CHO-dense foods was associated with a 44% increased risk of CHD mortality (risk ratio between extreme quintiles=1.44; 95% CI: 1.06, 1.94; P for trend=0.02). No significant (NS) association was found for poultry or eggs. The authors concluded that long-term adherence to high-protein diets, without discrimination toward protein source, may have potentially adverse health consequences.

Djoussé et al, 2008 (positive quality) examined the association between egg consumption and the risk of CVD and mortality among 21,327 males (age 53.7±9.5 years) from the Physicians' Health Study I in the US. Myocardial infarction (MI) and stroke were self-reported with follow-up confirmation. Egg consumption was assessed using an abbreviated semi-quantitative FFQ in which participants were asked to report how often they had eaten eggs (one) during the past year: Rarely or never, one to three times per month, once per week, two to four times per week, five to six times per week, daily and two or more times per day. After an average follow-up of 20 years, a total of 1,550 new MI and 1,342 incident strokes were observed. Egg consumption was not significantly associated with incident MI, total stroke or types of stroke in multivariable Cox regression.

Nakamura et al, 2006 (neutral quality) examined the association between egg consumption and total cholesterol concentration and CHD incidence in 90,735 adults (52% female; age 40 to 69 years) from the Japan Public Health Center-based prospective study. Incident CHD (non-fatal MI and CHD death) was determined by review of medical records. Two waves of the cohort were included in the analyses. In cohort I, participants self-reported egg consumption as less than one day per week, one to two days per week, three to four days per week and almost every day. In cohort II, participants were also given the option of never consuming eggs. During the mean follow-up of 10.2 years, there were 462 incident cases of CHD (120 fatal, 342 non-fatal). There was no significant association between egg consumption and CHD incidence. The authors concluded that eating eggs more frequently, up to almost daily, was not associated with any consistent adverse effect on CHD incidence.

Nakamura et al, 2004 (neutral quality) examined the relations of egg consumption to serum cholesterol and cause-specific and all-cause mortality among 9,263 adults (56% female; age≥30 years) in the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980 (NIPPON DATA80) in Japan. Cause of death (stroke, ischemic heart disease [IHD]) was confirmed by computer matching of data from the National Vital Statistics. Egg consumption was queried using a self-administered question with the options of: At least two per day, approximately one per day, approximately one to two per day, approximately one to two per week and seldom. During 14 years of follow-up, 219 stroke and 80 IHD deaths were identified. In women, unadjusted IHD mortality differed significantly between egg consumption groups. However, these differences were no longer present in multivariate analyses. The multivariate-adjusted relative risk of deaths from stroke and IHD did not differ significantly between the egg consumption categories among women or men. The authors concluded that, among women, there were tendencies for lower mortality due to stroke and IHD in the one to two eggs per week group than in the one egg per day group, but no associations were noted in men.

Qureshi et al, 2007 (positive quality) examined the association between egg

consumption and risk of CVD and mortality in a 9,734 adults (age 25 to 74 years) from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHEFS). Risk of CVD was determined by assessing incident stroke and CHD at follow-up during in-person interview, collection of hospital records and review of death certificates. Egg intake at baseline was assessed using a detailed questionnaire that included questions about egg consumption in the form of fried, boiled, poached, deviled or egg salad. Eggs in cooked or baked dishes were not included. Egg intake was divided into three groups: No or less than one egg per week, one to six eggs per week and more than six eggs per week. During 15.9±5.6 years of follow-up, 655 strokes and 1,584 MI were observed. A univariate analysis demonstrated a trend for increased rates of coronary artery disease (CAD) with intake of greater than six eggs per week. However, in multivariate analysis, there was no relationship with consumption of greater than six eggs per week and risk of stroke or ischemic stroke. Similarly, compared with persons without any egg intake or less than one egg per week, there was no significant difference in RR for persons with intake of greater than six eggs per week for risk of MI. The authors concluded that consumption of greater than six eggs per week or one egg or greater per day did not increase the risk of CAD, ischemic stroke or all strokes in a cohort representative of the US population.

Overview table

Author, Year, Study Design, Class, Rating	Name of Study/Location	Total Meat Association (Pos, Neg, None)	Red Meat Association (Pos, Neg, None)	Processed Meat Association (Pos, Neg, None)	Poultry Association (Pos, Neg, None)
Djousse et al 2008 Study Design: Prospective Cohort Study Class: B Positive quality	Physicians' Health Study. Location: US.	Not examined.	Not examined.	Not examined.	Eggs: Ø MI, stroke or type of stroke.

Halton et al 2006 Study Design: Prospective Cohort Study Class: B Positive quality	Nurses' Health Study. Location: US.	Animal protein: Ø CHD (non-fatal MI and fatal coronary events).	Not examined.	Not examined.	Not examined.
Kelemen et al 2005 Study Design: Prospective cohort study Class: B Neutral quality	Iowa Women's Health Study. Location: US.	Substituting animal protein for CHO: Ø CHD morality.	Substituting red or processed meat (combined) for CHO-dense food: (+) CHD mortality.	Substituting red or processed meat (combined) for CHO-dense food: (+) CHD mortality.	Substituting poultry for CHO-dense foods: Ø CHD mortality. Substituting eggs for CHO-dense foods: Ø CHD mortality.
Nakamura et al 2006 Study Design: Prospective Cohort Study Class: B Neutral quality	Japan Public Health Center-based prospective study. Location: Japan.	Not examined.	Not examined.	Not examined.	Eggs: Ø incident CHD (non-fatal MI and CHD death).

Nakamura, Okamura et al 2004 Study Design: Prospective cohort study Class: B Neutral quality	National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980 (NIPPON DATA80). Location: Japan.	Not examined.	Not examined.	Not examined.	Eggs: Ø stroke or IHD in men or women.
Qureshi Al, Suri FK et al, 2007 Study Design: Prospective cohort study Class: B Positive quality	National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHEFS). Location: US.	Not examined.	Not examined.	Not examined.	Eggs: Ø MI, stroke, or ischemic stroke.
Sinha R, Cross AJ et al, 2009 Study Design: Prospective cohort study Class: B Positive quality	NIH-AARP Diet and Health Study. Location: US.	Not examined.	Red meat: (+) CVD mortality in men and women.	Processed meat: (+) CVD mortality in men and women.	White meat: (+) CVD mortality in men only.

Search plan and results

Inclusion criteria

- January 2000 to September 2009
- Prospective cohort studies on colorectal, breast and prostate cancers

- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children two to 18 years; Adults 19 years and older
- *Populations:* Healthy, those with elevated chronic disease risk.

Exclusion criteria

- With the exception of the body weight outcome, cross-sectional studies were excluded from the review
- Systematic reviews and meta-analyses on colorectal, breast and prostate cancers. Only original research studies with prospective cohort design were included in the review
- Studies specifically related to seafood or milk product intake (considered as separate questions)
- Studies that reported on animal protein intake as a component of a dietary pattern and not as an individual variable
- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: (Animal protein* OR meat[mh] OR "Egg Proteins, Dietary"[mh] OR "Fish Proteins"[mh]) AND ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "overweight"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mh:NoExp] OR “heart diseases”[mh] OR "Coronary Disease"[Mesh] OR “blood pressure”[mh] OR “chronic disease”[mh] OR obesity[mh] OR "Body Weights and Measures"[mh] OR "Colorectal Neoplasms"[mesh])
  (Animal protein* OR meat[mh] OR "Egg Proteins, Dietary"[mh] OR "Fish Proteins"[mh] OR seafood[majr] OR crustacea[majr]) AND (systematic[sb] OR Meta-Analysis[ptyp] OR "Cohort Studies"[Mesh]) AND ("Prostatic Neoplasms"[Mesh] OR "Breast Neoplasms"[Mesh])
  eggs [mh] AND ("Diabetes Mellitus, Type 2"[majr] OR "metabolic syndrome X"[majr] OR "overweight"[majr] OR "hypertension"[majr] OR "dyslipidemias"[majr] OR "cardiovascular diseases"[majr:NoExp] OR “heart diseases”[majr] OR "Coronary Disease"[Mesh] OR “blood pressure”[majr] OR “chronic disease”[majr] OR obesity[majr] OR "Body Weights and Measures"[majr])
  (Note: "Cohort Studies"[Mesh]) includes prospective studies)

Date searched: 09/01/2009; update 09/18/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 771
- Total articles identified to review from electronic databases: 166
- Articles identified via handsearch or other means: 2
- Number of Primary Articles Identified: 47
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 47
- Number of Articles Reviewed but Excluded: 121

Included articles (References)

What is the relationship between the intake of animal protein products and cardiovascular disease?

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What is the relationship between the intake of animal protein products and blood pressure?

Primary Citations

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3. Steffen LM, Kroenke CH, Yu X, Pereira MA, Slattery ML, Van Horn L, Gross MD, Jacobs DR Jr. Associations of plant food, dairy product, and meat intakes with 15-year incidence of elevated blood pressure in young black and white adults: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr.* 2005 Dec; 82(6): 1, 169-1, 177; quiz 1, 363-1, 364. PMID: 16332648.
4. Wagemakers JJ, Prynne CJ, Stephen AM, Wadsworth ME. Consumption of red or processed meat does not predict risk factors for coronary heart disease; results from a cohort of British adults in 1989 and 1999. *Eur J Clin Nutr.* 2009 Mar; 63(3): 303-311. Epub 2007 Nov 14. PMID: 18000518.
5. Wang YF, Yancy WS Jr, Yu D, Champagne C, Appel LJ, Lin PH. The relationship between dietary protein intake and blood pressure: Results from the PREMIER study. *J Hum Hypertens*. 2008 Nov; 22(11): 745-754. Epub 2008 Jun 26. PMID: 18580887.

What is the relationship between the intake of animal protein products and type 2 diabetes?

1. Djoussé L, Gaziano JM, Buring JE, Lee IM. Egg consumption and risk of type 2 diabetes in men and women. *Diabetes Care*. 2009 Feb; 32(2): 295-300. Epub 2008 Nov 18. PMID: 19017774; PMCID: PMC2628696.
2. Fung TT, Schulze M, Manson JE, Willett WC, Hu FB. Dietary patterns, meat intake, and the risk of type 2 diabetes in women. *Arch Intern Med.* 2004 Nov 8; 164(20): 2, 235-2, 240. PMID: 15534160.
3. Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. *Am J Clin Nutr.* 2008 Feb; 87(2): 339-346. PMID: 18258623.
4. Schulze MB, Manson JE, Willett WC, Hu FB. Processed meat intake and incidence of type 2 diabetes in younger and middle-aged women.*Diabetologia.* 2003 Nov; 46(11): 1, 465-1, 473. Epub 2003 Oct 24. PMID: 14576980.
5. Song Y, Manson JE, Buring JE, Liu S. A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: The women's health study. *Diabetes Care*. 2004 Sep; 27(9): 2, 108-2, 115. PMID: 15333470.
6. van Dam RM, Willett WC, Rimm EB, Stampfer MJ, Hu FB. Dietary fat and meat intake in relation to risk of type 2 diabetes in men. *Diabetes Care.* 2002 Mar; 25(3): 417-424. PMID: 11874924.
7. Vang A, Singh PN, Lee JW, Haddad EH, Brinegar CH. Meats, processed meats, obesity, weight gain and occurrence of diabetes among adults: Findings from Adventist Health Studies. *Ann Nutr Metab*. 2008; 52(2): 96-104. Epub 2008 Mar 18. PMID: 18349528.

What is the relationship between the intake of animal protein products and body weight?

1. Mahon AK, Flynn MG, Stewart LK, McFarlin BK, Iglay HB, Mattes RD, Lyle RM, Considine RV, Campbell WW. Protein intake during energy restriction: effects

on body composition and markers of metabolic and cardiovascular health in postmenopausal women. *J Am Coll Nutr.* 2007 Apr; 26(2): 182-189. PMID: 17536130; PMCID: PMC2556253.
2. Wagemakers JJ, Prynne CJ, Stephen AM, Wadsworth ME. Consumption of red or processed meat does not predict risk factors for coronary heart disease: Results from a cohort of British adults in 1989 and 1999. *Eur J Clin Nutr.* 2009 Mar; 63(3): 303-311. Epub 2007 Nov 14. PMID: 18000518.
3. Xu F, Yin XM, Tong SL. Association between excess bodyweight and intake of red meat and vegetables among urban and rural adult Chinese in Nanjing, China. *Asia Pac J Public Health*. 2007; 19(3): 3-9. PubMed PMID: 18330398.

What is the relationship between the intake of animal protein products and colorectal cancer?

1. Chao A, Thun MJ, Connell CJ, McCullough ML, Jacobs EJ, Flanders WD, Rodriguez C, Sinha R, Calle EE. Meat consumption and risk of colorectal cancer. *JAMA.* 2005 Jan 12; 293(2): 172-182. PMID: 15644544.
2. Cross AJ, Leitzmann MF, Gail MH, Hollenbeck AR, Schatzkin A, Sinha R. A prospective study of red and processed meat intake in relation to cancer risk. *PLoS Med.* 2007 Dec; 4(12): e325. PMID: 18076279; PMCID: PMC2121107.
3. English DR, MacInnis RJ, Hodge AM, Hopper JL, Haydon AM, Giles GG. Red meat, chicken, and fish consumption and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev.* 2004 Sep; 13(9): 1, 509-1, 514. PMID: 15342453.
4. Flood A, Velie EM, Sinha R, Chaterjee N, Lacey JV Jr, Schairer C, Schatzkin A. Meat, fat, and their subtypes as risk factors for colorectal cancer in a prospective cohort of women. *Am J Epidemiol.* 2003 Jul 1; 158(1): 59-68. PMID: 12835287.
5. Järvinen R, Knekt P, Hakulinen T, Rissanen H, Heliövaara M. Dietary fat, cholesterol and colorectal cancer in a prospective study. *Br J Cancer.* 2001 Aug 3; 85(3): 357-361. PMID: 11487265; PMCID: PMC2364063. (Hand search)
6. Kojima M, Wakai K, Tamakoshi K, Tokudome S, Toyoshima H, Watanabe Y, Hayakawa N, Suzuki K, Hashimoto S, Ito Y, Tamakoshi A; Japan Collaborative Cohort Study Group. Diet and colorectal cancer mortality: Results from the Japan Collaborative Cohort Study. *Nutr Cancer.* 2004; 50(1): 23-32. PMID: 15572294.
7. Larsson SC, Rafter J, Holmberg L, Bergkvist L, Wolk A. Red meat consumption and risk of cancers of the proximal colon, distal colon and rectum: the Swedish Mammography Cohort. *Int J Cancer.* 2005 Feb 20; 113(5): 829-834. PMID: 15499619.
8. Lee SA, Shu XO, Yang G, Li H, Gao YT, Zheng W. Animal origin foods and colorectal cancer risk: a report from the Shanghai Women's Health Study. *Nutr Cancer.* 2009; 61(2): 194-205. PMID: 19235035.
9. Norat T, Bingham S, Ferrari P, Slimani N, Jenab M, Mazuir M, Overvad K, Olsen A, Tjønneland A, Clavel F, Boutron-Ruault MC, Kesse E, Boeing H, Bergmann MM, Nieters A, Linseisen J, Trichopoulou A, Trichopoulos D, Tountas Y, Berrino F, Palli D, Panico S, Tumino R, Vineis P, Bueno-de-Mesquita HB, Peeters PH, Engeset D, Lund E, Skeie G, Ardanaz E, González C, Navarro C, Quirós JR, Sanchez MJ, Berglund G, Mattisson I, Hallmans G, Palmqvist R, Day NE, Khaw KT, Key TJ, San Joaquin M, Hémon B, Saracci R,

Kaaks R, Riboli E. Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. *J Natl Cancer Inst.* 2005 Jun 15; 97(12): 906-916. PMID: 15956652; PMCID: PMC1913932.
10. Oba S, Shimizu N, Nagata C, Shimizu H, Kametani M, Takeyama N, Ohnuma T, Matsushita S. The relationship between the consumption of meat, fat, and coffee and the risk of colon cancer: a prospective study in Japan. *Cancer Lett.* 2006 Dec 8; 244(2): 260-267. Epub 2006 Mar 6. PMID: 16519996.
11. Sato Y, Nakaya N, Kuriyama S, Nishino Y, Tsubono Y, Tsuji I. Meat consumption and risk of colorectal cancer in Japan: the Miyagi Cohort Study. *Eur J Cancer Prev.* 2006 Jun; 15(3): 211-218. PMID: 16679863.
12. Wei EK, Giovannucci E, Wu K, Rosner B, Fuchs CS, Willett WC, Colditz GA. Comparison of risk factors for colon and rectal cancer. *Int J Cancer*. 2004 Jan 20; 108(3): 433-442. PMID: 14648711. (Hand search)
13. Wu K, Giovannucci E, Byrne C, Platz EA, Fuchs C, Willett WC, Sinha R. Meat mutagens and risk of distal colon adenoma in a cohort of U.S. men. *Cancer Epidemiol Biomarkers* Prev. 2006 Jun; 15(6): 1, 120-1, 125. PMID: 16775169.

What is the relationship between the intake of animal protein products and prostate cancer?

1. Cross AJ, Peters U, Kirsh VA, Andriole GL, Reding D, Hayes RB, Sinha R. A prospective study of meat and meat mutagens and prostate cancer risk. *Cancer Res*. 2005 Dec 15; 65(24): 11, 779-11, 784. PMID: 16357191.
2. Koutros S, Cross AJ, Sandler DP, Hoppin JA, Ma X, Zheng T, Alavanja MC, Sinha R. Meat and meat mutagens and risk of prostate cancer in the Agricultural Health Study. *Cancer Epidemiol Biomarkers Prev*. 2008 Jan; 17(1): 80-87. PMID: 18199713.
3. Michaud DS, Augustsson K, Rimm EB, Stampfer MJ, Willet WC, Giovannucci E. A prospective study on intake of animal products and risk of prostate cancer. *Cancer Causes Control.* 2001 Aug; 12(6): 557-567. PMID: 11519764.
4. Park SY, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. Fat and meat intake and prostate cancer risk: The multiethnic cohort study. *Int J Cancer.* 2007 Sep 15; 121(6): 1, 339-1, 345. PMID: 17487838.
5. Rodriguez C, McCullough ML, Mondul AM, Jacobs EJ, Chao A, Patel AV, Thun MJ, Calle EE. Meat consumption among black and white men and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev*. 2006 Feb; 15(2): 211-216. PMID: 16492907.
6. Rohrmann S, Platz EA, Kavanaugh CJ, Thuita L, Hoffman SC, Helzlsouer KJ. Meat and dairy consumption and subsequent risk of prostate cancer in a US cohort study. *Cancer Causes Control.* 2007 Feb; 18(1): 41-50. PMID: 17315319.

What is the relationship between the intake of animal protein products and breast cancer?

1. Cho E, Chen WY, Hunter DJ, Stampfer MJ, Colditz GA, Hankinson SE, Willett WC. Red meat intake and risk of breast cancer among premenopausal women. *Arch Intern Med.* 2006 Nov 13; 166(20): 2, 253-2, 259. PMID: 17101944.
2. Ferrucci LM, Cross AJ, Graubard BI, Brinton LA, McCarty CA, Ziegler RG, Ma X, Mayne ST, Sinha R. Intake of meat, meat mutagens, and iron and the risk of breast cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening

Trial. *Br J Cancer.* 2009 Jul 7; 101(1): 178-184. Epub 2009 Jun 9. PMID: 19513076.

3. Fung TT, Hu FB, Holmes MD, Rosner BA, Hunter DJ, Colditz GA, Willett WC. Dietary patterns and the risk of postmenopausal breast cancer. *Int J Cancer.* 2005 Aug 10; 116(1): 116-121. PMID: 15756679.
4. Kabat GC, Cross AJ, Park Y, Schatzkin A, Hollenbeck AR, Rohan TE, Sinha R. Meat intake and meat preparation in relation to risk of postmenopausal breast cancer in the NIH-AARP diet and health study. *Int J Cancer.* 2009 May 15; 124(10): 2, 430-2, 435. PMID: 19165862.
5. Linos E, Willett WC, Cho E, Colditz G, Frazier LA. Red meat consumption during adolescence among premenopausal women and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2008 Aug; 17(8): 2, 146-2, 151. Epub 2008 Jul 31. PMID: 18669582.
6. Taylor EF, Burley VJ, Greenwood DC, Cade JE. Meat consumption and risk of breast cancer in the UK Women's Cohort Study. *Br J Cancer.* 2007 Apr 10; 96(7): 1, 139-1, 146. Erratum in: Br J Cancer. 2007 Jun 4; 96 (11): 1, 780. PMID: 17406351.
7. Wang L, Manson JE, Buring JE, Sesso HD. Meat intake and the risk of hypertension in middle-aged and older women. *J Hypertens.* 2008 Feb; 26(2): 215-222. PMID: 18192834.

Excluded articles

Article	Reason for Exclusion
Alexander DD, Cushing CA, Lowe KA, Sceurman B, Roberts MA. Meta-analysis of animal fat or animal protein intake and colorectal cancer. *Am J Clin Nutr.* 2009 May; 89(5): 1, 402-1, 409. Epub 2009 Mar 4. PMID: 19261724.	Study design is meta-analysis (colorectal cancer).
Appleby PN, Davey GK, Key TJ. Hypertension and blood pressure among meat eaters, fish eaters, vegetarians and vegans in EPIC-Oxford. *Public Health Nutr.* 2002 Oct; 5(5): 645-654. PMID: 12372158.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Augustsson K, Michaud DS, Rimm EB, Leitzmann MF, Stampfer MJ, Willett WC, Giovannucci E. A prospective study of intake of fish and marine fatty acids and prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2003 Jan; 12(1): 64-67. PMID: 12540506.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Azadbakht L, Esmaillzadeh A. Red meat intake is associated with metabolic syndrome and the plasma C-reactive protein concentration in women. *J Nutr.* 2009 Feb; 139(2): 335-339. Epub 2008 Dec 11. PMID: 19074209.	Does not answer question: Examined relationship between red meat intake and metabolic syndrome.
Balder HF, Vogel J, Jansen MC, Weijenberg MP, van den Brandt PA, Westenbrink S, van der Meer R, Goldbohm RA. Heme and chlorophyll intake and risk of colorectal cancer in the Netherlands cohort study. *Cancer Epidemiol Biomarkers Prev.* 2006 Apr; 15(4): 717-725. PMID: 16614114.	Does not answer question: Examined relationship between heme and chlorophyll intake and colorectal cancer.

Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: A systematic literature review and meta-analysis. *Cancer Causes Control.* 2007 Nov; 18(9): 967-988. Epub 2007 Jul 19. Review. PMID: 17638104; PMCID: PMC2592095.	Does not include colorectal, breast, or prostate cancer in analyses.
Barraj L, Tran N, Mink P. A comparison of egg consumption with other modifiable coronary heart disease lifestyle risk factors: a relative risk apportionment study. *Risk Anal*. 2009 Mar; 29(3): 401-415. Epub 2008 Nov 4. PMID: 19000074.	Does not answer question: Used risk apportionment approach to estimate contribution of egg intake to coronary heart disease (CHD) risk at the population level.
Benassi-Evans B, Clifton PM, Noakes M, Keogh JB, Fenech M. High protein-high red meat versus high carbohydrate weight loss diets do not differ in effect on genome stability and cell death in lymphocytes of overweight men. *Mutagenesis.* 2009 May; 24(3): 271-277. Epub 2009 Mar 5. PMID: 19264840.	Does not include animal protein product intake in analyses.
Brink M, Weijenberg MP, de Goeij AF, Roemen GM, Lentjes MH, de Bruïne AP, Goldbohm RA, van den Brandt PA. Meat consumption and K-ras mutations in sporadic colon and rectal cancer in The Netherlands Cohort Study. *Br J Cancer.* 2005 Apr 11; 92(7): 1, 310-1, 320. PMID: 15812479.	Study design is case-cohort.
Cade JE, Burley VJ, Greenwood DC; UK Women's Cohort Study Steering Group. The UK Women's Cohort Study: Comparison of vegetarians, fish-eaters and meat-eaters. *Public Health Nutr.* 2004 Oct; 7(7): 871-878. PMID: 15482612.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Chan AT, Tranah GJ, Giovannucci EL, Willett WC, Hunter DJ, Fuchs CS. Prospective study of N-acetyltransferase-2 genotypes, meat intake, smoking and risk of colorectal cancer. *Int J Cancer.* 2005 Jul 1; 115(4): 648-652. PMID: 15700302.	Study design is case-control study (colorectal cancer).
Chavarro JE, Stampfer MJ, Hall MN, Sesso HD, Ma J. A 22-y prospective study of fish intake in relation to prostate cancer incidence and mortality. *Am J Clin Nutr.* 2008 Nov; 88(5): 1, 297-1, 303. PMID: 18996866.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Chrysohoou C, Panagiotakos DB, Pitsavos C, Skoumas J, Krinos X, Chloptsios Y, Nikolaou V, Stefanadis C. Long-term fish consumption is associated with protection against arrhythmia in healthy persons in a Mediterranean region: The ATTICA study. *Am J Clin Nutr.* 2007 May; 85(5): 1, 385-1, 391. PMID: 17490977.	Does not answer question: Examined relationship between fish intake and arrhythmia.
Cotterchio M, Boucher BA, Manno M, Gallinger S, Okey AB, Harper PA. Red meat intake, doneness, polymorphisms in genes that encode carcinogen-metabolizing enzymes, and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2008 Nov; 17(11): 3, 098-3, 107. PMID: 18990750.	Study design is case-control (colorectal cancer).

Crowe FL, Key TJ, Appleby PN, Travis RC, Overvad K, Jakobsen MU, Johnsen NF, Tjønneland A, Linseisen J, Rohrmann S, Boeing H, Pischon T, Trichopoulou A, Lagiou P, Trichopoulos D, Sacerdote C, Palli D, Tumino R, Krogh V, Bueno-de-Mesquita HB, Kiemeney LA, Chirlaque MD, Ardanaz E, Sánchez MJ, Larrañaga N, González CA, Quirós JR, Manjer J, Wirfält E, Stattin P, Hallmans G, Khaw KT, Bingham S, Ferrari P, Slimani N, Jenab M, Riboli E. Dietary fat intake and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr.* 2008 May; 87(5): 1, 405-1, 413. PMID: 18469265.	Does not answer question: Examined relationship between animal fat intake and prostate cancer.
Dallongeville J, Yarnell J, Ducimetière P, Arveiler D, Ferrières J, Montaye M, Luc G, Evans A, Bingham A, Hass B, Ruidavets JB, Amouyel P. Fish consumption is associated with lower heart rates.*Circulation.* 2003 Aug 19; 108(7): 820-825. Epub 2003 Aug 11. PMID: 12912821.	Does not answer question: Examined relationship between fish intake and heart rates.
Davey GK, Spencer EA, Appleby PN, Allen NE, Knox KH, Key TJ. EPIC-Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33 883 meat-eaters and 31 546 non meat-eaters in the UK. *Public Health Nutr.* 2003 May; 6(3): 259-269. PMID: 12740075.	Does not include health outcomes in analyses.
de Mello VD, Zelmanovitz T, Perassolo MS, Azevedo MJ, Gross JL. Withdrawal of red meat from the usual diet reduces albuminuria and improves serum fatty acid profile in type 2 diabetes patients with macroalbuminuria. *Am J Clin Nutr*. 2006 May; 83(5): 1, 032-1, 038. PMID: 16685043.	Participants diagnosed with type 2 diabetes (T2D).
Dixon LB, Balder HF, Virtanen MJ, Rashidkhani B, Männistö S, Krogh V, van Den Brandt PA, Hartman AM, Pietinen P, Tan F, Virtamo J, Wolk A, Goldbohm RA. Dietary patterns associated with colon and rectal cancer: results from the Dietary Patterns and Cancer (DIETSCAN) Project. *Am J Clin Nutr.* 2004 Oct; 80(4): 1, 003-1, 011. PMID: 15447912.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Djoussé L, Gaziano JM. Egg consumption and risk of heart failure in the Physicians' Health Study. *Circulation.* 2008 Jan 29; 117(4): 512-516. Epub 2008 Jan 14. PMID: 18195171; PMCID: PMC2706003.	Does not answer question: Examined relationship between egg consumption and heart failure.
Egeberg R, Olsen A, Autrup H, Christensen J, Stripp C, Tetens I, Overvad K, Tjønneland A. Meat consumption, N-acetyl transferase 1 and 2 polymorphism and risk of breast cancer in Danish postmenopausal women. *Eur J Cancer Prev.* 2008 Feb; 17(1): 39-47. PMID: 18090909.	Study design is nested case-control study (breast cancer).
Eichholzer M, Bisig B. Daily consumption of (red) meat or meat products in Switzerland: Results of the 1992/93 Swiss Health Survey. *Eur J Clin Nutr.* 2000 Feb; 54(2): 136-142. PMID: 10694784.	Does not include health outcomes in analyses.
Elliott P, Stamler J, Dyer AR, Appel L, Dennis B, Kesteloot H, Ueshima H, Okayama A, Chan Q, Garside DB, Zhou B. Association between protein intake and blood pressure: The INTERMAP Study. *Arch Intern Med.* 2006 Jan 9; 166(1): 79-87. PMID: 16401814.	Study design is cross-sectional epidemiological study.

Engeset D, Andersen V, Hjartåker A, Lund E. Consumption of fish and risk of colon cancer in the Norwegian Women and Cancer (NOWAC) study. *Br J Nutr.* 2007 Sep; 98(3): 576-582. Epub 2007 Apr 10. Erratum in: *Br J Nutr.* 2008 Mar; 99(3): 696. PMID: 17419892.	Does not answer question: Examined relationship between fish intake and colon cancer.
Erkkilä AT, Lichtenstein AH, Mozaffarian D, Herrington DM. Fish intake is associated with a reduced progression of coronary artery atherosclerosis in postmenopausal women with coronary artery disease. *Am J Clin Nutr.* 2004 Sep; 80(3): 626-632. PMID: 15321802.	Participants diagnosed with CHD.
Erkkilä AT, Schwab US, de Mello VD, Lappalainen T, Mussalo H, Lehto S, Kemi V, Lamberg-Allardt C, Uusitupa MI. Effects of fatty and lean fish intake on blood pressure in subjects with coronary heart disease using multiple medications. *Eur J Nutr.* 2008 Sep; 47(6): 319-328. Epub 2008 Jul 29. PMID: 18665413.	Participants diagnosed with CHD.
Faramawi MF, Johnson E, Fry MW, Sall M, Zhou Y. Consumption of different types of meat and the risk of renal cancer: Meta-analysis of case-control studies. *Cancer Causes Control.* 2007 Mar; 18(2): 125-133. Epub 2007 Jan 22. Erratum in: *Cancer Causes Control.* 2007 Jun; 18 (5): 581. Yi, Zhou [corrected to Zhou, Yi]. PMID: 17242980.	Does not include colorectal, breast or prostate cancer in analyses.
Ferrucci LM, Sinha R, Graubard BI, Mayne ST, Ma X, Schatzkin A, Schoenfeld PS, Cash BD, Flood A, Cross AJ. Dietary meat intake in relation to colorectal adenoma in asymptomatic women. *Am J Gastroenterol.* 2009 May; 104(5): 1, 231-1, 140. Epub 2009 Apr 14. PMID: 19367270.	Study design is case-control study (colorectal cancer).
Geelen A, Schouten JM, Kamphuis C, Stam BE, Burema J, Renkema JM, Bakker EJ, van't Veer P, Kampman E. Fish consumption, n-3 fatty acids, and colorectal cancer: a meta-analysis of prospective cohort studies. *Am J Epidemiol*. 2007 Nov 15; 166(10): 1, 116-1, 125. Epub 2007 Sep 6. PMID: 17823383.	Study design is meta-analysis (colorectal cancer).
Gillum RF, Mussolino ME, Madans JH. Fish consumption and hypertension incidence in African Americans and whites: The NHANES I Epidemiologic Follow-up Study. *J Natl Med Assoc.* 2001 Apr; 93(4): 124-128. PMID: 12653399; PMCID: PMC2593988.	Does not answer question: Examined relationship between fish intake and hypertension (HTN).
Goldin BR, Brauner E, Adlercreutz H, Ausman LM, Lichtenstein AH. Hormonal response to diets high in soy or animal protein without and with isoflavones in moderately hypercholesterolemic subjects. *Nutr Cancer.* 2005; 51(1): 1-6. PMID: 15749623.	Does not answer question: Examined hormonal response to diets high in soy or animal protein.
Gonzalez CA, Riboli E. Diet and cancer prevention: Where we are, where we are going. Nutr Cancer. 2006; 56(2): 225-31. Review. PMID: 17474869.	Study design is narrative review.
Grillenberger M, Neumann CG, Murphy SP, Bwibo NO, Weiss RE, Jiang L, Hautvast JG, West CE. Intake of micronutrients high in animal-source foods is associated with better growth in rural Kenyan school children. *Br J Nutr*. 2006 Feb; 95(2): 379-390. PMID: 16469157.	Study population not from a developed country as defined by the Human Development Index (2009).

Gross JL, Zelmanovitz T, Moulin CC, De Mello V, Perassolo M, Leitão C, Hoefel A, Paggi A, Azevedo MJ. Effect of a chicken-based diet on renal function and lipid profile in patients with type 2 diabetes: a randomized crossover trial. *Diabetes Care.* 2002 Apr; 25(4): 645-651. PMID: 11919119.	Participants diagnosed with T2D.
Günther AL, Remer T, Kroke A, Buyken AE. Early protein intake and later obesity risk: which protein sources at which time points throughout infancy and childhood are important for body mass index and body fat percentage at 7 y of age? *Am J Clin Nutr.* 2007 Dec; 86(6): 1, 765-1, 772. PMID: 18065597.	Does not answer question: Examined protein intake during infancy and childhood and body weight outcomes at age seven years.
He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, Greenland P. Accumulated evidence on fish consumption and coronary heart disease mortality: A meta-analysis of cohort studies. *Circulation.* 2004 Jun 8; 109(22): 2, 705-2, 711. PMID: 15184295.	Does not answer question: examined relationship between fish intake and CHD.
High red-meat intake, obesity linked to cancer.*Health News.* 2002 Feb; 8(2): 9. PMID: 11862847.	News article.
Hodgson JM, Burke V, Beilin LJ, Puddey IB. Partial substitution of carbohydrate intake with protein intake from lean red meat lowers blood pressure in hypertensive persons. *Am J Clin Nutr.* 2006 Apr; 83(4): 780-787. PMID: 16600928.	Participants diagnosed with HTN.
Hu FB, Manson JE, Willett WC. Types of dietary fat and risk of coronary heart disease: a critical review.*J Am Coll Nutr.* 2001 Feb; 20(1): 5-19. Review. PMID: 11293467.	Study design is narrative review.
Huncharek M, Kupelnick B, Wheeler L. Dietary cured meat and the risk of adult glioma: A meta-analysis of nine observational studies. *J Environ Pathol Toxicol* Oncol. 2003; 22(2): 129-137. PMID: 14533876.	Does not include colorectal, breast, or prostate cancer in analyses.
Huncharek M, Kupelnick B. A meta-analysis of maternal cured meat consumption during pregnancy and the risk of childhood brain tumors. *Neuroepidemiology.* 2004 Jan-Apr; 23(1-2): 78-84. PMID: 14739572.	Does not include colorectal, breast, or prostate cancer in analyses.
Hunninghake DB, Maki KC, Kwiterovich PO Jr, Davidson MH, Dicklin MR, Kafonek SD. Incorporation of lean red meat into a National Cholesterol Education Program Step I diet: A long-term, randomized clinical trial in free-living persons with hypercholesterolemia. *J Am Coll Nutr.* 2000 Jun; 19(3): 351-360. PMID: 10872897.	Participants diagnosed with hypercholesterolemia.
Iso H, Sato S, Kitamura A, Naito Y, Shimamoto T, Komachi Y. Fat and protein intakes and risk of intraparenchymal hemorrhage among middle-aged Japanese. *Am J Epidemiol.* 2003 Jan 1; 157(1): 32-39. Erratum in: *Am J Epidemiol.* 2004 Feb 1; 159(3): 318. PMID: 12505888.	Does not answer question: examined relationship between protein intake and intraparenchymal hemorrhage.
Järvinen R, Knekt P, Rissanen H, Reunanen A. Intake of fish and long-chain n-3 fatty acids and the risk of coronary heart mortality in men and women. *Br J Nutr.* 2006 Apr; 95(4): 824-829. PMID: 16571163.	Does not answer question: examined relationship between fish intake and CHD.

Jenkins DJ, Wong JM, Kendall CW, Esfahani A, Ng VW, Leong TC, Faulkner DA, Vidgen E, Greaves KA, Paul G, Singer W. The effect of a plant-based low-carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. *Arch Intern Med.* 2009 Jun 8; 169(11): 1, 046-1, 054. PMID: 19506174.	Participants diagnosed hyperlipidemia.
Joshi AD, Corral R, Siegmund KD, Haile RW, Le Marchand L, Martínez ME, Ahnen DJ, Sandler RS, Lance P, Stern MC. Red meat and poultry intake, polymorphisms in the nucleotide excision repair and mismatch repair pathways and colorectal cancer risk. 2009 Mar; 30(3): 472-479. Epub 2008 Nov 24. PMID: 19029193; PMCID: PMC2722151.	Study design is case-control family-based study (colorectal cancer).
Kabat GC, Miller AB, Jain M, Rohan TE. A cohort study of dietary iron and heme iron intake and risk of colorectal cancer in women. *Br J Cancer.* 2007 Jul 2; 97 (1): 118-122. Epub 2007 Jun 5. Erratum in: *Br J Cancer.* 2007 Dec 3; 97(11): 1, 600. PMID: 77551493; PMCID: PMC2359661.	Does not answer question: examined relationship between iron and heme iron intake and colorectal cancer.
König A, Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, Lawrence RS, Savitz DA, Teutsch SM. A quantitative analysis of fish consumption and coronary heart disease mortality. *Am J Prev Med.* 2005 Nov; 29(4): 335-346. PMID: 16242600.	Does not answer question: examined relationship between fish intake and CHD.
Kono S. Secular trend of colon cancer incidence and mortality in relation to fat and meat intake in Japan. *Eur J Cancer Prev*. 2004 Apr; 13(2): 127-132. PMID: 15100579.	Study design is non-comparative, correlational study.
Kontogianni MD, Panagiotakos DB, Pitsavos C, Chrysohoou C, Stefanadis C. Relationship between meat intake and the development of acute coronary syndromes: the CARDIO2000 case-control study. *Eur J Clin Nutr.* 2008 Feb; 62(2): 171-177. Epub 2007 Mar 14. PMID: 17356558.	Does not include health outcome of interest in analyses.
Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation*. 2002 Nov 19; 106(21): 2, 747-2, 757. Erratum in: *Circulation.* 2003 Jan 28; 107 (3): 512. PMID: 12438303.	Expert opinion.
Larsson SC, Orsini N, Wolk A. Processed meat consumption and stomach cancer risk: A meta-analysis. *J Natl Cancer Inst.* 2006 Aug 2; 98(15): 1, 078-1, 087. PMID: 16882945.	Does not include colorectal, breast or prostate cancer in analyses.
Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: A meta-analysis of prospective studies. *Int J Cancer.* 2006 Dec 1; 119(11): 2, 657-2, 664. PMID: 16991129.	Study design is meta-analysis (colorectal cancer).
Lee JE, Spiegelman D, Hunter DJ, Albanes D, Bernstein L, van den Brandt PA, Buring JE, Cho E, English DR, Freudenheim JL, Giles GG, Graham S, Horn-Ross PL, Håkansson N, Leitzmann MF, Männistö S, McCullough ML, Miller AB, Parker AS, Rohan TE, Schatzkin A, Schouten LJ, Sweeney C, Willett WC, Wolk A, Zhang SM, Smith-Warner SA. Fat, protein, and meat consumption and renal cell cancer risk: A pooled analysis of 13 prospective studies. *J Natl Cancer Inst*. 2008 Dec 3; 100(23): 1, 695-1, 706. Epub 2008 Nov 25. PMID: 19033572; PMCID: PMC2727138.	Does not include colorectal, breast or prostate cancer in analyses.

Levitan EB, Wolk A, Mittleman MA. Fish consumption, marine omega-3 fatty acids, and incidence of heart failure: A population-based prospective study of middle-aged and elderly men. *Eur Heart J.* 2009 Jun; 30(12): 1, 495-1, 500. Epub 2009 Apr 21. PMID: 19383731; PMCID: PMC2695952.	Does not answer question: Examined relationship between fish intake and heart failure.
Lichtenstein AH, Jalbert SM, Adlercreutz H, Goldin BR, Rasmussen H, Schaefer EJ, Ausman LM. Lipoprotein response to diets high in soy or animal protein with and without isoflavones in moderately hypercholesterolemic subjects. *Arterioscler Thromb Vasc Biol.* 2002 Nov 1; 22(11): 1, 852-1, 858. PMID: 12426215.	Participants diagnosed with hypercholesterolemia.
Linseisen J, Kesse E, Slimani N; EPIC Working Group on Dietary Pattern, Subgroup Meat. Meat consumption in Europe: Results from the EPIC study.*IARC Sci Publ*. 2002; 156: 211-212. PMID: 12484168.	Does not include health outcomes in analyses.
Liu L, Ikeda K, Yamori Y; WHO-CARDIAC Study Group. Inverse relationship between urinary markers of animal protein intake and blood pressure in Chinese: results from the WHO Cardiovascular Diseases and Alimentary Comparison (CARDIAC) Study. *Int J Epidemiol*. 2002 Feb; 31(1): 227-233. PMID: 11914325.	Does not answer question: Examined the relationship between urinary excretion of 3-methylhistidine (as marker of animal protein intake) and blood pressure (BP).
Lucey AJ, Paschos GK, Cashman KD, Martínéz JA, Thorsdottir I, Kiely M. Influence of moderate energy restriction and seafood consumption on bone turnover in overweight young adults. *Am J Clin Nutr.* 2008 Apr; 87(4): 1, 045-1, 052. PMID: 18400730.	Does not include health outcome of interest in analyses.
Lüchtenborg M, Weijenberg MP, de Goeij AF, Wark PA, Brink M, Roemen GM, Lentjes MH, de Bruïne AP, Goldbohm RA, van 't Veer P, van den Brandt PA. Meat and fish consumption, APC gene mutations and hMLH1 expression in colon and rectal cancer: A prospective cohort study (The Netherlands). *Cancer Causes Control.* 2005 Nov; 16(9): 1, 041-1, 054. PMID: 16184469.	Results reported based on the same dataset as Brink, 2005.
Mamo JC, James AP, Soares MJ, Griffiths DG, Purcell K, Schwenke JL. A low-protein diet exacerbates postprandial chylomicron concentration in moderately dyslipidaemic subjects in comparison to a lean red meat protein-enriched diet. *Eur J Clin Nutr.* 2005 Oct; 59(10): 1, 142-1, 148. PMID: 16015257.	Does not answer question: Examined relationship between protein intake and postprandial response.
Männistö S, Dixon LB, Balder HF, Virtanen MJ, Krogh V, Khani BR, Berrino F, van den Brandt PA, Hartman AM, Pietinen P, Tan F, Wolk A, Goldbohm RA. Dietary patterns and breast cancer risk: Results from three cohort studies in the DIETSCAN project. *Cancer Causes Control.* 2005 Aug; 16(6): 725-733. PMID: 16049811.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Marques-Vidal P, Ravasco P, Ermelinda Camilo M. Foodstuffs and colorectal cancer risk: A review. *Clin Nutr.* 2006 Feb; 25(1): 14-36. Epub 2005 Nov 14. Review. PMID: 16290272.	Study design is systematic review (colorectal cancer).
Matheson EM, Mainous AG 3rd, Hill EG, Carnemolla MA. Shellfish consumption and risk of coronary heart disease. *J Am Diet Assoc.* 2009 Aug; 109(8): 1, 422-1, 426. PMID: 19631050.	Does not answer question: Examined relationship between shellfish intake and CHD.

Matthan NR, Jalbert SM, Ausman LM, Kuvin JT, Karas RH, Lichtenstein AH. Effect of soy protein from differently processed products on cardiovascular disease risk factors and vascular endothelial function in hypercholesterolemic subjects. *Am J Clin Nutr.* 2007 Apr; 85(4): 960-966. Erratum in: *Am J Clin Nutr.* 2007 Aug; 86(2): 525. PMID: 17413093.	Participants were hypercholesterolemic.
McCarty MF. The origins of western obesity: A role for animal protein? *Med Hypotheses.* 2000 Mar; 54(3): 488-494. PMID: 10783494.	Study design is narrative review.
McNaughton SA, Mishra GD, Stephen AM, Wadsworth ME. Dietary patterns throughout adult life are associated with body mass index, waist circumference, blood pressure, and red cell folate. *J Nutr.* 2007 Jan; 137(1): 99-105. PMID: 17182808.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Melanson K, Gootman J, Myrdal A, Kline G, Rippe JM. Weight loss and total lipid profile changes in overweight women consuming beef or chicken as the primary protein source. *Nutrition.* 2003 May; 19(5): 409-414. PMID: 12714091.	Dropout rate is higher than inclusion criteria.
Missmer SA, Smith-Warner SA, Spiegelman D, Yaun SS, Adami HO, Beeson WL, van den Brandt PA, Fraser GE, Freudenheim JL, Goldbohm RA, Graham S, Kushi LH, Miller AB, Potter JD, Rohan TE, Speizer FE, Toniolo P, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Hunter DJ. Meat and dairy food consumption and breast cancer: A pooled analysis of cohort studies. *Int J Epidemiol.* 2002 Feb; 31(1): 78-85. PMID: 11914299.	Study design is meta-analysis (breast cancer).
Möllsten AV, Dahlquist GG, Stattin EL, Rudberg S. Higher intakes of fish protein are related to a lower risk of microalbuminuria in young Swedish type 1 diabetic patients. *Diabetes Care.* 2001 May; 24(5): 805-810. PMID: 11347734.	Participants diagnosed with T2D.
Mortensen LS, Hartvigsen ML, Brader LJ, Astrup A, Schrezenmeir J, Holst JJ, Thomsen C, Hermansen K. Differential effects of protein quality on postprandial lipemia in response to a fat-rich meal in type 2 diabetes: comparison of whey, casein, gluten, and cod protein. *Am J Clin Nutr.* 2009 Jul; 90(1): 41-48. Epub 2009 May 20. PMID: 19458012.	Participants diagnosed with T2D.
Mozaffarian D, Psaty BM, Rimm EB, Lemaitre RN, Burke GL, Lyles MF, Lefkowitz D, Siscovick DS. Fish intake and risk of incident atrial fibrillation. *Circulation.* 2004 Jul 27; 110(4): 368-373. Epub 2004 Jul 19. PMID: 15262826; PMCID: PMC1201400.	Does not answer question: Examined relationship between fish intake and atrial fibrillation.
Nagata C, Shimizu H, Kametani M, Takeyama N, Ohnuma T, Matsushita S. Diet and colorectal adenoma in Japanese males and females. *Dis Colon Rectum.* 2001 Jan; 44(1): 105-111. PMID: 11805576.	Study design is case-control study (colorectal cancer).
Nenseter MS, Østerud B, Larsen T, Strøm E, Bergei C, Hewitt S, Holven KB, Hagve TA, Mjøs SA, Solvang M, Pettersen J, Opstvedt J, Ose L. Effect of Norwegian fish powder on risk factors for coronary heart disease among hypercholesterolemic individuals. *Nutr Metab Cardiovasc Dis.* 2000 Dec; 10(6): 323-330. PMID: 11302007.	Did not answer question: Examined relationship between fish powder and CHD.

Nettleton JA, Steffen LM, Loehr LR, Rosamond WD, Folsom AR. Incident heart failure is associated with lower whole-grain intake and greater high-fat dairy and egg intake in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Diet Assoc*. 2008 Nov; 108(11): 1, 881-1, 887. PMID: 18954578; PMCID: PMC2650810.	Does not answer question: Examined relationship between egg intake and heart failure.
Nkondjock A, Receveur O. Fish-seafood consumption, obesity, and risk of type 2 diabetes: an ecological study. *Diabetes Metab.* 2003 Dec; 29(6): 635-642. PMID: 14707894.	Does not answer question: Examined relationship between fish intake and T2D.
Norat T, Lukanova A, Ferrari P, Riboli E. Meat consumption and colorectal cancer risk: Dose-response meta-analysis of epidemiological studies. *Int J Cancer.* 2002 Mar 10; 98(2): 241-256. PMID: 11857415.	Study design is meta-analysis (colorectal cancer).
Norat T, Riboli E. Meat consumption and colorectal cancer: A review of epidemiologic evidence. *Nutr Rev.* 2001 Feb; 59(2): 37-47. Review. PMID: 11310774.	Study design is meta-analysis (colorectal cancer).
Norat T, Riboli E. Meat consumption and colorectal cancer: A review of epidemiologic evidence. *Nutr Rev.* 2001 Feb; 59(2): 37-47. Review. PMID: 11310774.	Study design is narrative review (colorectal cancer).
Nowson CA, Wattanapenpaiboon N, Pachett A. Low-sodium Dietary Approaches to Stop Hypertension-type diet including lean red meat lowers blood pressure in postmenopausal women. *Nutr Res.* 2009 Jan; 29(1): 8-18. PMID: 19185772.	Does not include animal protein products in analyses.
Olmedilla-Alonso B, Granado-Lorencio F, Herrero-Barbudo C, Blanco-Navarro I, Blázquez-García S, Pérez-Sacristán B. Consumption of restructured meat products with added walnuts has a cholesterol-lowering effect in subjects at high cardiovascular risk: a randomised, crossover, placebo-controlled study. *J Am Coll Nutr.* 2008 Apr; 27(2): 342-348. PMID: 18689569.	Does not answer question: Examined effect of restructured meat product on cholesterol.
Panagiotakos DB, Pitsavos C, Zampelas A, Chrysohoou C, Griffin BA, Stefanadis C, Toutouzas P. Fish consumption and the risk of developing acute coronary syndromes: The CARDIO2000 study. *Int J Cardiol.* 2005 Jul 20; 102(3): 403-409. PMID: 16004884.	Does not answer question: Examined relationship between fish intake and health outcomes.
Panagiotakos DB, Zeimbekis A, Boutziouka V, Economou M, Kourlaba G, Toutouzas P, Polychronopoulos E. Long-term fish intake is associated with better lipid profile, arterial blood pressure, and blood glucose levels in elderly people from Mediterranean islands (MEDIS epidemiological study). *Med Sci Monit.* 2007 Jul; 13(7): CR307-CR312. PMID: 17599024.	Does not answer question: Examined relationship between fish intake and health outcomes.
Pham TM, Fujino Y, Kubo T, Ide R, Tokui N, Mizoue T, Ogimoto I, Matsuda S, Yoshimura T. Fish intake and the risk of fatal prostate cancer: Findings from a cohort study in Japan. *Public Health Nutr.* 2009 May; 12(5): 609-613. Epub 2008 Jul 29. PMID: 18664313.	Does not answer question: Examined relationship between fish intake and prostate cancer.

Pieniak Z, Verbeke W, Perez-Cueto F, Brunsø K, De Henauw S. Fish consumption and its motives in households with versus without self-reported medical history of CVD: A consumer survey from five European countries. *BMC Public Health.* 2008 Sep 10; 8: 306. PMID: 18783593; PMCID: PMC2556335.	Does not include health outcomes in analyses.
Processed meat consumption linked to type 2 diabetes. *Nephrol News Issues.* 2002 Apr; 16(5): 68-69. PMID: 11962157.	News article.
Ramel A, Parra D, Martinéz JA, Kiely M, Thorsdottir I. Effects of seafood consumption and weight loss on fasting leptin and ghrelin concentrations in overweight and obese European young adults. *Eur J Nutr.* 2009 Mar; 48(2): 107-114. Epub 2009 Jan 13. PMID: 19142567.	Does not answer question: Examined relationship between seafood and leptin and ghrelin concentrations.
Rosell M, Appleby P, Spencer E, Key T. Weight gain over 5 years in 21, 966 meat-eating, fish-eating, vegetarian, and vegan men and women in EPIC-Oxford. *Int J Obes (Lond).* 2006 Sep; 30(9): 1, 389-1, 396. Epub 2006 Mar 14. PMID: 16534521.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Sandhu MS, White IR, McPherson K. Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: A meta-analytical approach. *Cancer Epidemiol Biomarkers Prev.* 2001 May; 10(5): 439-446. PMID: 11352852.	Study design is systematic review/meta-analysis (colorectal cancer).
Santarelli RL, Pierre F, Corpet DE. Processed meat and colorectal cancer: A review of epidemiologic and experimental evidence. *Nutr Cancer.* 2008; 60(2): 131-144. Review. PMID: 18444144; PMCID: PMC2661797.	Study design is narrative review.
Satia JA, Tseng M, Galanko JA, Martin C, Sandler RS. Dietary patterns and colon cancer risk in Whites and African Americans in the North Carolina Colon Cancer Study. *Nutr Cancer.* 2009; 61(2): 179-193. PMID: 19235034.	Study design is case-control study (colon cancer).
Schulz M, Hoffmann K, Weikert C, Nöthlings U, Schulze MB, Boeing H. Identification of a dietary pattern characterized by high-fat food choices associated with increased risk of breast cancer: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Br J Nutr.* 2008 Nov; 100(5): 942-946. PMID: 18377685.	Does not answer question: Examines relationship between high fat foods and breast cancer.
Seierstad SL, Seljeflot I, Johansen O, Hansen R, Haugen M, Rosenlund G, Frøyland L, Arnesen H. Dietary intake of differently fed salmon: The influence on markers of human atherosclerosis. *Eur J Clin Invest.* 2005 Jan; 35(1): 52-59. PMID: 15638820.	Participants diagnosed with T2D.
Shiell AW, Campbell-Brown M, Haselden S, Robinson S, Godfrey KM, Barker DJ. High-meat, low-carbohydrate diet in pregnancy: Relation to adult blood pressure in the offspring. *Hypertension*. 2001 Dec 1; 38(6): 1, 282-1, 288. PMID: 11751704.	Does not answer question: Examines relationship between dietary intake during pregnancy and health of adult offspring.
Sieri S, Krogh V, Muti P, Micheli A, Pala V, Crosignani P, Berrino F. Fat and protein intake and subsequent breast cancer risk in postmenopausal women. *Nutr Cancer.* 2002; 42(1): 10-17. PMID: 12235640.	Study design is case-control study (breast cancer).

Skjelbred CF, Saebø M, Hjartåker A, Grotmol T, Hansteen IL, Tveit KM, Hoff G, Kure EH. Meat, vegetables and genetic polymorphisms and the risk of colorectal carcinomas and adenomas. *BMC Cancer*. 2007 Dec 19; 7: 228. PMID: 18093316; PMCID: PMC2228310.	Study design is case-control study (colorectal cancer).
Smith DR, Wood R, Tseng S, Smith SB. Increased beef consumption increases apolipoprotein A-I but not serum cholesterol of mildly hypercholesterolemic men with different levels of habitual beef intake. *Exp Biol Med (Maywood).* 2002 Apr; 227(4): 266-275. PMID: 11910049.	Participants diagnosed with mild hypercholesterolemia.
SoRelle R. Fish and long-chain omega-3 fatty acids could be lifesavers for diabetic women. *Circulation.* 2003 Apr 22; 107(15): e9, 033-9, 035. PMID: 12707254.	Participants were diagnosed with diabetes.
Sørensen M, Autrup H, Olsen A, Tjønneland A, Overvad K, Raaschou-Nielsen O. Prospective study of NAT1 and NAT2 polymorphisms, tobacco smoking and meat consumption and risk of colorectal cancer. *Cancer Lett.* 2008 Aug 8; 266(2): 186-193. Epub 2008 Mar 26. PMID: 18372103.	Study design is case-control study (colorectal cancer).
Spencer EA, Appleby PN, Davey GK, Key TJ. Diet and body mass index in 38000 EPIC-Oxford meat-eaters, fish-eaters, vegetarians and vegans. *Int J Obes Relat Metab Disord.* 2003 Jun; 27(6): 728-734. PMID: 12833118.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Stewart JW, Kaplan ML, Beitz DC. Pork with a high content of polyunsaturated fatty acids lowers LDL cholesterol in women. *Am J Clin Nutr.* 2001 Aug; 74(2): 179-187. PMID: 11470718.	Intervention consisted of modified pork high in PUFAs.
Tanskanen A, Hibbeln JR, Tuomilehto J, Uutela A, Haukkala A, Viinamäki H, Lehtonen J, Vartiainen E. Fish consumption and depressive symptoms in the general population in Finland. *Psychiatr Serv.* 2001 Apr; 52(4): 529-531. PMID: 11274502.	Does not include health outcome of interest in analyses.
Tapola NS, Lyyra ML, Karvonen HM, Uusitupa MI, Sarkkinen ES. The effect of meat products enriched with plant sterols and minerals on serum lipids and blood pressure. *Int J Food Sci Nutr.* 2004 Aug; 55(5): 389-397. PMID: 15545047.	Intervention consisted of meat products enriched with plant sterols; participants diagnosed with hypercholesterolemia.
Tappel A. Heme of consumed red meat can act as a catalyst of oxidative damage and could initiate colon, breast and prostate cancers, heart disease and other diseases. *Med Hypotheses*. 2007; 68(3): 562-564. Epub 2006 Oct 11. PMID: 17045417.	Study design is narrative review.
Teixeira Rde C, Molina Mdel C, Zandonade E, Mill JG. Cardiovascular risk in vegetarians and omnivores: A comparative study. *Arq Bras Cardiol.* 2007 Oct; 89(4): 237-244. English, Portuguese. PMID: 17992380.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Terry P, Rohan TE, Wolk A, Maehle-Schmidt M, Magnusson C. Fish consumption and breast cancer risk. *Nutr Cancer.* 2002; 44(1): 1-6. PMID: 12672635.	Study design is case-control study (breast cancer).

Thorsdottir I, Birgisdottir B, Kiely M, Martinez J, Bandarra N. Fish consumption among young overweight European adults and compliance to varying seafood content in four weight loss intervention diets. *Public Health Nutr.* 2009 May; 12(5): 592-598. Epub 2008 Jun 19. PMID: 18561865.	Does not answer question: Examined compliance to eating varying types of seafood in weight loss intervention diets.
Thorsdottir I, Tomasson H, Gunnarsdottir I, Gisladottir E, Kiely M, Parra MD, Bandarra NM, Schaafsma G, Martinéz JA. Randomized trial of weight-loss-diets for young adults varying in fish and fish oil content. *Int J Obes* (Lond). 2007 Oct; 31(10): 1, 560-1, 566. Epub 2007 May 15. PMID: 17502874.	Does not answer question: Examined fish intake and weight loss.
Tiemersma EW, Kampman E, Bueno de Mesquita HB, Bunschoten A, van Schothorst EM, Kok FJ, Kromhout D. Meat consumption, cigarette smoking, and genetic susceptibility in the etiology of colorectal cancer: results from a Dutch prospective study. *Cancer Causes Control.* 2002 May; 13(4): 383-393. PMID: 12074508.	Study design is case-control study (colorectal cancer).
Timonen M, Horrobin D, Jokelainen J, Laitinen J, Herva A, Räsänen P. Fish consumption and depression: The Northern Finland 1966 birth cohort study. *J Affect Disord.* 2004 Nov 1; 82(3): 447-452. PMID: 15555697.	Does not include health outcome of interest in analyses.
Tzoulaki I, Brown IJ, Chan Q, Van Horn L, Ueshima H, Zhao L, Stamler J, Elliott P; International Collaborative Research Group on Macro-/Micronutrients and Blood Pressure. Relation of iron and red meat intake to blood pressure: cross sectional epidemiological study. *BMJ.* 2008 Jul 15; 337: a258. doi: 10.1136/bmj.a258. PMID: 18632704; PMCID: PMC2658466.	Study design is cross-sectional epidemiological study.
Umesawa M, Sato S, Imano H, Kitamura A, Shimamoto T, Yamagishi K, Tanigawa T, Iso H. Relations between protein intake and blood pressure in Japanese men and women: the Circulatory Risk in Communities Study (CIRCS). *Am J Clin Nutr.* 2009 Aug; 90(2): 377-384. Epub 2009 Jun 10. PMID: 19515740.	Study design is cross-sectional.
Varraso R, Jiang R, Barr RG, Willett WC, Camargo CA Jr. Prospective study of cured meats consumption and risk of chronic obstructive pulmonary disease in men. *Am J Epidemiol*. 2007 Dec 15; 166(12): 1, 438-1, 445. Epub 2007 Sep 4. PMID: 17785711; PMCID: PMC2573990.	Does not include health outcome of interest in analyses.
Virtanen JK, Mozaffarian D, Chiuve SE, Rimm EB. Fish consumption and risk of major chronic disease in men. *Am J Clin Nutr.* 2008 Dec; 88(6): 1, 618-1, 625. PubMed PMID: 19064523; PMCID: PMC2613199.	Does not answer question: Examined relationship between fish intake and chronic disease.
Wakai K, Tamakoshi K, Date C, Fukui M, Suzuki S, Lin Y, Niwa Y, Nishio K, Yatsuya H, Kondo T, Tokudome S, Yamamoto A, Toyoshima H, Tamakoshi A; JACC Study Group. Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. *Cancer Sci.* 2005 Sep; 96(9): 590-599. PMID: 16128744.	Does not answer question: Examined relationship between breast cancer and fat intake, not animal protein.

Weggemans RM, Zock PL, Katan MB. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: A meta-analysis. *Am J Clin Nutr.* 2001 May; 73(5): 885-891. PMID: 11333841.	Does not examine relationship between intake of animal protein product and health outcome.
Weghuber D, Widhalm K. Effect of 3-month treatment of children and adolescents with familial and polygenic hypercholesterolaemia with a soya-substituted diet. *Br J Nutr.* 2008 Feb; 99(2): 281-286. Epub 2007 Aug 13. PMID: 17697400.	Participants diagnosed with hypercholesterolemia.
Welch AA, Bingham SA, Ive J, Friesen MD, Wareham NJ, Riboli E, Khaw KT. Dietary fish intake and plasma phospholipid n-3 polyunsaturated fatty acid concentrations in men and women in the European Prospective Investigation into Cancer-Norfolk United Kingdom cohort. *Am J Clin Nutr.* 2006 Dec; 84(6): 1, 330-1, 339. PMID: 17158413.	Does not include health outcomes in analyses; fish is the independent variable.
Wu K, Hu FB, Willett WC, Giovannucci E. Dietary patterns and risk of prostate cancer in U.S. men. *Cancer Epidemiol Biomarkers Prev.* 2006 Jan; 15(1): 167-171. PMID: 16434606.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Yoon H, Benamouzig R, Little J, François-Collange M, Tomé D. Systematic review of epidemiological studies on meat, dairy products and egg consumption and risk of colorectal adenomas. *Eur J Cancer Prev*. 2000 Jun; 9(3): 151-164. PMID: 10954254.	Study design is systematic review (colorectal cancer).
Yuan JM, Ross RK, Gao YT, Yu MC. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *Am J Epidemiol.* 2001 Nov 1; 154(9): 809-816. PMID: 11682363.	Does not answer question: Examined relationship between fish intake and myocardial infarction.

CHAPTER 3. ANIMAL PROTEIN PRODUCTS – BLOOD PRESSURE

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF ANIMAL PROTEIN PRODUCTS AND BLOOD PRESSURE?

Conclusion statement

Moderate evidence found no clear association between intake of animal protein products and blood pressure in prospective cohort studies.

Grade

Moderate

Evidence summary overview

This review included six articles (Alonso, 2006; Miura, 2004; Steffen, 2005; Wagemakers, 2009; Wang, 2008a; Wang, 2008b) representing prospective cohorts from the US, United Kingdom and Spain published since 2000. No relationship between intake of animal protein and hypertension (HTN) was observed in the Seguimiento Universidad de Navarra (SUN) cohort in Spain (Alonso, 2006). Similarly, no association between intake of animal protein and systolic or diastolic blood pressure (SBP and DBP) was observed in the PREMIER Study (Wang, 2008a) and no association between the intake of red or processed meat and SBP and DBP was observed in a cohort in the UK (Wagemakers, 2009).

In contrast, in the Women's Health Study (Wang, 2008b), total red meat intake was positively associated with risk of developing HTN. In addition, each individual unprocessed and processed red meat item, including hot dogs, hamburgers and bacon, beef or lamb as a main dish were positively associated with the risk of developing HTN. Similarly, the CARDIA study (Steffen, 2005) found a positive association between consumption of total meat and red and processed meat (combined) and risk of developing elevated blood pressure (BP). The Chicago Western Electric Study also showed a positive association between SBP and DBP and red meat, but observed no association with processed meat.

Differences in dietary assessment methodology likely affected the results in this review. Assessment methods included 24-hour recalls, five-day diaries, diet histories, interviews and food frequency questionnaires (FFQ). Studies that used 24-hour recalls (Wang, 2008a) and five-day diaries (Wagemakers, 2009) observed no associations between animal protein products and SBP and DBP.

Evidence summary paragraphs

Alonso et al, 2006 (positive quality) prospectively assessed the role of different nutritional factors, especially protein and fiber from different sources, on the risk of incident HTN in 5,880 adults (61% female; age>20 years) from the Seguimiento Universidad de Navarra (SUN) Follow-up Study in Spain. New cases of medically diagnosed HTN were identified through responses to a mailed questionnaire after at least two years from recruitment. Dietary intake over the previous year was assessed at baseline with a 136-item semi-quantitative FFQ validated in a Spanish population. Over a median follow-up of 28 months, 180 new cases of HTN were ascertained.

Animal protein was not associated with the risk of HTN (multivariate HR between extreme quintiles=1.0; 95% CI: 0.6, 1.8; P for trend=0.70).The authors concluded that animal protein did not show any association with the incidence of HTN in this cohort of adults.

Wang et al, 2008a (positive quality) examined the association of dietary protein intake with BP and particularly, the independent relationship of animal and plant protein with BP over 18 months of follow-up. Participants were 810 adults (62% female; age 25 to 79 years) from the PREMIER Trial (US). Blood pressure measurements were obtained by study personnel at baseline, six and 18 months. Two 24-hour recalls, one on a weekday and the other on a weekend day, were obtained at baseline, six and 18 months. No significant association was found between animal protein intake and SBP or DBP at any time-point.

Miura et al, 2004 (positive quality) examined relations of food intake, including meat intake, to seven-year BP change in 1,710 men (age 41 to 57 years) from the Chicago Western Electric Study in the US. Blood pressure was measured annually by study personnel from 1958-1959 through 1966. Dietary intake information was obtained at the first (1957-1958) and second (1958-1959) examinations, one year apart, by study personnel using standardized interviews and questionnaires. Baseline nutrient intake data are means from these two examinations. Specific meats included in analyses were beef-veal-lamb (less than eight, eight to 20, >20 120-gram portions per month), pork-ham-bacon (less than four, four to eight, more than eight 120-gram portions per month) and poultry (less than four, four to eight, more than eight 120-gram portions per month). Average SBP/DBP increase was 1.9/0.3mmHg per year. Beef-veal-lamb and poultry intakes were related directly to a greater SBP/DBP increase (P<0.05). Men who reported eight to 20 or >20 servings of 120-gram portions of meat had a 5.4mmHg or 6.0mmHg, respectively, greater increase in SBP over seven years compared with men who reported less than eight servings per month. In all models, men whose poultry intake was the highest (more than eight portions per month) had a significantly greater rise in SBP. In the fully adjusted model, there was no significant (NS) association between pork intake and SBP. Men with the highest intake of beef-veal-lamb had a significantly greater increase in DBP (P<0.05). Higher poultry intake was also associated with a greater increase in DBP (P<0.05). However, there was no significant association between pork and DBP in any of the models. The authors concluded that men with a higher intake of red meat had a significantly greater increase in BP; also, men with a higher poultry intake had a significantly greater annual increase in BP, independent of other factors.

Steffen et al, 2005 (positive quality) evaluated associations of dietary intake, including meat intake, with the 15-year incidence of elevated BP among 4,304 adults (883 black men, 1,249 black women, 989 white men and 1,183 white women; age 18 to 30 years) from the Coronary Artery Risk Development in Young Adults (CARDIA) Study in the US. Blood pressure was assessed at six clinic exams at years zero, two, five, seven, 10 and 15. Dietary intake was assessed with an interviewer-administered diet history at years zero and seven. The analyses were conducted by using the average of year zero and year seven dietary data. Meat as a group as well as red and processed meat, poultry and eggs were considered. Over 15 years, 23.2% of study participants experienced incident elevated blood pressure (EBP), of whom 13.7% had HTN and 9.4% had high-normal BP. Consumption of meat (meat, poultry, eggs, fish and

seafood) was positively related with the risk of developing EBP, even after adjustment for possible explanatory factors (HR between extreme quintiles=1.67; 95% CI: 1.21, 2.30; P for trend=0.003). There was no association between poultry and EBP (P for trend=0.19). However, consumption of red and processed meat was positively associated with EBP (HR between extreme quintiles=1.39; 95% CI: 1.05, 1.82; P for trend=0.006), whereas egg intake was inversely associated with EBP (HR between extreme quintiles=0.79; 95% CI: 0.64, 0.98; P for trend=0.05). Further adjustment of these foods for body mass index (BMI) attenuated these relations slightly (data not provided). The authors concluded that greater plant food intakes and lower meat intakes may prevent the development of EBP when consumed by free-living black and white men and women as part of a habitual diet.

Wagemakers et al, 2009 (neutral quality) investigated whether a high consumption of red or processed meat is associated with coronary heart disease (CHD) risk factors in a cohort of British adults (N=1,152; 55% female; age 43 at baseline) followed from 1989 to 1999 in the Medical Research Council National Survey of Health and Development. Blood pressure was measured in 1999. Systolic blood pressure and DBP were measured twice by study personnel and means of duplicate measurements were used in analyses. Food intake was self-recorded using five-day diaries in 1989 and 1999. Meat consumption was estimated by adding individual meat portions to the meat fractions of composite dishes. Red meat, processed meat, and combined red and processed meat intake were considered. There was no significant (NS) association between red or processed meat consumption in 1989 or 1999 and SBP or DBP measured in 1999. There was also no significant association between combined intake of red and processed meat in 1989 and SBP or DBP measured in 1999. However, among men only, the combined intake of red and processed meat in 1999 had a significant positive association with SBP (P=0.014) and DBP (P=0.009) measured in 1999. The authors concluded that red or processed meat consumption measured 10 years earlier does not predict an increased risk of cardiovascular disease (CVD) as indicated by BP.

Wang et al, 2008b (positive quality) investigated the association of total red meat, types of red meat and poultry intake with the incidence of HTN over 10 years of follow-up among 28,766 women (age ≥45 years) in the Women's Health Study (US). Incident HTN was self-reported on annual follow-up questionnaires. Baseline red meat and poultry intake were assessed from a 131-item validated semi-quantitative FFQ. Total red meat (including unprocessed and processed red meat), total poultry and individual red meat items were considered. During 10 years of follow-up, 8,693 incident cases of HTN were identified. Total red meat intake was significantly and positively associated with the risk of developing HTN (multivariate RR between extreme quintiles=1.13; 95% CI: 1.04, 1.23; P for trend=0.008). No association between intake of poultry and incident HTN was found. Comparing women who consumed more than one serving per week of a specific red meat product with those who consumed no red meat, the multivariate RRs of HTN were 1.33 for hot dogs, 1.27 for bacon, 1.26 for other processed red meats, 1.31 for beef or lamb as main dish, 1.22 for pork as main dish, 1.28 for beef, pork or lamb as sandwich or mixed dish and 1.27 for hamburgers (all P<0.05). The authors concluded that red meat intake was positively associated, whereas poultry intake was unassociated, with the risk of HTN in middle-aged and older women.

Overview table

Author, Year, Study Design, Class, Rating	Study Name/Location	Total Meat Association (Pos, Neg, None)	Red Meat Association (Pos, Neg, None)	Processed Meat Association (Pos, Neg, None)	Poultry Association (Pos, Neg, None)
Alonso A, Beunza JJ et al, 2006 Study Design: Prospective cohort study Class: B Positive quality	Seguimiento Universidad de Navarra (SUN) Follow-up Study. Location: Spain.	Animal protein: Ø HTN.	Not examined.	Not examined.	Not examined.
Miura K, Greenland P et al 2004 Study Design: Prospective Cohort Study Class: B Positive quality	Chicago Western Electric Study. Location: US.	Not examined.	Beef-veal-lamb: (+) SBP and (+) DBP.	Pork-ham-bacon: Ø SBP and Ø DBP.	Poultry: (+) SBP and (+) DBP.
Steffen LM, Kroenke CH et al, 2005 Study Design: Prospective cohort study Class: B Positive quality	Coronary Artery Risk Development in Young Adults (CARDIA) Study. Location: US.	Meat (red and processed meat, poultry, eggs, fish and seafood): (+) EBP.	Red and processed meat (combined): (+) EBP.	Red and processed meat (combined): (+) EBP.	Poultry: Ø EBP. Eggs: (-) EBP.

Wagemakers et al 2009 Study Design: Cohort Class: B Neutral quality	Medical Research Council National Survey of Health and Development. Location: United Kingdom.	Not examined.	Red meat: Ø SBP and Ø DBP. Red and processed meat (combined): Ø SBP and Ø DBP.	Processed meat: Ø SBP and Ø DBP. Red and processed meat (combined): Ø SBP and Ø DBP.	Not examined.
Wang L, Manson JE et al, 2008 Study Design: Prospective cohort study Class: B Positive quality	Women's Health Study. Location: US.	Not examined.	Total red meat (unprocessed and processed red meat): (+) HTN. Individual foods: Hot dogs; bacon; other processed red meats; beef or lamb as main dish; pork as main dish; beef, pork or lamb as sandwich or mixed dish; hamburgers: All (+) HTN.	Total red meat (unprocessed and processed red meat): (+) HTN. Individual foods: Hot dogs; bacon; other processed red meats; beef or lamb as main dish; pork as main dish; beef, pork or lamb as sandwich or mixed dish; hamburgers: All (+) HTN.	Poultry: Ø HTN.
Wang YF, Yancy WS et al, 2008 Study Design: Prospective cohort Class: B Positive quality	PREMIER Study. Location: US.	Animal protein: Ø SBP and Ø DBP.	Not examined.	Not examined.	Not examined

Search plan and results

Inclusion criteria

- January 2000 to September 2009
- Prospective cohort studies on colorectal, breast and prostate cancers
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children two to 18 years; Adults 19 years and older
- *Populations:* Healthy, those with elevated chronic disease risk.

Exclusion criteria

- With the exception of the body weight outcome, cross-sectional studies were excluded from the review
- Systematic reviews and meta-analyses on colorectal, breast and prostate cancers. Only original research studies with prospective cohort design were included in the review
- Studies specifically related to seafood or milk product intake (considered as separate questions)
- Studies that reported on animal protein intake as a component of a dietary pattern and not as an individual variable
- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: (Animal protein* OR meat[mh] OR "Egg Proteins, Dietary"[mh] OR "Fish Proteins"[mh]) AND ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "overweight"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mh:NoExp] OR “heart diseases”[mh] OR "Coronary Disease"[Mesh] OR “blood pressure”[mh] OR “chronic disease”[mh] OR obesity[mh] OR "Body Weights and Measures"[mh] OR "Colorectal Neoplasms"[mesh])
  (Animal protein* OR meat[mh] OR "Egg Proteins, Dietary"[mh] OR "Fish Proteins"[mh] OR seafood[majr] OR crustacea[majr]) AND (systematic[sb] OR Meta-Analysis[ptyp] OR "Cohort Studies"[Mesh]) AND ("Prostatic Neoplasms"[Mesh] OR "Breast Neoplasms"[Mesh])
  eggs [mh] AND ("Diabetes Mellitus, Type 2"[majr] OR "metabolic syndrome X"[majr] OR "overweight"[majr] OR "hypertension"[majr] OR "dyslipidemias"[majr] OR "cardiovascular diseases"[majr:NoExp] OR “heart diseases”[majr] OR "Coronary Disease"[Mesh] OR “blood pressure”[majr] OR

"chronic disease"[majr] OR obesity[majr] OR "Body Weights and Measures"[majr])
(Note: "Cohort Studies"[Mesh]) includes prospective studies)

Date searched: 09/01/2009; update 09/18/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 771
- Total articles identified to review from electronic databases: 166
- Articles identified via handsearch or other means: 2
- Number of Primary Articles Identified: 47
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 47
- Number of Articles Reviewed but Excluded: 121

Included articles (References)

What is the relationship between the intake of animal protein products and cardiovascular disease?

1. Djoussé L, Gaziano JM. Egg consumption in relation to cardiovascular disease and mortality: the Physicians' Health Study.*Am J Clin Nutr.* 2008 Apr; 87(4): 964-969. PMID: 18400720; PMCID: PMC2386667.
2. Halton TL, Willett WC, Liu S, Manson JE, Albert CM, Rexrode K, Hu FB. Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med.* 2006 Nov 9; 355(19): 1, 991-2, 002. PMID: 17093250.
3. Kelemen LE, Kushi LH, Jacobs DR Jr, Cerhan JR. Associations of dietary protein with disease and mortality in a prospective study of postmenopausal women. *Am J Epidemiol.* 2005 Feb 1; 161(3): 239-249. PMID: 15671256.
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7. Sinha R, Cross AJ, Graubard BI, Leitzmann MF, Schatzkin A. Meat intake and mortality: A prospective study of over half a million people. *Arch Intern Med.* 2009 Mar 23; 169(6): 562-571. PMID: 19307518.

What is the relationship between the intake of animal protein products and blood pressure?

Primary Citations

1. Alonso A, Beunza JJ, Bes-Rastrollo M, Pajares RM, Martínez-González MA.

Vegetable protein and fiber from cereal are inversely associated with the risk of hypertension in a Spanish cohort. *Arch Med Res*. 2006 Aug; 37(6): 778-786. PMID: 16824939.
2. Miura K, Greenland P, Stamler J, Liu K, Daviglus ML, Nakagawa H. Relation of vegetable, fruit, and meat intake to 7-year blood pressure change in middle-aged men: The Chicago Western Electric Study. *Am J Epidemiol.* 2004 Mar 15; 159(6): 572-580. PMID: 15003961.
3. Steffen LM, Kroenke CH, Yu X, Pereira MA, Slattery ML, Van Horn L, Gross MD, Jacobs DR Jr. Associations of plant food, dairy product, and meat intakes with 15-year incidence of elevated blood pressure in young black and white adults: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr.* 2005 Dec; 82(6): 1, 169-1, 177; quiz 1, 363-1, 364. PMID: 16332648.
4. Wagemakers JJ, Prynne CJ, Stephen AM, Wadsworth ME. Consumption of red or processed meat does not predict risk factors for coronary heart disease; results from a cohort of British adults in 1989 and 1999. *Eur J Clin Nutr.* 2009 Mar; 63(3): 303-311. Epub 2007 Nov 14. PMID: 18000518.
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What is the relationship between the intake of animal protein products and type 2 diabetes?

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3. Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. *Am J Clin Nutr.* 2008 Feb; 87(2): 339-346. PMID: 18258623.
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What is the relationship between the intake of animal protein products and body

weight?

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What is the relationship between the intake of animal protein products and colorectal cancer?

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What is the relationship between the intake of animal protein products and prostate cancer?

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What is the relationship between the intake of animal protein products and breast cancer?

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Excluded articles

Article	Reason for Exclusion
Alexander DD, Cushing CA, Lowe KA, Sceurman B, Roberts MA. Meta-analysis of animal fat or animal protein intake and colorectal cancer. *Am J Clin Nutr.* 2009 May; 89(5): 1, 402-1, 409. Epub 2009 Mar 4. PMID: 19261724.	Study design is meta-analysis (colorectal cancer).
Appleby PN, Davey GK, Key TJ. Hypertension and blood pressure among meat eaters, fish eaters, vegetarians and vegans in EPIC-Oxford. *Public Health Nutr.* 2002 Oct; 5(5): 645-654. PMID: 12372158.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Augustsson K, Michaud DS, Rimm EB, Leitzmann MF, Stampfer MJ, Willett WC, Giovannucci E. A prospective study of intake of fish and marine fatty acids and prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2003 Jan; 12(1): 64-67. PMID: 12540506.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Azadbakht L, Esmaillzadeh A. Red meat intake is associated with metabolic syndrome and the plasma C-reactive protein concentration in women. *J Nutr.* 2009 Feb; 139(2): 335-339. Epub 2008 Dec 11. PMID: 19074209.	Does not answer question: Examined relationship between red meat intake and metabolic syndrome.

Balder HF, Vogel J, Jansen MC, Weijenberg MP, van den Brandt PA, Westenbrink S, van der Meer R, Goldbohm RA. Heme and chlorophyll intake and risk of colorectal cancer in the Netherlands cohort study. *Cancer Epidemiol Biomarkers Prev.* 2006 Apr; 15(4): 717-725. PMID: 16614114.	Does not answer question: Examined relationship between heme and chlorophyll intake and colorectal cancer.
Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: A systematic literature review and meta-analysis. *Cancer Causes Control.* 2007 Nov; 18(9): 967-988. Epub 2007 Jul 19. Review. PMID: 17638104; PMCID: PMC2592095.	Does not include colorectal, breast, or prostate cancer in analyses.
Barraj L, Tran N, Mink P. A comparison of egg consumption with other modifiable coronary heart disease lifestyle risk factors: a relative risk apportionment study. *Risk Anal*. 2009 Mar; 29(3): 401-415. Epub 2008 Nov 4. PMID: 19000074.	Does not answer question: Used risk apportionment approach to estimate contribution of egg intake to coronary heart disease (CHD) risk at the population level.
Benassi-Evans B, Clifton PM, Noakes M, Keogh JB, Fenech M. High protein-high red meat versus high carbohydrate weight loss diets do not differ in effect on genome stability and cell death in lymphocytes of overweight men. *Mutagenesis.* 2009 May; 24(3): 271-277. Epub 2009 Mar 5. PMID: 19264840.	Does not include animal protein product intake in analyses.
Brink M, Weijenberg MP, de Goeij AF, Roemen GM, Lentjes MH, de Bruïne AP, Goldbohm RA, van den Brandt PA. Meat consumption and K-ras mutations in sporadic colon and rectal cancer in The Netherlands Cohort Study. *Br J Cancer.* 2005 Apr 11; 92(7): 1, 310-1, 320. PMID: 15812479.	Study design is case-cohort.
Cade JE, Burley VJ, Greenwood DC; UK Women's Cohort Study Steering Group. The UK Women's Cohort Study: Comparison of vegetarians, fish-eaters and meat-eaters. *Public Health Nutr.* 2004 Oct; 7(7): 871-878. PMID: 15482612.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Chan AT, Tranah GJ, Giovannucci EL, Willett WC, Hunter DJ, Fuchs CS. Prospective study of N-acetyltransferase-2 genotypes, meat intake, smoking and risk of colorectal cancer. *Int J Cancer.* 2005 Jul 1; 115(4): 648-652. PMID: 15700302.	Study design is case-control study (colorectal cancer).
Chavarro JE, Stampfer MJ, Hall MN, Sesso HD, Ma J. A 22-y prospective study of fish intake in relation to prostate cancer incidence and mortality. *Am J Clin Nutr.* 2008 Nov; 88(5): 1, 297-1, 303. PMID: 18996866.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Chrysohoou C, Panagiotakos DB, Pitsavos C, Skoumas J, Krinos X, Chloptsios Y, Nikolaou V, Stefanadis C. Long-term fish consumption is associated with protection against arrhythmia in healthy persons in a Mediterranean region: The ATTICA study. *Am J Clin Nutr.* 2007 May; 85(5): 1, 385-1, 391. PMID: 17490977.	Does not answer question: Examined relationship between fish intake and arrhythmia.

Cotterchio M, Boucher BA, Manno M, Gallinger S, Okey AB, Harper PA. Red meat intake, doneness, polymorphisms in genes that encode carcinogen-metabolizing enzymes, and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2008 Nov; 17(11): 3, 098-3, 107. PMID: 18990750.	Study design is case-control (colorectal cancer).
Crowe FL, Key TJ, Appleby PN, Travis RC, Overvad K, Jakobsen MU, Johnsen NF, Tjønneland A, Linseisen J, Rohrmann S, Boeing H, Pischon T, Trichopoulou A, Lagiou P, Trichopoulos D, Sacerdote C, Palli D, Tumino R, Krogh V, Bueno-de-Mesquita HB, Kiemeney LA, Chirlaque MD, Ardanaz E, Sánchez MJ, Larrañaga N, González CA, Quirós JR, Manjer J, Wirfält E, Stattin P, Hallmans G, Khaw KT, Bingham S, Ferrari P, Slimani N, Jenab M, Riboli E. Dietary fat intake and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr.* 2008 May; 87(5): 1, 405-1, 413. PMID: 18469265.	Does not answer question: Examined relationship between animal fat intake and prostate cancer.
Dallongeville J, Yarnell J, Ducimetière P, Arveiler D, Ferrières J, Montaye M, Luc G, Evans A, Bingham A, Hass B, Ruidavets JB, Amouyel P. Fish consumption is associated with lower heart rates.*Circulation.* 2003 Aug 19; 108(7): 820-825. Epub 2003 Aug 11. PMID: 12912821.	Does not answer question: Examined relationship between fish intake and heart rates.
Davey GK, Spencer EA, Appleby PN, Allen NE, Knox KH, Key TJ. EPIC-Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33 883 meat-eaters and 31 546 non meat-eaters in the UK. *Public Health Nutr.* 2003 May; 6(3): 259-269. PMID: 12740075.	Does not include health outcomes in analyses.
de Mello VD, Zelmanovitz T, Perassolo MS, Azevedo MJ, Gross JL. Withdrawal of red meat from the usual diet reduces albuminuria and improves serum fatty acid profile in type 2 diabetes patients with macroalbuminuria. *Am J Clin Nutr*. 2006 May; 83(5): 1, 032-1, 038. PMID: 16685043.	Participants diagnosed with type 2 diabetes (T2D).
Dixon LB, Balder HF, Virtanen MJ, Rashidkhani B, Männistö S, Krogh V, van Den Brandt PA, Hartman AM, Pietinen P, Tan F, Virtamo J, Wolk A, Goldbohm RA. Dietary patterns associated with colon and rectal cancer: results from the Dietary Patterns and Cancer (DIETSCAN) Project. *Am J Clin Nutr.* 2004 Oct; 80(4): 1, 003-1, 011. PMID: 15447912.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Djoussé L, Gaziano JM. Egg consumption and risk of heart failure in the Physicians' Health Study. *Circulation.* 2008 Jan 29; 117(4): 512-516. Epub 2008 Jan 14. PMID: 18195171; PMCID: PMC2706003.	Does not answer question: Examined relationship between egg consumption and heart failure.
Egeberg R, Olsen A, Autrup H, Christensen J, Stripp C, Tetens I, Overvad K, Tjønneland A. Meat consumption, N-acetyl transferase 1 and 2 polymorphism and risk of breast cancer in Danish postmenopausal women. *Eur J Cancer Prev.* 2008 Feb; 17(1): 39-47. PMID: 18090909.	Study design is nested case-control study (breast cancer).
Eichholzer M, Bisig B. Daily consumption of (red) meat or meat products in Switzerland: Results of the 1992/93 Swiss Health Survey. *Eur J Clin Nutr.* 2000 Feb; 54(2): 136-142. PMID: 10694784.	Does not include health outcomes in analyses.

Elliott P, Stamler J, Dyer AR, Appel L, Dennis B, Kesteloot H, Ueshima H, Okayama A, Chan Q, Garside DB, Zhou B. Association between protein intake and blood pressure: The INTERMAP Study. *Arch Intern Med.* 2006 Jan 9; 166(1): 79-87. PMID: 16401814.	Study design is cross-sectional epidemiological study.
Engeset D, Andersen V, Hjartåker A, Lund E. Consumption of fish and risk of colon cancer in the Norwegian Women and Cancer (NOWAC) study. *Br J Nutr.* 2007 Sep; 98(3): 576-582. Epub 2007 Apr 10. Erratum in: *Br J Nutr.* 2008 Mar; 99(3): 696. PMID: 17419892.	Does not answer question: Examined relationship between fish intake and colon cancer.
Erkkilä AT, Lichtenstein AH, Mozaffarian D, Herrington DM. Fish intake is associated with a reduced progression of coronary artery atherosclerosis in postmenopausal women with coronary artery disease. *Am J Clin Nutr.* 2004 Sep; 80(3): 626-632. PMID: 15321802.	Participants diagnosed with CHD.
Erkkilä AT, Schwab US, de Mello VD, Lappalainen T, Mussalo H, Lehto S, Kemi V, Lamberg-Allardt C, Uusitupa MI. Effects of fatty and lean fish intake on blood pressure in subjects with coronary heart disease using multiple medications. *Eur J Nutr.* 2008 Sep; 47(6): 319-328. Epub 2008 Jul 29. PMID: 18665413.	Participants diagnosed with CHD.
Faramawi MF, Johnson E, Fry MW, Sall M, Zhou Y. Consumption of different types of meat and the risk of renal cancer: Meta-analysis of case-control studies. *Cancer Causes Control.* 2007 Mar; 18(2): 125-133. Epub 2007 Jan 22. Erratum in: *Cancer Causes Control.* 2007 Jun; 18 (5): 581. Yi, Zhou [corrected to Zhou, Yi]. PMID: 17242980.	Does not include colorectal, breast or prostate cancer in analyses.
Ferrucci LM, Sinha R, Graubard BI, Mayne ST, Ma X, Schatzkin A, Schoenfeld PS, Cash BD, Flood A, Cross AJ. Dietary meat intake in relation to colorectal adenoma in asymptomatic women. *Am J Gastroenterol.* 2009 May; 104(5): 1, 231-1, 140. Epub 2009 Apr 14. PMID: 19367270.	Study design is case-control study (colorectal cancer).
Geelen A, Schouten JM, Kamphuis C, Stam BE, Burema J, Renkema JM, Bakker EJ, van't Veer P, Kampman E. Fish consumption, n-3 fatty acids, and colorectal cancer: a meta-analysis of prospective cohort studies. *Am J Epidemiol*. 2007 Nov 15; 166(10): 1, 116-1, 125. Epub 2007 Sep 6. PMID: 17823383.	Study design is meta-analysis (colorectal cancer).
Gillum RF, Mussolino ME, Madans JH. Fish consumption and hypertension incidence in African Americans and whites: The NHANES I Epidemiologic Follow-up Study. *J Natl Med Assoc.* 2001 Apr; 93(4): 124-128. PMID: 12653399; PMCID: PMC2593988.	Does not answer question: Examined relationship between fish intake and hypertension (HTN).
Goldin BR, Brauner E, Adlercreutz H, Ausman LM, Lichtenstein AH. Hormonal response to diets high in soy or animal protein without and with isoflavones in moderately hypercholesterolemic subjects. *Nutr Cancer.* 2005; 51(1): 1-6. PMID: 15749623.	Does not answer question: Examined hormonal response to diets high in soy or animal protein.
Gonzalez CA, Riboli E. Diet and cancer prevention: Where we are, where we are going. Nutr Cancer. 2006; 56(2): 225-31. Review. PMID: 17474869.	Study design is narrative review.

Grillenberger M, Neumann CG, Murphy SP, Bwibo NO, Weiss RE, Jiang L, Hautvast JG, West CE. Intake of micronutrients high in animal-source foods is associated with better growth in rural Kenyan school children. *Br J Nutr*. 2006 Feb; 95(2): 379-390. PMID: 16469157.	Study population not from a developed country as defined by the Human Development Index (2009).
Gross JL, Zelmanovitz T, Moulin CC, De Mello V, Perassolo M, Leitão C, Hoefel A, Paggi A, Azevedo MJ. Effect of a chicken-based diet on renal function and lipid profile in patients with type 2 diabetes: a randomized crossover trial. *Diabetes Care.* 2002 Apr; 25(4): 645-651. PMID: 11919119.	Participants diagnosed with T2D.
Günther AL, Remer T, Kroke A, Buyken AE. Early protein intake and later obesity risk: which protein sources at which time points throughout infancy and childhood are important for body mass index and body fat percentage at 7 y of age? *Am J Clin Nutr.* 2007 Dec; 86(6): 1, 765-1, 772. PMID: 18065597.	Does not answer question: Examined protein intake during infancy and childhood and body weight outcomes at age seven years.
He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, Greenland P. Accumulated evidence on fish consumption and coronary heart disease mortality: A meta-analysis of cohort studies. *Circulation.* 2004 Jun 8; 109(22): 2, 705-2, 711. PMID: 15184295.	Does not answer question: examined relationship between fish intake and CHD.
High red-meat intake, obesity linked to cancer.*Health News.* 2002 Feb; 8(2): 9. PMID: 11862847.	News article.
Hodgson JM, Burke V, Beilin LJ, Puddey IB. Partial substitution of carbohydrate intake with protein intake from lean red meat lowers blood pressure in hypertensive persons. *Am J Clin Nutr.* 2006 Apr; 83(4): 780-787. PMID: 16600928.	Participants diagnosed with HTN.
Hu FB, Manson JE, Willett WC. Types of dietary fat and risk of coronary heart disease: a critical review.*J Am Coll Nutr.* 2001 Feb; 20(1): 5-19. Review. PMID: 11293467.	Study design is narrative review.
Huncharek M, Kupelnick B, Wheeler L. Dietary cured meat and the risk of adult glioma: A meta-analysis of nine observational studies. *J Environ Pathol Toxicol* Oncol. 2003; 22(2): 129-137. PMID: 14533876.	Does not include colorectal, breast, or prostate cancer in analyses.
Huncharek M, Kupelnick B. A meta-analysis of maternal cured meat consumption during pregnancy and the risk of childhood brain tumors. *Neuroepidemiology.* 2004 Jan-Apr; 23(1-2): 78-84. PMID: 14739572.	Does not include colorectal, breast, or prostate cancer in analyses.
Hunninghake DB, Maki KC, Kwiterovich PO Jr, Davidson MH, Dicklin MR, Kafonek SD. Incorporation of lean red meat into a National Cholesterol Education Program Step I diet: A long-term, randomized clinical trial in free-living persons with hypercholesterolemia. *J Am Coll Nutr.* 2000 Jun; 19(3): 351-360. PMID: 10872897.	Participants diagnosed with hypercholesterolemia.
Iso H, Sato S, Kitamura A, Naito Y, Shimamoto T, Komachi Y. Fat and protein intakes and risk of intraparenchymal hemorrhage among middle-aged Japanese. *Am J Epidemiol.* 2003 Jan 1; 157(1): 32-39. Erratum in: *Am J Epidemiol.* 2004 Feb 1; 159(3): 318. PMID: 12505888.	Does not answer question: examined relationship between protein intake and intraparenchymal hemorrhage.

Järvinen R, Knekt P, Rissanen H, Reunanen A. Intake of fish and long-chain n-3 fatty acids and the risk of coronary heart mortality in men and women. *Br J Nutr.* 2006 Apr; 95(4): 824-829. PMID: 16571163.	Does not answer question: examined relationship between fish intake and CHD.
Jenkins DJ, Wong JM, Kendall CW, Esfahani A, Ng VW, Leong TC, Faulkner DA, Vidgen E, Greaves KA, Paul G, Singer W. The effect of a plant-based low-carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. *Arch Intern Med.* 2009 Jun 8; 169(11): 1, 046-1, 054. PMID: 19506174.	Participants diagnosed hyperlipidemia.
Joshi AD, Corral R, Siegmund KD, Haile RW, Le Marchand L, Martínez ME, Ahnen DJ, Sandler RS, Lance P, Stern MC. Red meat and poultry intake, polymorphisms in the nucleotide excision repair and mismatch repair pathways and colorectal cancer risk. 2009 Mar; 30(3): 472-479. Epub 2008 Nov 24. PMID: 19029193; PMCID: PMC2722151.	Study design is case-control family-based study (colorectal cancer).
Kabat GC, Miller AB, Jain M, Rohan TE. A cohort study of dietary iron and heme iron intake and risk of colorectal cancer in women. *Br J Cancer.* 2007 Jul 2; 97 (1): 118-122. Epub 2007 Jun 5. Erratum in: *Br J Cancer.* 2007 Dec 3; 97(11): 1, 600. PMID: 77551493; PMCID: PMC2359661.	Does not answer question: examined relationship between iron and heme iron intake and colorectal cancer.
König A, Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, Lawrence RS, Savitz DA, Teutsch SM. A quantitative analysis of fish consumption and coronary heart disease mortality. *Am J Prev Med.* 2005 Nov; 29(4): 335-346. PMID: 16242600.	Does not answer question: examined relationship between fish intake and CHD.
Kono S. Secular trend of colon cancer incidence and mortality in relation to fat and meat intake in Japan. *Eur J Cancer Prev*. 2004 Apr; 13(2): 127-132. PMID: 15100579.	Study design is non-comparative, correlational study.
Kontogianni MD, Panagiotakos DB, Pitsavos C, Chrysohoou C, Stefanadis C. Relationship between meat intake and the development of acute coronary syndromes: the CARDIO2000 case-control study. *Eur J Clin Nutr.* 2008 Feb; 62(2): 171-177. Epub 2007 Mar 14. PMID: 17356558.	Does not include health outcome of interest in analyses.
Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation*. 2002 Nov 19; 106(21): 2, 747-2, 757. Erratum in: *Circulation.* 2003 Jan 28; 107 (3): 512. PMID: 12438303.	Expert opinion.
Larsson SC, Orsini N, Wolk A. Processed meat consumption and stomach cancer risk: A meta-analysis. *J Natl Cancer Inst.* 2006 Aug 2; 98(15): 1, 078-1, 087. PMID: 16882945.	Does not include colorectal, breast or prostate cancer in analyses.
Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: A meta-analysis of prospective studies. *Int J Cancer.* 2006 Dec 1; 119(11): 2, 657-2, 664. PMID: 16991129.	Study design is meta-analysis (colorectal cancer).

Lee JE, Spiegelman D, Hunter DJ, Albanes D, Bernstein L, van den Brandt PA, Buring JE, Cho E, English DR, Freudenheim JL, Giles GG, Graham S, Horn-Ross PL, Håkansson N, Leitzmann MF, Männistö S, McCullough ML, Miller AB, Parker AS, Rohan TE, Schatzkin A, Schouten LJ, Sweeney C, Willett WC, Wolk A, Zhang SM, Smith-Warner SA. Fat, protein, and meat consumption and renal cell cancer risk: A pooled analysis of 13 prospective studies. *J Natl Cancer Inst*. 2008 Dec 3; 100(23): 1, 695-1, 706. Epub 2008 Nov 25. PMID: 19033572; PMCID: PMC2727138.	Does not include colorectal, breast or prostate cancer in analyses.
Levitan EB, Wolk A, Mittleman MA. Fish consumption, marine omega-3 fatty acids, and incidence of heart failure: A population-based prospective study of middle-aged and elderly men. *Eur Heart J.* 2009 Jun; 30(12): 1, 495-1, 500. Epub 2009 Apr 21. PMID: 19383731; PMCID: PMC2695952.	Does not answer question: Examined relationship between fish intake and heart failure.
Lichtenstein AH, Jalbert SM, Adlercreutz H, Goldin BR, Rasmussen H, Schaefer EJ, Ausman LM. Lipoprotein response to diets high in soy or animal protein with and without isoflavones in moderately hypercholesterolemic subjects. *Arterioscler Thromb Vasc Biol.* 2002 Nov 1; 22(11): 1, 852-1, 858. PMID: 12426215.	Participants diagnosed with hypercholesterolemia.
Linseisen J, Kesse E, Slimani N; EPIC Working Group on Dietary Pattern, Subgroup Meat. Meat consumption in Europe: Results from the EPIC study.*IARC Sci Publ*. 2002; 156: 211-212. PMID: 12484168.	Does not include health outcomes in analyses.
Liu L, Ikeda K, Yamori Y; WHO-CARDIAC Study Group. Inverse relationship between urinary markers of animal protein intake and blood pressure in Chinese: results from the WHO Cardiovascular Diseases and Alimentary Comparison (CARDIAC) Study. *Int J Epidemiol*. 2002 Feb; 31(1): 227-233. PMID: 11914325.	Does not answer question: Examined the relationship between urinary excretion of 3-methylhistidine (as marker of animal protein intake) and blood pressure (BP).
Lucey AJ, Paschos GK, Cashman KD, Martínéz JA, Thorsdottir I, Kiely M. Influence of moderate energy restriction and seafood consumption on bone turnover in overweight young adults. *Am J Clin Nutr.* 2008 Apr; 87(4): 1, 045-1, 052. PMID: 18400730.	Does not include health outcome of interest in analyses.
Lüchtenborg M, Weijenberg MP, de Goeij AF, Wark PA, Brink M, Roemen GM, Lentjes MH, de Bruïne AP, Goldbohm RA, van 't Veer P, van den Brandt PA. Meat and fish consumption, APC gene mutations and hMLH1 expression in colon and rectal cancer: A prospective cohort study (The Netherlands). *Cancer Causes Control.* 2005 Nov; 16(9): 1, 041-1, 054. PMID: 16184469.	Results reported based on the same dataset as Brink, 2005.
Mamo JC, James AP, Soares MJ, Griffiths DG, Purcell K, Schwenke JL. A low-protein diet exacerbates postprandial chylomicron concentration in moderately dyslipidaemic subjects in comparison to a lean red meat protein-enriched diet. *Eur J Clin Nutr.* 2005 Oct; 59(10): 1, 142-1, 148. PMID: 16015257.	Does not answer question: Examined relationship between protein intake and postprandial response.

Männistö S, Dixon LB, Balder HF, Virtanen MJ, Krogh V, Khani BR, Berrino F, van den Brandt PA, Hartman AM, Pietinen P, Tan F, Wolk A, Goldbohm RA. Dietary patterns and breast cancer risk: Results from three cohort studies in the DIETSCAN project. *Cancer Causes Control.* 2005 Aug; 16(6): 725-733. PMID: 16049811.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Marques-Vidal P, Ravasco P, Ermelinda Camilo M. Foodstuffs and colorectal cancer risk: A review. *Clin Nutr.* 2006 Feb; 25(1): 14-36. Epub 2005 Nov 14. Review. PMID: 16290272.	Study design is systematic review (colorectal cancer).
Matheson EM, Mainous AG 3rd, Hill EG, Carnemolla MA. Shellfish consumption and risk of coronary heart disease. *J Am Diet Assoc.* 2009 Aug; 109(8): 1, 422-1, 426. PMID: 19631050.	Does not answer question: Examined relationship between shellfish intake and CHD.
Matthan NR, Jalbert SM, Ausman LM, Kuvin JT, Karas RH, Lichtenstein AH. Effect of soy protein from differently processed products on cardiovascular disease risk factors and vascular endothelial function in hypercholesterolemic subjects. *Am J Clin Nutr.* 2007 Apr; 85(4): 960-966. Erratum in: *Am J Clin Nutr.* 2007 Aug; 86(2): 525. PMID: 17413093.	Participants were hypercholesterolemic.
McCarty MF. The origins of western obesity: A role for animal protein? *Med Hypotheses.* 2000 Mar; 54(3): 488-494. PMID: 10783494.	Study design is narrative review.
McNaughton SA, Mishra GD, Stephen AM, Wadsworth ME. Dietary patterns throughout adult life are associated with body mass index, waist circumference, blood pressure, and red cell folate. *J Nutr.* 2007 Jan; 137(1): 99-105. PMID: 17182808.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Melanson K, Gootman J, Myrdal A, Kline G, Rippe JM. Weight loss and total lipid profile changes in overweight women consuming beef or chicken as the primary protein source. *Nutrition.* 2003 May; 19(5): 409-414. PMID: 12714091.	Dropout rate is higher than inclusion criteria.
Missmer SA, Smith-Warner SA, Spiegelman D, Yaun SS, Adami HO, Beeson WL, van den Brandt PA, Fraser GE, Freudenheim JL, Goldbohm RA, Graham S, Kushi LH, Miller AB, Potter JD, Rohan TE, Speizer FE, Toniolo P, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Hunter DJ. Meat and dairy food consumption and breast cancer: A pooled analysis of cohort studies. *Int J Epidemiol.* 2002 Feb; 31(1): 78-85. PMID: 11914299.	Study design is meta-analysis (breast cancer).
Möllsten AV, Dahlquist GG, Stattin EL, Rudberg S. Higher intakes of fish protein are related to a lower risk of microalbuminuria in young Swedish type 1 diabetic patients. *Diabetes Care.* 2001 May; 24(5): 805-810. PMID: 11347734.	Participants diagnosed with T2D.
Mortensen LS, Hartvigsen ML, Brader LJ, Astrup A, Schrezenmeir J, Holst JJ, Thomsen C, Hermansen K. Differential effects of protein quality on postprandial lipemia in response to a fat-rich meal in type 2 diabetes: comparison of whey, casein, gluten, and cod protein. *Am J Clin Nutr.* 2009 Jul; 90(1): 41-48. Epub 2009 May 20. PMID: 19458012.	Participants diagnosed with T2D.

Mozaffarian D, Psaty BM, Rimm EB, Lemaitre RN, Burke GL, Lyles MF, Lefkowitz D, Siscovick DS. Fish intake and risk of incident atrial fibrillation. *Circulation.* 2004 Jul 27; 110(4): 368-373. Epub 2004 Jul 19. PMID: 15262826; PMCID: PMC1201400.	Does not answer question: Examined relationship between fish intake and atrial fibrillation.
Nagata C, Shimizu H, Kametani M, Takeyama N, Ohnuma T, Matsushita S. Diet and colorectal adenoma in Japanese males and females. *Dis Colon Rectum.* 2001 Jan; 44(1): 105-111. PMID: 11805576.	Study design is case-control study (colorectal cancer).
Nenseter MS, Østerud B, Larsen T, Strøm E, Bergei C, Hewitt S, Holven KB, Hagve TA, Mjøs SA, Solvang M, Pettersen J, Opstvedt J, Ose L. Effect of Norwegian fish powder on risk factors for coronary heart disease among hypercholesterolemic individuals. *Nutr Metab Cardiovasc Dis.* 2000 Dec; 10(6): 323-330. PMID: 11302007.	Did not answer question: Examined relationship between fish powder and CHD.
Nettleton JA, Steffen LM, Loehr LR, Rosamond WD, Folsom AR. Incident heart failure is associated with lower whole-grain intake and greater high-fat dairy and egg intake in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Diet Assoc*. 2008 Nov; 108(11): 1, 881-1, 887. PMID: 18954578; PMCID: PMC2650810.	Does not answer question: Examined relationship between egg intake and heart failure.
Nkondjock A, Receveur O. Fish-seafood consumption, obesity, and risk of type 2 diabetes: an ecological study. *Diabetes Metab.* 2003 Dec; 29(6): 635-642. PMID: 14707894.	Does not answer question: Examined relationship between fish intake and T2D.
Norat T, Lukanova A, Ferrari P, Riboli E. Meat consumption and colorectal cancer risk: Dose-response meta-analysis of epidemiological studies. *Int J Cancer.* 2002 Mar 10; 98(2): 241-256. PMID: 11857415.	Study design is meta-analysis (colorectal cancer).
Norat T, Riboli E. Meat consumption and colorectal cancer: A review of epidemiologic evidence. *Nutr Rev.* 2001 Feb; 59(2): 37-47. Review. PMID: 11310774.	Study design is meta-analysis (colorectal cancer).
Norat T, Riboli E. Meat consumption and colorectal cancer: A review of epidemiologic evidence. *Nutr Rev.* 2001 Feb; 59(2): 37-47. Review. PMID: 11310774.	Study design is narrative review (colorectal cancer).
Nowson CA, Wattanapenpaiboon N, Pachett A. Low-sodium Dietary Approaches to Stop Hypertension-type diet including lean red meat lowers blood pressure in postmenopausal women. *Nutr Res.* 2009 Jan; 29(1): 8-18. PMID: 19185772.	Does not include animal protein products in analyses.
Olmedilla-Alonso B, Granado-Lorencio F, Herrero-Barbudo C, Blanco-Navarro I, Blázquez-García S, Pérez-Sacristán B. Consumption of restructured meat products with added walnuts has a cholesterol-lowering effect in subjects at high cardiovascular risk: a randomised, crossover, placebo-controlled study. *J Am Coll Nutr.* 2008 Apr; 27(2): 342-348. PMID: 18689569.	Does not answer question: Examined effect of restructured meat product on cholesterol.
Panagiotakos DB, Pitsavos C, Zampelas A, Chrysohoou C, Griffin BA, Stefanadis C, Toutouzas P. Fish consumption and the risk of developing acute coronary syndromes: The CARDIO2000 study. *Int J Cardiol.* 2005 Jul 20; 102(3): 403-409. PMID: 16004884.	Does not answer question: Examined relationship between fish intake and health outcomes.

Panagiotakos DB, Zeimbekis A, Boutziouka V, Economou M, Kourlaba G, Toutouzas P, Polychronopoulos E. Long-term fish intake is associated with better lipid profile, arterial blood pressure, and blood glucose levels in elderly people from Mediterranean islands (MEDIS epidemiological study). *Med Sci Monit.* 2007 Jul; 13(7): CR307-CR312. PMID: 17599024.	Does not answer question: Examined relationship between fish intake and health outcomes.
Pham TM, Fujino Y, Kubo T, Ide R, Tokui N, Mizoue T, Ogimoto I, Matsuda S, Yoshimura T. Fish intake and the risk of fatal prostate cancer: Findings from a cohort study in Japan. *Public Health Nutr.* 2009 May; 12(5): 609-613. Epub 2008 Jul 29. PMID: 18664313.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Pieniak Z, Verbeke W, Perez-Cueto F, Brunsø K, De Henauw S. Fish consumption and its motives in households with versus without self-reported medical history of CVD: A consumer survey from five European countries. *BMC Public Health.* 2008 Sep 10; 8: 306. PMID: 18783593; PMCID: PMC2556335.	Does not include health outcomes in analyses.
Processed meat consumption linked to type 2 diabetes. *Nephrol News Issues.* 2002 Apr; 16(5): 68-69. PMID: 11962157.	News article.
Ramel A, Parra D, Martinéz JA, Kiely M, Thorsdottir I. Effects of seafood consumption and weight loss on fasting leptin and ghrelin concentrations in overweight and obese European young adults. *Eur J Nutr.* 2009 Mar; 48(2): 107-114. Epub 2009 Jan 13. PMID: 19142567.	Does not answer question: Examined relationship between seafood and leptin and ghrelin concentrations.
Rosell M, Appleby P, Spencer E, Key T. Weight gain over 5 years in 21, 966 meat-eating, fish-eating, vegetarian, and vegan men and women in EPIC-Oxford. *Int J Obes (Lond).* 2006 Sep; 30(9): 1, 389-1, 396. Epub 2006 Mar 14. PMID: 16534521.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Sandhu MS, White IR, McPherson K. Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: A meta-analytical approach. *Cancer Epidemiol Biomarkers Prev.* 2001 May; 10(5): 439-446. PMID: 11352852.	Study design is systematic review/meta-analysis (colorectal cancer).
Santarelli RL, Pierre F, Corpet DE. Processed meat and colorectal cancer: A review of epidemiologic and experimental evidence. *Nutr Cancer.* 2008; 60(2): 131-144. Review. PMID: 18444144; PMCID: PMC2661797.	Study design is narrative review.
Satia JA, Tseng M, Galanko JA, Martin C, Sandler RS. Dietary patterns and colon cancer risk in Whites and African Americans in the North Carolina Colon Cancer Study. *Nutr Cancer.* 2009; 61(2): 179-193. PMID: 19235034.	Study design is case-control study (colon cancer).
Schulz M, Hoffmann K, Weikert C, Nöthlings U, Schulze MB, Boeing H. Identification of a dietary pattern characterized by high-fat food choices associated with increased risk of breast cancer: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Br J Nutr.* 2008 Nov; 100(5): 942-946. PMID: 18377685.	Does not answer question: Examines relationship between high fat foods and breast cancer.

Seierstad SL, Seljeflot I, Johansen O, Hansen R, Haugen M, Rosenlund G, Frøyland L, Arnesen H. Dietary intake of differently fed salmon: The influence on markers of human atherosclerosis. *Eur J Clin Invest.* 2005 Jan; 35(1): 52-59. PMID: 15638820.	Participants diagnosed with T2D.
Shiell AW, Campbell-Brown M, Haselden S, Robinson S, Godfrey KM, Barker DJ. High-meat, low-carbohydrate diet in pregnancy: Relation to adult blood pressure in the offspring. *Hypertension*. 2001 Dec 1; 38(6): 1, 282-1, 288. PMID: 11751704.	Does not answer question: Examines relationship between dietary intake during pregnancy and health of adult offspring.
Sieri S, Krogh V, Muti P, Micheli A, Pala V, Crosignani P, Berrino F. Fat and protein intake and subsequent breast cancer risk in postmenopausal women. *Nutr Cancer.* 2002; 42(1): 10-17. PMID: 12235640.	Study design is case-control study (breast cancer).
Skjelbred CF, Saebø M, Hjartåker A, Grotmol T, Hansteen IL, Tveit KM, Hoff G, Kure EH. Meat, vegetables and genetic polymorphisms and the risk of colorectal carcinomas and adenomas. *BMC Cancer*. 2007 Dec 19; 7: 228. PMID: 18093316; PMCID: PMC2228310.	Study design is case-control study (colorectal cancer).
Smith DR, Wood R, Tseng S, Smith SB. Increased beef consumption increases apolipoprotein A-I but not serum cholesterol of mildly hypercholesterolemic men with different levels of habitual beef intake. *Exp Biol Med (Maywood).* 2002 Apr; 227(4): 266-275. PMID: 11910049.	Participants diagnosed with mild hypercholesterolemia.
SoRelle R. Fish and long-chain omega-3 fatty acids could be lifesavers for diabetic women. *Circulation.* 2003 Apr 22; 107(15): e9, 033-9, 035. PMID: 12707254.	Participants were diagnosed with diabetes.
Sørensen M, Autrup H, Olsen A, Tjønneland A, Overvad K, Raaschou-Nielsen O. Prospective study of NAT1 and NAT2 polymorphisms, tobacco smoking and meat consumption and risk of colorectal cancer. *Cancer Lett.* 2008 Aug 8; 266(2): 186-193. Epub 2008 Mar 26. PMID: 18372103.	Study design is case-control study (colorectal cancer).
Spencer EA, Appleby PN, Davey GK, Key TJ. Diet and body mass index in 38000 EPIC-Oxford meat-eaters, fish-eaters, vegetarians and vegans. *Int J Obes Relat Metab Disord.* 2003 Jun; 27(6): 728-734. PMID: 12833118.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Stewart JW, Kaplan ML, Beitz DC. Pork with a high content of polyunsaturated fatty acids lowers LDL cholesterol in women. *Am J Clin Nutr.* 2001 Aug; 74(2): 179-187. PMID: 11470718.	Intervention consisted of modified pork high in PUFAs.
Tanskanen A, Hibbeln JR, Tuomilehto J, Uutela A, Haukkala A, Viinamäki H, Lehtonen J, Vartiainen E. Fish consumption and depressive symptoms in the general population in Finland. *Psychiatr Serv.* 2001 Apr; 52(4): 529-531. PMID: 11274502.	Does not include health outcome of interest in analyses.
Tapola NS, Lyyra ML, Karvonen HM, Uusitupa MI, Sarkkinen ES. The effect of meat products enriched with plant sterols and minerals on serum lipids and blood pressure. *Int J Food Sci Nutr.* 2004 Aug; 55(5): 389-397. PMID: 15545047.	Intervention consisted of meat products enriched with plant sterols; participants diagnosed with hypercholesterolemia.

Tappel A. Heme of consumed red meat can act as a catalyst of oxidative damage and could initiate colon, breast and prostate cancers, heart disease and other diseases. *Med Hypotheses*. 2007; 68(3): 562-564. Epub 2006 Oct 11. PMID: 17045417.	Study design is narrative review.
Teixeira Rde C, Molina Mdel C, Zandonade E, Mill JG. Cardiovascular risk in vegetarians and omnivores: A comparative study. *Arq Bras Cardiol.* 2007 Oct; 89(4): 237-244. English, Portuguese. PMID: 17992380.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Terry P, Rohan TE, Wolk A, Maehle-Schmidt M, Magnusson C. Fish consumption and breast cancer risk. *Nutr Cancer.* 2002; 44(1): 1-6. PMID: 12672635.	Study design is case-control study (breast cancer).
Thorsdottir I, Birgisdottir B, Kiely M, Martinez J, Bandarra N. Fish consumption among young overweight European adults and compliance to varying seafood content in four weight loss intervention diets. *Public Health Nutr.* 2009 May; 12(5): 592-598. Epub 2008 Jun 19. PMID: 18561865.	Does not answer question: Examined compliance to eating varying types of seafood in weight loss intervention diets.
Thorsdottir I, Tomasson H, Gunnarsdottir I, Gisladottir E, Kiely M, Parra MD, Bandarra NM, Schaafsma G, Martinéz JA. Randomized trial of weight-loss-diets for young adults varying in fish and fish oil content. *Int J Obes* (Lond). 2007 Oct; 31(10): 1, 560-1, 566. Epub 2007 May 15. PMID: 17502874.	Does not answer question: Examined fish intake and weight loss.
Tiemersma EW, Kampman E, Bueno de Mesquita HB, Bunschoten A, van Schothorst EM, Kok FJ, Kromhout D. Meat consumption, cigarette smoking, and genetic susceptibility in the etiology of colorectal cancer: results from a Dutch prospective study. *Cancer Causes Control.* 2002 May; 13(4): 383-393. PMID: 12074508.	Study design is case-control study (colorectal cancer).
Timonen M, Horrobin D, Jokelainen J, Laitinen J, Herva A, Räsänen P. Fish consumption and depression: The Northern Finland 1966 birth cohort study. *J Affect Disord.* 2004 Nov 1; 82(3): 447-452. PMID: 15555697.	Does not include health outcome of interest in analyses.
Tzoulaki I, Brown IJ, Chan Q, Van Horn L, Ueshima H, Zhao L, Stamler J, Elliott P; International Collaborative Research Group on Macro-/Micronutrients and Blood Pressure. Relation of iron and red meat intake to blood pressure: cross sectional epidemiological study. *BMJ.* 2008 Jul 15; 337: a258. doi: 10.1136/bmj.a258. PMID: 18632704; PMCID: PMC2658466.	Study design is cross-sectional epidemiological study.
Umesawa M, Sato S, Imano H, Kitamura A, Shimamoto T, Yamagishi K, Tanigawa T, Iso H. Relations between protein intake and blood pressure in Japanese men and women: the Circulatory Risk in Communities Study (CIRCS). *Am J Clin Nutr.* 2009 Aug; 90(2): 377-384. Epub 2009 Jun 10. PMID: 19515740.	Study design is cross-sectional.
Varraso R, Jiang R, Barr RG, Willett WC, Camargo CA Jr. Prospective study of cured meats consumption and risk of chronic obstructive pulmonary disease in men. *Am J Epidemiol*. 2007 Dec 15; 166(12): 1, 438-1, 445. Epub 2007 Sep 4. PMID: 17785711; PMCID: PMC2573990.	Does not include health outcome of interest in analyses.

Virtanen JK, Mozaffarian D, Chiuve SE, Rimm EB. Fish consumption and risk of major chronic disease in men. *Am J Clin Nutr.* 2008 Dec; 88(6): 1, 618-1, 625. PubMed PMID: 19064523; PMCID: PMC2613199.	Does not answer question: Examined relationship between fish intake and chronic disease.
Wakai K, Tamakoshi K, Date C, Fukui M, Suzuki S, Lin Y, Niwa Y, Nishio K, Yatsuya H, Kondo T, Tokudome S, Yamamoto A, Toyoshima H, Tamakoshi A; JACC Study Group. Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. *Cancer Sci.* 2005 Sep; 96(9): 590-599. PMID: 16128744.	Does not answer question: Examined relationship between breast cancer and fat intake, not animal protein.
Weggemans RM, Zock PL, Katan MB. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: A meta-analysis. *Am J Clin Nutr.* 2001 May; 73(5): 885-891. PMID: 11333841.	Does not examine relationship between intake of animal protein product and health outcome.
Weghuber D, Widhalm K. Effect of 3-month treatment of children and adolescents with familial and polygenic hypercholesterolaemia with a soya-substituted diet. *Br J Nutr.* 2008 Feb; 99(2): 281-286. Epub 2007 Aug 13. PMID: 17697400.	Participants diagnosed with hypercholesterolemia.
Welch AA, Bingham SA, Ive J, Friesen MD, Wareham NJ, Riboli E, Khaw KT. Dietary fish intake and plasma phospholipid n-3 polyunsaturated fatty acid concentrations in men and women in the European Prospective Investigation into Cancer-Norfolk United Kingdom cohort. *Am J Clin Nutr.* 2006 Dec; 84(6): 1, 330-1, 339. PMID: 17158413.	Does not include health outcomes in analyses; fish is the independent variable.
Wu K, Hu FB, Willett WC, Giovannucci E. Dietary patterns and risk of prostate cancer in U.S. men. *Cancer Epidemiol Biomarkers Prev.* 2006 Jan; 15(1): 167-171. PMID: 16434606.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Yoon H, Benamouzig R, Little J, François-Collange M, Tomé D. Systematic review of epidemiological studies on meat, dairy products and egg consumption and risk of colorectal adenomas. *Eur J Cancer Prev*. 2000 Jun; 9(3): 151-164. PMID: 10954254.	Study design is systematic review (colorectal cancer).
Yuan JM, Ross RK, Gao YT, Yu MC. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *Am J Epidemiol.* 2001 Nov 1; 154(9): 809-816. PMID: 11682363.	Does not answer question: Examined relationship between fish intake and myocardial infarction.

CHAPTER 4. ANIMAL PROTEIN PRODUCTS – TYPE 2 DIABETES

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF ANIMAL PROTEIN PRODUCTS AND TYPE 2 DIABETES?

Conclusion statement

Limited inconsistent evidence from prospective cohort studies suggests that intake of animal protein products, mainly processed meat, may have a link to type 2 diabetes.

Grade

Limited

Evidence summary overview

This review included seven articles (Djousse, 2009; Fung, 2004; Halton, 2008; Schulze, 2003; Song, 2004; van Dam, 2002; Vang, 2008) published since 2000 representing prospective cohorts from the US. In the three studies examining total animal protein intake, two reported a positive association with type 2 diabetes (T2D) (Song, 2004; Vang, 2008) and one reported no association (Halton, 2008). All five studies that reported on the relationship between the intake of processed meats and T2D reported a positive association (Fung, 2004; Schulze, 2003; Song, 2004; van Dam, 2002; Vang, 2008). Inconsistent findings were reported related to the intake of red meat and poultry. Some of the reported risk found in these studies may be attributed to obesity or weight gain, but controlling for this supported meat intake as an important risk factor for diabetes. Other dietary factors, such cereal fiber, fat and total calories, also are strong in this relationship and the association between T2D and animal protein is attenuated when there is adjustment for these factors.

Evidence summary paragraphs

Djousse et al, 2009 (positive quality) prospectively examined the association between egg consumption and incident T2D among men and women in the US. Participants were 20,703 men (age 53.5±9.4 years) from the Physician's Health Study (PHS) I and 36,295 women (age 54.5±7 years) from the Women's Health Study (WHS). Type 2 diabetes was ascertained by self-report on annual follow-up questionnaires for both men and women. Among participants in the WHS, self-reporting was validated using telephone interviews, supplemental questionnaires or review of medical records. Information on egg consumption in the past year from the PHS and WHS was self-reported. For men, the information was obtained using a semi-quantitative food-frequency questionnaire (FFQ) at baseline and at 24, 48, 72, 96 and 120 months. For women, the information was self-reported using a 131-item validated FFQ at baseline. During mean follow-up of 20.0 years in men and 11.7 years in women, 1,921 men and 2,112 women developed T2D. Compared with no egg consumption, multivariable adjusted hazard ratios (HRs) for T2D were 1.09 (95% CI: 0.87, 1.37), 1.09 (0.88, 1.34), 1.18 (0.95, 1.45), 1.46 (1.14, 1.86) and 1.58 (1.25, 2.01) for consumption of less than one, one, two to four, five to six and at least seven eggs per week, respectively, in men (P for trend<0.0001). Corresponding multivariable HRs for women were 1.06 (95% CI: 0.92, 1.22), 0.97 (0.83, 1.12), 1.19 (1.03, 1.38), 1.18 (0.88, 1.58) and 1.77 (1.28, 2.43), respectively (P for trend<0.0001). The authors concluded that daily consumption of at

least one egg is associated with an increased risk of T2D in men and women, independently of traditional risk factors for T2D.

Fung et al, 2004 (positive quality) prospectively examined the association between major dietary patterns and the risk of T2D among women in the US. Participants were 69,554 women (age 38 to 63 years) from the Nurses' Health Study cohort. Type 2 diabetes was ascertained by self-report on biennial questionnaires. Women reporting a diagnosis of diabetes were sent supplementary questionnaires asking about symptoms, diagnostic tests and treatment to confirm the diagnosis. Dietary intake information was collected by FFQs designed to assess average food intake over the previous year. Information from the FFQs administered in 1984, 1986, 1990 and 1994 were used in this analysis. Factor analysis identified two major dietary patterns: "Prudent" and "Western." During 14 years of follow-up, 2,699 incident cases of T2D were identified. After adjusting for potential confounders, the relative risk (RR) for diabetes was 1.49 (95% CI: 1.26, 1.76, P for trend<0.001) when comparing the highest to lowest quintiles of the Western pattern. Positive associations were observed between T2D and red meat and other processed meats. Intake of total processed meats showed the strongest positive association, with an RR of 1.60 (95% CI: 1.39, 1.83; P for trend, <0.001) between the top and bottom quintile of intake. When meat products were analyzed as a continuous variable, the RR for diabetes for every one-serving increase in intake was 1.26 (95% CI: 1.21, 1.42) for red meat, 1.38 (95% CI: 1.23, 1.56) for total processed meats, 1.73 (95% CI: 1.39, 2.16) for bacon, 1.49 (95% CI: 1.04, 2.11) for hot dogs and 1.43 (95% CI: 1.22, 1.69) for processed meats. The authors concluded that the Western dietary pattern, especially a diet higher in processed meats, may increase the risk of T2D in women.

Halton et al, 2008 (positive quality) prospectively examined the association between a low-carbohydrate diet and the risk of T2D among females in the US. Additional analyses examined the relationship between macronutrient intake, including animal protein and T2D. Participants were 85,059 women (age 30 to 55 years, 98% white) from the Nurses' Health Study cohort. Type 2 diabetes was ascertained by self-report on biennial questionnaires. If a participant reported a diagnosis of diabetes, a supplementary questionnaire was mailed regarding symptoms, diagnostic testing and treatment to confirm the diagnosis. Diet over the previous year was assessed by means of a semi-quantitative FFQ in 1980, 1984, 1986, 1990, 1994 and 1998. During 20 years of follow-up, 4,670 cases of T2D were documented. Animal protein intake was positively associated with T2D risk, with an age adjusted RR of 1.74 (95% CI: 1.51, 2.01; P for trend<0.0001) between extreme deciles. However, this relationship was attenuated when further adjusted for non-dietary factors plus cereal fiber, saturated fat, polyunsaturated fat, monounsaturated fat, trans fat, vegetable protein and total calories (multivariate RR=1.01; 95% CI: 0.87, 1.17; P for trend=0.55). The authors concluded that animal protein intakes were not associated with risk of T2D in women.

Schulze et al, 2003 (positive quality) prospectively investigated the association between processed and other meat intake and incidence of T2D in a large cohort of young and middle-aged women in the US. Participants were 91,246 women (age 24 to 44 years) from the Nurses' Health Study II. Type 2 diabetes was ascertained by self-report on biennial questionnaires. Women reporting a new diagnosis of diabetes were sent supplementary questionnaires asking about diagnosis, treatment and symptoms

to confirm diagnosis. Food consumption over the previous year was assessed using a 133-item semi-quantitative FFQ at baseline (1991). During eight years of follow-up, 741 incident cases of T2D were confirmed. The multivariate RRs across frequencies of processed meat consumption (less than one per week, one per week, two to four per week and at least five per week) were 1.00, 1.16 (95% CI: 0.97, 1.39), 1.44 (95% CI: 1.14, 1.82) and 1.91 (95% CI: 1.42-2.57) (P for trend<0.001). Further adjustment for intakes of magnesium, cereal fiber, glycemic index and caffeine or for a Western dietary pattern did not appreciably change the results and associations remained strong after further adjustment for fatty acid and cholesterol intake. The multivariate RRs across categories of total red meat consumption (less than one per week, one per week, two to four per week and at least five per week) were 1.00, 1.19 (95% CI: 0.79, 1.80), 1.38 (95% CI: 0.91, 2.09) and 1.58 (95% CI: 1.03, 2.42) (P for trend=0.003). Total red meat intake was associated with only a modest and non-significant (NS) increase of diabetes risk (RR for extreme categories: 1.44; 95% CI: 0.92, 2.24) in multivariate analysis after additional adjustment for magnesium, glycemic index, cereal fiber and caffeine. Frequent consumption of bacon, hot dogs, sausage and hamburgers was each associated with an increased risk of diabetes. More frequent poultry intake was associated with a moderately decreased risk of diabetes. The multivariate-adjusted RRs across categories of poultry intake (no more than one per week, two to four per week and at least five per week) were 1.00, 0.87 (95% CI: 0.74, 1.02) and 0.78 (95% CI: 0.62, 0.98) (P for trend=0.017). Further adjustment for nutrient intake or the “Prudent” dietary pattern did not materially change this result. The authors concluded that diets high in processed meats could increase the risk for developing T2D in young and middle-aged women.

Song et al, 2004 (positive quality) prospectively assessed the associations between red meat and processed meat consumption and incidence of T2D in US women. Participants were 37,309 women (age ≥45 years) from the Women’s Health Study. Type 2 diabetes was ascertained by self-report on annual questionnaires with confirmation in a sub-set of the sample. Dietary intake was assessed with a 131-item semi-quantitative FFQ at baseline (1993). Over an average of 8.8 years, 1,558 incident cases of T2D were identified. Comparing women in extreme quintiles, the multivariate-adjusted RR of T2D were 1.28 for red meat (95% CI: 1.07, 1.53; P for trend<0.001) and 1.23 for processed meat intake (95% CI: 1.05, 1.45; P for trend=0.001). Furthermore, the significantly increased diabetes risk appeared to be most pronounced for frequent consumption of total processed meat (RR=1.43; 95% CI: 1.17, 1.75 for at least five per week vs. less than one per month; P for trend<0.001) and two major sub-types, which were bacon (RR=1.21; 95% CI: 1.06, 1.39 for at least two per week vs. less than one per week; P for trend=0.004) and hot dogs (RR=1.28; 95% CI: 1.09, 1.50 for at least two per week vs. less than one per week; P for trend=0.003). These results remained significant after further adjustment for intakes of dietary fiber, magnesium, glycemic load and total fat. Multivariate adjusted RR comparing extreme quintiles of animal protein intake was 1.44 (95% CI: 1.16, 1.78; P for trend=0.001). The authors concluded that higher consumption of total red meat, especially various processed meats, may increase risk of developing T2D in women.

van Dam et al, 2002 (positive quality) prospectively examined the association between risk of T2D and trans-fat, specific polyunsaturated fats and meats in US men. Participants were 42,504 men (age 40-75 years) from the Health Professionals Follow-

Up Study. Diabetes was assessed by questionnaire every two years from baseline (1986) through 1998. A supplementary questionnaire on symptoms, diagnostic tests and medication was mailed to all men to confirm diagnosis. Diet was assessed by a semi-quantitative FFQ in 1986 and again in 1990 and 1994 to update dietary information. During 12 years of follow-up, 1,321 incident cases of T2D were identified. Frequent consumption of processed meat was associated with a higher risk for T2D (RR=1.46; 95% CI: 1.14, 1.86 for at least five per week vs. less than one per month; P for trend<0.0001). Consumption of unprocessed red meat (RR=1.05; 95% CI: 0.85, 1.30 for highest vs. lowest quintile) and of poultry (RR=1.12; 95% CI: 0.95, 1.32) was not substantially associated with risk for T2D. Of the eight questionnaire items on meat and poultry consumption, only consumption of the three processed meat items: Bacon (RR=1.33; 95% CI: 1.11, 1.58; P for trend=0.0002), hot dogs (RR=1.26; 95% CI: 1.00, 1.60; P for trend=0.03) and other processed meats (RR=1.18; 95% CI: 0.99, 1.41; P for trend=0.01) plus hamburgers (RR=1.27; 95% CI: 0.99, 1.62) were appreciably associated with diabetes risk. Consumption of beef, lamb or pork as a main dish or a mixed dish; or chicken or turkey with or without skin was not substantially associated with risk of T2D. The authors concluded that frequent consumption of processed meats may increase risk of T2D in men.

Vang et al, 2008 (positive quality) prospectively examined the relationship between total animal product consumption, specific animal product consumption (red meat, poultry, fish, processed meats, eggs, milk, cheese) and diabetes occurrence. Participants were 8,401 adults (age 45 to 88 years) from the Adventist Mortality Study and the Adventist Health Study in the US. Participants completed questionnaires in 1960 and 1976. Incident diabetes cases were based on disease history data from the 1976 questionnaire. Dietary intake was assessed in 1960 and 1976 with questionnaires containing food frequency questions. Specific animal product consumption included: Red meat/poultry, eggs and processed meats (salted fish and frankfurters). During the 17-year follow-up, 543 incident diabetes cases were identified. Participants who were weekly consumers of all meats (red meat, poultry, fish) were 29% more likely relative to zero meat intake to develop diabetes (OR=1.29; 95% CI: 1.08, 1.55). An increase in risk for weekly intake of red meat and poultry (OR=1.27; 95% CI: 1.06, 1.53), but not for weekly intake of fish (OR=1.12; 95% CI: 0.88, 1.44) was observed. Subjects who consumed any processed meats (salted fish and frankfurters) were 38% more likely to develop diabetes than those who did not consume any processed meats (OR=1.38; 95% CI: 1.05, 1.82). Long-term adherence (over the 17-year interval) to a diet that included at least weekly meat intake was associated with a 74% increase in odds of diabetes relative to long-term adherence to a vegetarian diet (zero meat intake) (OR=1.74; 95% CI: 1.36, 2.22). Further analyses indicated that some of this risk may be attributable to obesity or weight gain; both of which were strong risk factors in this cohort. Even after control for weight and weight change, weekly meat intake remained an important risk factor (OR=1.38; 95% CI 1.06-1.08) for diabetes. The authors concluded that meat intake, particularly processed meats, may be a dietary risk factor for diabetes.

Overview table

Author, Year, Study Design, Class, Rating	Study Name/Location	Total Meat Association (Pos, Neg, None)	Red Meat Association (Pos, Neg, None)	Processed Meat Association (Pos, Neg, None)	Poultry Association (Pos, Neg, None)
Djousse et al 2009 Study Design: Prospective Cohort study Class: B Positive quality	Physician's Health Study I and Women's Health Study. Location: US.	Not examined.	Not examined.	Not examined.	Eggs: (+) for men and women.
Fung et al 2004 Study Design: Prospective cohort study Class: B Positive quality	Nurses' Health Study. Location: US.	Not examined.	Red meat: (+).	Total: (+) Bacon; hot dogs; other processed meats: (+).	Not examined.
Halton TL, Liu S et al, 2008 Study Design: Prospective cohort Class: B Positive quality	Nurses' Health Study. Location: US.	Animal protein: Ø.	Not examined.	Not examined.	Not examined.

Schulze et al 2003 Study Design: Prospective cohort study Class: B Positive quality	Nurses' Health Study II. Location: US.	Not examined.	Total: Ø. Hamburgers: (+).	Total: (+). Bacon; hot dogs; sausage: (+).	Poultry: (-).
Song Y, Manson JE et al, 2004 Study Design: Prospective cohort study Class: B Positive quality	Women's Health Study. Location: US.	Animal protein: (+).	Total: (+).	Total: (+). Bacon; hot dogs: (+).	Not examined.
van Dam RM, Willett WC et al, 2002 Study Design: Prospective cohort Class: B Positive quality	Health Professionals Follow-Up Study. Location: US.	Not examined.	Unprocessed red meat: Ø. Hamburgers: (+). Beef, pork, or lamb as main or mixed dish: Ø.	Total: (+). Bacon; hot dogs; other processed meats: (+).	Poultry: Ø.

Vang A, Singh PN et al, 2008 Study Design: Prospective cohort Class: B Positive quality	Adventist Morality and Adventist Health Studies. Location: US.	Total (red meat, poultry, and fish): (+)	Red meat and poultry: (+).	"Salted fish and frankfurters": (+).	Red meat and poultry: (+).

Search plan and results

Inclusion criteria

- January 2000 to September 2009
- Prospective cohort studies on colorectal, breast and prostate cancers
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children two to 18 years; Adults 19 years and older
- *Populations:* Healthy, those with elevated chronic disease risk.

Exclusion criteria

- With the exception of the body weight outcome, cross-sectional studies were excluded from the review
- Systematic reviews and meta-analyses on colorectal, breast and prostate cancers. Only original research studies with prospective cohort design were included in the review
- Studies specifically related to seafood or milk product intake (considered as separate questions)
- Studies that reported on animal protein intake as a component of a dietary pattern and not as an individual variable
- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: (Animal protein* OR meat[mh] OR "Egg Proteins, Dietary"[mh] OR "Fish Proteins"[mh]) AND ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "overweight"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mh:NoExp] OR “heart diseases”[mh] OR "Coronary Disease"[Mesh] OR “blood pressure”[mh] OR “chronic disease”[mh] OR obesity[mh] OR "Body Weights and Measures"[mh] OR "Colorectal Neoplasms"[mesh])
  (Animal protein* OR meat[mh] OR "Egg Proteins, Dietary"[mh] OR "Fish Proteins"[mh] OR seafood[majr] OR crustacea[majr]) AND (systematic[sb] OR Meta-Analysis[ptyp] OR "Cohort Studies"[Mesh]) AND ("Prostatic Neoplasms"[Mesh] OR "Breast Neoplasms"[Mesh])
  eggs [mh] AND ("Diabetes Mellitus, Type 2"[majr] OR "metabolic syndrome X"[majr] OR "overweight"[majr] OR "hypertension"[majr] OR "dyslipidemias"[majr] OR "cardiovascular diseases"[majr:NoExp] OR “heart diseases”[majr] OR "Coronary Disease"[Mesh] OR “blood pressure”[majr] OR “chronic disease”[majr] OR obesity[majr] OR "Body Weights and Measures"[majr])
  (Note: "Cohort Studies"[Mesh]) includes prospective studies)

Date searched: 09/01/2009; update 09/18/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 771
- Total articles identified to review from electronic databases: 166
- Articles identified via handsearch or other means: 2
- Number of Primary Articles Identified: 47
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 47
- Number of Articles Reviewed but Excluded: 121

Included articles (References)

What is the relationship between the intake of animal protein products and cardiovascular disease?

1. Djoussé L, Gaziano JM. Egg consumption in relation to cardiovascular disease and mortality: the Physicians' Health Study.*Am J Clin Nutr.* 2008 Apr; 87(4): 964-969. PMID: 18400720; PMCID: PMC2386667.
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What is the relationship between the intake of animal protein products and blood pressure?

Primary Citations

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What is the relationship between the intake of animal protein products and body weight?

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What is the relationship between the intake of animal protein products and colorectal cancer?

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Hayakawa N, Suzuki K, Hashimoto S, Ito Y, Tamakoshi A; Japan Collaborative Cohort Study Group. Diet and colorectal cancer mortality: Results from the Japan Collaborative Cohort Study. *Nutr Cancer.* 2004; 50(1): 23-32. PMID: 15572294.

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What is the relationship between the intake of animal protein products and prostate cancer?

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intake and prostate cancer risk: The multiethnic cohort study. *Int J Cancer.* 2007 Sep 15; 121(6): 1, 339-1, 345. PMID: 17487838.
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What is the relationship between the intake of animal protein products and breast cancer?

1. Cho E, Chen WY, Hunter DJ, Stampfer MJ, Colditz GA, Hankinson SE, Willett WC. Red meat intake and risk of breast cancer among premenopausal women. *Arch Intern Med.* 2006 Nov 13; 166(20): 2, 253-2, 259. PMID: 17101944.
2. Ferrucci LM, Cross AJ, Graubard BI, Brinton LA, McCarty CA, Ziegler RG, Ma X, Mayne ST, Sinha R. Intake of meat, meat mutagens, and iron and the risk of breast cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Br J Cancer.* 2009 Jul 7; 101(1): 178-184. Epub 2009 Jun 9. PMID: 19513076.
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4. Kabat GC, Cross AJ, Park Y, Schatzkin A, Hollenbeck AR, Rohan TE, Sinha R. Meat intake and meat preparation in relation to risk of postmenopausal breast cancer in the NIH-AARP diet and health study. *Int J Cancer.* 2009 May 15; 124(10): 2, 430-2, 435. PMID: 19165862.
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7. Wang L, Manson JE, Buring JE, Sesso HD. Meat intake and the risk of hypertension in middle-aged and older women. *J Hypertens.* 2008 Feb; 26(2): 215-222. PMID: 18192834.

Excluded articles

Article	Reason for Exclusion
Alexander DD, Cushing CA, Lowe KA, Sceurman B, Roberts MA. Meta-analysis of animal fat or animal protein intake and colorectal cancer. *Am J Clin Nutr.* 2009 May; 89(5): 1, 402-1, 409. Epub 2009 Mar 4. PMID: 19261724.	Study design is meta-analysis (colorectal cancer).

Appleby PN, Davey GK, Key TJ. Hypertension and blood pressure among meat eaters, fish eaters, vegetarians and vegans in EPIC-Oxford. *Public Health Nutr.* 2002 Oct; 5(5): 645-654. PMID: 12372158.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Augustsson K, Michaud DS, Rimm EB, Leitzmann MF, Stampfer MJ, Willett WC, Giovannucci E. A prospective study of intake of fish and marine fatty acids and prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2003 Jan; 12(1): 64-67. PMID: 12540506.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Azadbakht L, Esmaillzadeh A. Red meat intake is associated with metabolic syndrome and the plasma C-reactive protein concentration in women. *J Nutr.* 2009 Feb; 139(2): 335-339. Epub 2008 Dec 11. PMID: 19074209.	Does not answer question: Examined relationship between red meat intake and metabolic syndrome.
Balder HF, Vogel J, Jansen MC, Weijenberg MP, van den Brandt PA, Westenbrink S, van der Meer R, Goldbohm RA. Heme and chlorophyll intake and risk of colorectal cancer in the Netherlands cohort study. *Cancer Epidemiol Biomarkers Prev.* 2006 Apr; 15(4): 717-725. PMID: 16614114.	Does not answer question: Examined relationship between heme and chlorophyll intake and colorectal cancer.
Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: A systematic literature review and meta-analysis. *Cancer Causes Control.* 2007 Nov; 18(9): 967-988. Epub 2007 Jul 19. Review. PMID: 17638104; PMCID: PMC2592095.	Does not include colorectal, breast, or prostate cancer in analyses.
Barraj L, Tran N, Mink P. A comparison of egg consumption with other modifiable coronary heart disease lifestyle risk factors: a relative risk apportionment study. *Risk Anal*. 2009 Mar; 29(3): 401-415. Epub 2008 Nov 4. PMID: 19000074.	Does not answer question: Used risk apportionment approach to estimate contribution of egg intake to coronary heart disease (CHD) risk at the population level.
Benassi-Evans B, Clifton PM, Noakes M, Keogh JB, Fenech M. High protein-high red meat versus high carbohydrate weight loss diets do not differ in effect on genome stability and cell death in lymphocytes of overweight men. *Mutagenesis.* 2009 May; 24(3): 271-277. Epub 2009 Mar 5. PMID: 19264840.	Does not include animal protein product intake in analyses.
Brink M, Weijenberg MP, de Goeij AF, Roemen GM, Lentjes MH, de Bruïne AP, Goldbohm RA, van den Brandt PA. Meat consumption and K-ras mutations in sporadic colon and rectal cancer in The Netherlands Cohort Study. *Br J Cancer.* 2005 Apr 11; 92(7): 1, 310-1, 320. PMID: 15812479.	Study design is case-cohort.
Cade JE, Burley VJ, Greenwood DC; UK Women's Cohort Study Steering Group. The UK Women's Cohort Study: Comparison of vegetarians, fish-eaters and meat-eaters. *Public Health Nutr.* 2004 Oct; 7(7): 871-878. PMID: 15482612.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.

Chan AT, Tranah GJ, Giovannucci EL, Willett WC, Hunter DJ, Fuchs CS. Prospective study of N-acetyltransferase-2 genotypes, meat intake, smoking and risk of colorectal cancer. *Int J Cancer.* 2005 Jul 1; 115(4): 648-652. PMID: 15700302.	Study design is case-control study (colorectal cancer).
Chavarro JE, Stampfer MJ, Hall MN, Sesso HD, Ma J. A 22-y prospective study of fish intake in relation to prostate cancer incidence and mortality. *Am J Clin Nutr.* 2008 Nov; 88(5): 1, 297-1, 303. PMID: 18996866.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Chrysohoou C, Panagiotakos DB, Pitsavos C, Skoumas J, Krinos X, Chloptsios Y, Nikolaou V, Stefanadis C. Long-term fish consumption is associated with protection against arrhythmia in healthy persons in a Mediterranean region: The ATTICA study. *Am J Clin Nutr.* 2007 May; 85(5): 1, 385-1, 391. PMID: 17490977.	Does not answer question: Examined relationship between fish intake and arrhythmia.
Cotterchio M, Boucher BA, Manno M, Gallinger S, Okey AB, Harper PA. Red meat intake, doneness, polymorphisms in genes that encode carcinogen-metabolizing enzymes, and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2008 Nov; 17(11): 3, 098-3, 107. PMID: 18990750.	Study design is case-control (colorectal cancer).
Crowe FL, Key TJ, Appleby PN, Travis RC, Overvad K, Jakobsen MU, Johnsen NF, Tjønneland A, Linseisen J, Rohrmann S, Boeing H, Pischon T, Trichopoulou A, Lagiou P, Trichopoulos D, Sacerdote C, Palli D, Tumino R, Krogh V, Bueno-de-Mesquita HB, Kiemeney LA, Chirlaque MD, Ardanaz E, Sánchez MJ, Larrañaga N, González CA, Quirós JR, Manjer J, Wirfält E, Stattin P, Hallmans G, Khaw KT, Bingham S, Ferrari P, Slimani N, Jenab M, Riboli E. Dietary fat intake and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr.* 2008 May; 87(5): 1, 405-1, 413. PMID: 18469265.	Does not answer question: Examined relationship between animal fat intake and prostate cancer.
Dallongeville J, Yarnell J, Ducimetière P, Arveiler D, Ferrières J, Montaye M, Luc G, Evans A, Bingham A, Hass B, Ruidavets JB, Amouyel P. Fish consumption is associated with lower heart rates.*Circulation.* 2003 Aug 19; 108(7): 820-825. Epub 2003 Aug 11. PMID: 12912821.	Does not answer question: Examined relationship between fish intake and heart rates.
Davey GK, Spencer EA, Appleby PN, Allen NE, Knox KH, Key TJ. EPIC-Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33 883 meat-eaters and 31 546 non meat-eaters in the UK. *Public Health Nutr.* 2003 May; 6(3): 259-269. PMID: 12740075.	Does not include health outcomes in analyses.
de Mello VD, Zelmanovitz T, Perassolo MS, Azevedo MJ, Gross JL. Withdrawal of red meat from the usual diet reduces albuminuria and improves serum fatty acid profile in type 2 diabetes patients with macroalbuminuria. *Am J Clin Nutr*. 2006 May; 83(5): 1, 032-1, 038. PMID: 16685043.	Participants diagnosed with type 2 diabetes (T2D).
Dixon LB, Balder HF, Virtanen MJ, Rashidkhani B, Männistö S, Krogh V, van Den Brandt PA, Hartman AM, Pietinen P, Tan F, Virtamo J, Wolk A, Goldbohm RA. Dietary patterns associated with colon and rectal cancer: results from the Dietary Patterns and Cancer (DIETSCAN) Project. *Am J Clin Nutr.* 2004 Oct; 80(4): 1, 003-1, 011. PMID: 15447912.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.

Djoussé L, Gaziano JM. Egg consumption and risk of heart failure in the Physicians' Health Study. *Circulation.* 2008 Jan 29; 117(4): 512-516. Epub 2008 Jan 14. PMID: 18195171; PMCID: PMC2706003.	Does not answer question: Examined relationship between egg consumption and heart failure.
Egeberg R, Olsen A, Autrup H, Christensen J, Stripp C, Tetens I, Overvad K, Tjønneland A. Meat consumption, N-acetyl transferase 1 and 2 polymorphism and risk of breast cancer in Danish postmenopausal women. *Eur J Cancer Prev.* 2008 Feb; 17(1): 39-47. PMID: 18090909.	Study design is nested case-control study (breast cancer).
Eichholzer M, Bisig B. Daily consumption of (red) meat or meat products in Switzerland: Results of the 1992/93 Swiss Health Survey. *Eur J Clin Nutr.* 2000 Feb; 54(2): 136-142. PMID: 10694784.	Does not include health outcomes in analyses.
Elliott P, Stamler J, Dyer AR, Appel L, Dennis B, Kesteloot H, Ueshima H, Okayama A, Chan Q, Garside DB, Zhou B. Association between protein intake and blood pressure: The INTERMAP Study. *Arch Intern Med.* 2006 Jan 9; 166(1): 79-87. PMID: 16401814.	Study design is cross-sectional epidemiological study.
Engeset D, Andersen V, Hjartåker A, Lund E. Consumption of fish and risk of colon cancer in the Norwegian Women and Cancer (NOWAC) study. *Br J Nutr.* 2007 Sep; 98(3): 576-582. Epub 2007 Apr 10. Erratum in: *Br J Nutr.* 2008 Mar; 99(3): 696. PMID: 17419892.	Does not answer question: Examined relationship between fish intake and colon cancer.
Erkkilä AT, Lichtenstein AH, Mozaffarian D, Herrington DM. Fish intake is associated with a reduced progression of coronary artery atherosclerosis in postmenopausal women with coronary artery disease. *Am J Clin Nutr.* 2004 Sep; 80(3): 626-632. PMID: 15321802.	Participants diagnosed with CHD.
Erkkilä AT, Schwab US, de Mello VD, Lappalainen T, Mussalo H, Lehto S, Kemi V, Lamberg-Allardt C, Uusitupa MI. Effects of fatty and lean fish intake on blood pressure in subjects with coronary heart disease using multiple medications. *Eur J Nutr.* 2008 Sep; 47(6): 319-328. Epub 2008 Jul 29. PMID: 18665413.	Participants diagnosed with CHD.
Faramawi MF, Johnson E, Fry MW, Sall M, Zhou Y. Consumption of different types of meat and the risk of renal cancer: Meta-analysis of case-control studies. *Cancer Causes Control.* 2007 Mar; 18(2): 125-133. Epub 2007 Jan 22. Erratum in: *Cancer Causes Control.* 2007 Jun; 18 (5): 581. Yi, Zhou [corrected to Zhou, Yi]. PMID: 17242980.	Does not include colorectal, breast or prostate cancer in analyses.
Ferrucci LM, Sinha R, Graubard BI, Mayne ST, Ma X, Schatzkin A, Schoenfeld PS, Cash BD, Flood A, Cross AJ. Dietary meat intake in relation to colorectal adenoma in asymptomatic women. *Am J Gastroenterol.* 2009 May; 104(5): 1, 231-1, 140. Epub 2009 Apr 14. PMID: 19367270.	Study design is case-control study (colorectal cancer).
Geelen A, Schouten JM, Kamphuis C, Stam BE, Burema J, Renkema JM, Bakker EJ, van't Veer P, Kampman E. Fish consumption, n-3 fatty acids, and colorectal cancer: a meta-analysis of prospective cohort studies. *Am J Epidemiol*. 2007 Nov 15; 166(10): 1, 116-1, 125. Epub 2007 Sep 6. PMID: 17823383.	Study design is meta-analysis (colorectal cancer).

Gillum RF, Mussolino ME, Madans JH. Fish consumption and hypertension incidence in African Americans and whites: The NHANES I Epidemiologic Follow-up Study. *J Natl Med Assoc.* 2001 Apr; 93(4): 124-128. PMID: 12653399; PMCID: PMC2593988.	Does not answer question: Examined relationship between fish intake and hypertension (HTN).
Goldin BR, Brauner E, Adlercreutz H, Ausman LM, Lichtenstein AH. Hormonal response to diets high in soy or animal protein without and with isoflavones in moderately hypercholesterolemic subjects. *Nutr Cancer.* 2005; 51(1): 1-6. PMID: 15749623.	Does not answer question: Examined hormonal response to diets high in soy or animal protein.
Gonzalez CA, Riboli E. Diet and cancer prevention: Where we are, where we are going. Nutr Cancer. 2006; 56(2): 225-31. Review. PMID: 17474869.	Study design is narrative review.
Grillenberger M, Neumann CG, Murphy SP, Bwibo NO, Weiss RE, Jiang L, Hautvast JG, West CE. Intake of micronutrients high in animal-source foods is associated with better growth in rural Kenyan school children. *Br J Nutr*. 2006 Feb; 95(2): 379-390. PMID: 16469157.	Study population not from a developed country as defined by the Human Development Index (2009).
Gross JL, Zelmanovitz T, Moulin CC, De Mello V, Perassolo M, Leitão C, Hoefel A, Paggi A, Azevedo MJ. Effect of a chicken-based diet on renal function and lipid profile in patients with type 2 diabetes: a randomized crossover trial. *Diabetes Care.* 2002 Apr; 25(4): 645-651. PMID: 11919119.	Participants diagnosed with T2D.
Günther AL, Remer T, Kroke A, Buyken AE. Early protein intake and later obesity risk: which protein sources at which time points throughout infancy and childhood are important for body mass index and body fat percentage at 7 y of age? *Am J Clin Nutr.* 2007 Dec; 86(6): 1, 765-1, 772. PMID: 18065597.	Does not answer question: Examined protein intake during infancy and childhood and body weight outcomes at age seven years.
He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, Greenland P. Accumulated evidence on fish consumption and coronary heart disease mortality: A meta-analysis of cohort studies. *Circulation.* 2004 Jun 8; 109(22): 2, 705-2, 711. PMID: 15184295.	Does not answer question: examined relationship between fish intake and CHD.
High red-meat intake, obesity linked to cancer.*Health News.* 2002 Feb; 8(2): 9. PMID: 11862847.	News article.
Hodgson JM, Burke V, Beilin LJ, Puddey IB. Partial substitution of carbohydrate intake with protein intake from lean red meat lowers blood pressure in hypertensive persons. *Am J Clin Nutr.* 2006 Apr; 83(4): 780-787. PMID: 16600928.	Participants diagnosed with HTN.
Hu FB, Manson JE, Willett WC. Types of dietary fat and risk of coronary heart disease: a critical review.*J Am Coll Nutr.* 2001 Feb; 20(1): 5-19. Review. PMID: 11293467.	Study design is narrative review.
Huncharek M, Kupelnick B, Wheeler L. Dietary cured meat and the risk of adult glioma: A meta-analysis of nine observational studies. *J Environ Pathol Toxicol* Oncol. 2003; 22(2): 129-137. PMID: 14533876.	Does not include colorectal, breast, or prostate cancer in analyses.

Huncharek M, Kupelnick B. A meta-analysis of maternal cured meat consumption during pregnancy and the risk of childhood brain tumors. *Neuroepidemiology.* 2004 Jan-Apr; 23(1-2): 78-84. PMID: 14739572.	Does not include colorectal, breast, or prostate cancer in analyses.
Hunninghake DB, Maki KC, Kwiterovich PO Jr, Davidson MH, Dicklin MR, Kafonek SD. Incorporation of lean red meat into a National Cholesterol Education Program Step I diet: A long-term, randomized clinical trial in free-living persons with hypercholesterolemia. *J Am Coll Nutr.* 2000 Jun; 19(3): 351-360. PMID: 10872897.	Participants diagnosed with hypercholesterolemia.
Iso H, Sato S, Kitamura A, Naito Y, Shimamoto T, Komachi Y. Fat and protein intakes and risk of intraparenchymal hemorrhage among middle-aged Japanese. *Am J Epidemiol.* 2003 Jan 1; 157(1): 32-39. Erratum in: *Am J Epidemiol.* 2004 Feb 1; 159(3): 318. PMID: 12505888.	Does not answer question: examined relationship between protein intake and intraparenchymal hemorrhage.
Järvinen R, Knekt P, Rissanen H, Reunanen A. Intake of fish and long-chain n-3 fatty acids and the risk of coronary heart mortality in men and women. *Br J Nutr.* 2006 Apr; 95(4): 824-829. PMID: 16571163.	Does not answer question: examined relationship between fish intake and CHD.
Jenkins DJ, Wong JM, Kendall CW, Esfahani A, Ng VW, Leong TC, Faulkner DA, Vidgen E, Greaves KA, Paul G, Singer W. The effect of a plant-based low-carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. *Arch Intern Med.* 2009 Jun 8; 169(11): 1, 046-1, 054. PMID: 19506174.	Participants diagnosed hyperlipidemia.
Joshi AD, Corral R, Siegmund KD, Haile RW, Le Marchand L, Martínez ME, Ahnen DJ, Sandler RS, Lance P, Stern MC. Red meat and poultry intake, polymorphisms in the nucleotide excision repair and mismatch repair pathways and colorectal cancer risk. 2009 Mar; 30(3): 472-479. Epub 2008 Nov 24. PMID: 19029193; PMCID: PMC2722151.	Study design is case-control family-based study (colorectal cancer).
Kabat GC, Miller AB, Jain M, Rohan TE. A cohort study of dietary iron and heme iron intake and risk of colorectal cancer in women. *Br J Cancer.* 2007 Jul 2; 97 (1): 118-122. Epub 2007 Jun 5. Erratum in: *Br J Cancer.* 2007 Dec 3; 97(11): 1, 600. PMID: 77551493; PMCID: PMC2359661.	Does not answer question: examined relationship between iron and heme iron intake and colorectal cancer.
König A, Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, Lawrence RS, Savitz DA, Teutsch SM. A quantitative analysis of fish consumption and coronary heart disease mortality. *Am J Prev Med.* 2005 Nov; 29(4): 335-346. PMID: 16242600.	Does not answer question: examined relationship between fish intake and CHD.
Kono S. Secular trend of colon cancer incidence and mortality in relation to fat and meat intake in Japan. *Eur J Cancer Prev*. 2004 Apr; 13(2): 127-132. PMID: 15100579.	Study design is non-comparative, correlational study.
Kontogianni MD, Panagiotakos DB, Pitsavos C, Chrysohoou C, Stefanadis C. Relationship between meat intake and the development of acute coronary syndromes: the CARDIO2000 case-control study. *Eur J Clin Nutr.* 2008 Feb; 62(2): 171-177. Epub 2007 Mar 14. PMID: 17356558.	Does not include health outcome of interest in analyses.

Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation*. 2002 Nov 19; 106(21): 2, 747-2, 757. Erratum in: *Circulation.* 2003 Jan 28; 107 (3): 512. PMID: 12438303.	Expert opinion.
Larsson SC, Orsini N, Wolk A. Processed meat consumption and stomach cancer risk: A meta-analysis. *J Natl Cancer Inst.* 2006 Aug 2; 98(15): 1, 078-1, 087. PMID: 16882945.	Does not include colorectal, breast or prostate cancer in analyses.
Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: A meta-analysis of prospective studies. *Int J Cancer.* 2006 Dec 1; 119(11): 2, 657-2, 664. PMID: 16991129.	Study design is meta-analysis (colorectal cancer).
Lee JE, Spiegelman D, Hunter DJ, Albanes D, Bernstein L, van den Brandt PA, Buring JE, Cho E, English DR, Freudenheim JL, Giles GG, Graham S, Horn-Ross PL, Håkansson N, Leitzmann MF, Männistö S, McCullough ML, Miller AB, Parker AS, Rohan TE, Schatzkin A, Schouten LJ, Sweeney C, Willett WC, Wolk A, Zhang SM, Smith-Warner SA. Fat, protein, and meat consumption and renal cell cancer risk: A pooled analysis of 13 prospective studies. *J Natl Cancer Inst*. 2008 Dec 3; 100(23): 1, 695-1, 706. Epub 2008 Nov 25. PMID: 19033572; PMCID: PMC2727138.	Does not include colorectal, breast or prostate cancer in analyses.
Levitan EB, Wolk A, Mittleman MA. Fish consumption, marine omega-3 fatty acids, and incidence of heart failure: A population-based prospective study of middle-aged and elderly men. *Eur Heart J.* 2009 Jun; 30(12): 1, 495-1, 500. Epub 2009 Apr 21. PMID: 19383731; PMCID: PMC2695952.	Does not answer question: Examined relationship between fish intake and heart failure.
Lichtenstein AH, Jalbert SM, Adlercreutz H, Goldin BR, Rasmussen H, Schaefer EJ, Ausman LM. Lipoprotein response to diets high in soy or animal protein with and without isoflavones in moderately hypercholesterolemic subjects. *Arterioscler Thromb Vasc Biol.* 2002 Nov 1; 22(11): 1, 852-1, 858. PMID: 12426215.	Participants diagnosed with hypercholesterolemia.
Linseisen J, Kesse E, Slimani N; EPIC Working Group on Dietary Pattern, Subgroup Meat. Meat consumption in Europe: Results from the EPIC study.*IARC Sci Publ*. 2002; 156: 211-212. PMID: 12484168.	Does not include health outcomes in analyses.
Liu L, Ikeda K, Yamori Y; WHO-CARDIAC Study Group. Inverse relationship between urinary markers of animal protein intake and blood pressure in Chinese: results from the WHO Cardiovascular Diseases and Alimentary Comparison (CARDIAC) Study. *Int J Epidemiol*. 2002 Feb; 31(1): 227-233. PMID: 11914325.	Does not answer question: Examined the relationship between urinary excretion of 3-methylhistidine (as marker of animal protein intake) and blood pressure (BP).
Lucey AJ, Paschos GK, Cashman KD, Martínéz JA, Thorsdottir I, Kiely M. Influence of moderate energy restriction and seafood consumption on bone turnover in overweight young adults. *Am J Clin Nutr.* 2008 Apr; 87(4): 1, 045-1, 052. PMID: 18400730.	Does not include health outcome of interest in analyses.

Lüchtenborg M, Weijenberg MP, de Goeij AF, Wark PA, Brink M, Roemen GM, Lentjes MH, de Bruïne AP, Goldbohm RA, van 't Veer P, van den Brandt PA. Meat and fish consumption, APC gene mutations and hMLH1 expression in colon and rectal cancer: A prospective cohort study (The Netherlands). *Cancer Causes Control.* 2005 Nov; 16(9): 1, 041-1, 054. PMID: 16184469.	Results reported based on the same dataset as Brink, 2005.
Mamo JC, James AP, Soares MJ, Griffiths DG, Purcell K, Schwenke JL. A low-protein diet exacerbates postprandial chylomicron concentration in moderately dyslipidaemic subjects in comparison to a lean red meat protein-enriched diet. *Eur J Clin Nutr.* 2005 Oct; 59(10): 1, 142-1, 148. PMID: 16015257.	Does not answer question: Examined relationship between protein intake and postprandial response.
Männistö S, Dixon LB, Balder HF, Virtanen MJ, Krogh V, Khani BR, Berrino F, van den Brandt PA, Hartman AM, Pietinen P, Tan F, Wolk A, Goldbohm RA. Dietary patterns and breast cancer risk: Results from three cohort studies in the DIETSCAN project. *Cancer Causes Control.* 2005 Aug; 16(6): 725-733. PMID: 16049811.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Marques-Vidal P, Ravasco P, Ermelinda Camilo M. Foodstuffs and colorectal cancer risk: A review. *Clin Nutr.* 2006 Feb; 25(1): 14-36. Epub 2005 Nov 14. Review. PMID: 16290272.	Study design is systematic review (colorectal cancer).
Matheson EM, Mainous AG 3rd, Hill EG, Carnemolla MA. Shellfish consumption and risk of coronary heart disease. *J Am Diet Assoc.* 2009 Aug; 109(8): 1, 422-1, 426. PMID: 19631050.	Does not answer question: Examined relationship between shellfish intake and CHD.
Matthan NR, Jalbert SM, Ausman LM, Kuvin JT, Karas RH, Lichtenstein AH. Effect of soy protein from differently processed products on cardiovascular disease risk factors and vascular endothelial function in hypercholesterolemic subjects. *Am J Clin Nutr.* 2007 Apr; 85(4): 960-966. Erratum in: *Am J Clin Nutr.* 2007 Aug; 86(2): 525. PMID: 17413093.	Participants were hypercholesterolemic.
McCarty MF. The origins of western obesity: A role for animal protein? *Med Hypotheses.* 2000 Mar; 54(3): 488-494. PMID: 10783494.	Study design is narrative review.
McNaughton SA, Mishra GD, Stephen AM, Wadsworth ME. Dietary patterns throughout adult life are associated with body mass index, waist circumference, blood pressure, and red cell folate. *J Nutr.* 2007 Jan; 137(1): 99-105. PMID: 17182808.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Melanson K, Gootman J, Myrdal A, Kline G, Rippe JM. Weight loss and total lipid profile changes in overweight women consuming beef or chicken as the primary protein source. *Nutrition.* 2003 May; 19(5): 409-414. PMID: 12714091.	Dropout rate is higher than inclusion criteria.
Missmer SA, Smith-Warner SA, Spiegelman D, Yaun SS, Adami HO, Beeson WL, van den Brandt PA, Fraser GE, Freudenheim JL, Goldbohm RA, Graham S, Kushi LH, Miller AB, Potter JD, Rohan TE, Speizer FE, Toniolo P, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Hunter DJ. Meat and dairy food consumption and breast cancer: A pooled analysis of cohort studies. *Int J Epidemiol.* 2002 Feb; 31(1): 78-85. PMID: 11914299.	Study design is meta-analysis (breast cancer).

Möllsten AV, Dahlquist GG, Stattin EL, Rudberg S. Higher intakes of fish protein are related to a lower risk of microalbuminuria in young Swedish type 1 diabetic patients. *Diabetes Care.* 2001 May; 24(5): 805-810. PMID: 11347734.	Participants diagnosed with T2D.
Mortensen LS, Hartvigsen ML, Brader LJ, Astrup A, Schrezenmeir J, Holst JJ, Thomsen C, Hermansen K. Differential effects of protein quality on postprandial lipemia in response to a fat-rich meal in type 2 diabetes: comparison of whey, casein, gluten, and cod protein. *Am J Clin Nutr.* 2009 Jul; 90(1): 41-48. Epub 2009 May 20. PMID: 19458012.	Participants diagnosed with T2D.
Mozaffarian D, Psaty BM, Rimm EB, Lemaitre RN, Burke GL, Lyles MF, Lefkowitz D, Siscovick DS. Fish intake and risk of incident atrial fibrillation. *Circulation.* 2004 Jul 27; 110(4): 368-373. Epub 2004 Jul 19. PMID: 15262826; PMCID: PMC1201400.	Does not answer question: Examined relationship between fish intake and atrial fibrillation.
Nagata C, Shimizu H, Kametani M, Takeyama N, Ohnuma T, Matsushita S. Diet and colorectal adenoma in Japanese males and females. *Dis Colon Rectum.* 2001 Jan; 44(1): 105-111. PMID: 11805576.	Study design is case-control study (colorectal cancer).
Nenseter MS, Østerud B, Larsen T, Strøm E, Bergei C, Hewitt S, Holven KB, Hagve TA, Mjøs SA, Solvang M, Pettersen J, Opstvedt J, Ose L. Effect of Norwegian fish powder on risk factors for coronary heart disease among hypercholesterolemic individuals. *Nutr Metab Cardiovasc Dis.* 2000 Dec; 10(6): 323-330. PMID: 11302007.	Did not answer question: Examined relationship between fish powder and CHD.
Nettleton JA, Steffen LM, Loehr LR, Rosamond WD, Folsom AR. Incident heart failure is associated with lower whole-grain intake and greater high-fat dairy and egg intake in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Diet Assoc*. 2008 Nov; 108(11): 1, 881-1, 887. PMID: 18954578; PMCID: PMC2650810.	Does not answer question: Examined relationship between egg intake and heart failure.
Nkondjock A, Receveur O. Fish-seafood consumption, obesity, and risk of type 2 diabetes: an ecological study. *Diabetes Metab.* 2003 Dec; 29(6): 635-642. PMID: 14707894.	Does not answer question: Examined relationship between fish intake and T2D.
Norat T, Lukanova A, Ferrari P, Riboli E. Meat consumption and colorectal cancer risk: Dose-response meta-analysis of epidemiological studies. *Int J Cancer.* 2002 Mar 10; 98(2): 241-256. PMID: 11857415.	Study design is meta-analysis (colorectal cancer).
Norat T, Riboli E. Meat consumption and colorectal cancer: A review of epidemiologic evidence. *Nutr Rev.* 2001 Feb; 59(2): 37-47. Review. PMID: 11310774.	Study design is meta-analysis (colorectal cancer).
Norat T, Riboli E. Meat consumption and colorectal cancer: A review of epidemiologic evidence. *Nutr Rev.* 2001 Feb; 59(2): 37-47. Review. PMID: 11310774.	Study design is narrative review (colorectal cancer).
Nowson CA, Wattanapenpaiboon N, Pachett A. Low-sodium Dietary Approaches to Stop Hypertension-type diet including lean red meat lowers blood pressure in postmenopausal women. *Nutr Res.* 2009 Jan; 29(1): 8-18. PMID: 19185772.	Does not include animal protein products in analyses.

Olmedilla-Alonso B, Granado-Lorencio F, Herrero-Barbudo C, Blanco-Navarro I, Blázquez-García S, Pérez-Sacristán B. Consumption of restructured meat products with added walnuts has a cholesterol-lowering effect in subjects at high cardiovascular risk: a randomised, crossover, placebo-controlled study. *J Am Coll Nutr.* 2008 Apr; 27(2): 342-348. PMID: 18689569.	Does not answer question: Examined effect of restructured meat product on cholesterol.
Panagiotakos DB, Pitsavos C, Zampelas A, Chrysohoou C, Griffin BA, Stefanadis C, Toutouzas P. Fish consumption and the risk of developing acute coronary syndromes: The CARDIO2000 study. *Int J Cardiol.* 2005 Jul 20; 102(3): 403-409. PMID: 16004884.	Does not answer question: Examined relationship between fish intake and health outcomes.
Panagiotakos DB, Zeimbekis A, Boutziouka V, Economou M, Kourlaba G, Toutouzas P, Polychronopoulos E. Long-term fish intake is associated with better lipid profile, arterial blood pressure, and blood glucose levels in elderly people from Mediterranean islands (MEDIS epidemiological study). *Med Sci Monit.* 2007 Jul; 13(7): CR307-CR312. PMID: 17599024.	Does not answer question: Examined relationship between fish intake and health outcomes.
Pham TM, Fujino Y, Kubo T, Ide R, Tokui N, Mizoue T, Ogimoto I, Matsuda S, Yoshimura T. Fish intake and the risk of fatal prostate cancer: Findings from a cohort study in Japan. *Public Health Nutr.* 2009 May; 12(5): 609-613. Epub 2008 Jul 29. PMID: 18664313.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Pieniak Z, Verbeke W, Perez-Cueto F, Brunsø K, De Henauw S. Fish consumption and its motives in households with versus without self-reported medical history of CVD: A consumer survey from five European countries. *BMC Public Health.* 2008 Sep 10; 8: 306. PMID: 18783593; PMCID: PMC2556335.	Does not include health outcomes in analyses.
Processed meat consumption linked to type 2 diabetes. *Nephrol News Issues.* 2002 Apr; 16(5): 68-69. PMID: 11962157.	News article.
Ramel A, Parra D, Martinéz JA, Kiely M, Thorsdottir I. Effects of seafood consumption and weight loss on fasting leptin and ghrelin concentrations in overweight and obese European young adults. *Eur J Nutr.* 2009 Mar; 48(2): 107-114. Epub 2009 Jan 13. PMID: 19142567.	Does not answer question: Examined relationship between seafood and leptin and ghrelin concentrations.
Rosell M, Appleby P, Spencer E, Key T. Weight gain over 5 years in 21, 966 meat-eating, fish-eating, vegetarian, and vegan men and women in EPIC-Oxford. *Int J Obes (Lond).* 2006 Sep; 30(9): 1, 389-1, 396. Epub 2006 Mar 14. PMID: 16534521.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Sandhu MS, White IR, McPherson K. Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: A meta-analytical approach. *Cancer Epidemiol Biomarkers Prev.* 2001 May; 10(5): 439-446. PMID: 11352852.	Study design is systematic review/meta-analysis (colorectal cancer).
Santarelli RL, Pierre F, Corpet DE. Processed meat and colorectal cancer: A review of epidemiologic and experimental evidence. *Nutr Cancer.* 2008; 60(2): 131-144. Review. PMID: 18444144; PMCID: PMC2661797.	Study design is narrative review.

Satia JA, Tseng M, Galanko JA, Martin C, Sandler RS. Dietary patterns and colon cancer risk in Whites and African Americans in the North Carolina Colon Cancer Study. *Nutr Cancer.* 2009; 61(2): 179-193. PMID: 19235034.	Study design is case-control study (colon cancer).
Schulz M, Hoffmann K, Weikert C, Nöthlings U, Schulze MB, Boeing H. Identification of a dietary pattern characterized by high-fat food choices associated with increased risk of breast cancer: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Br J Nutr.* 2008 Nov; 100(5): 942-946. PMID: 18377685.	Does not answer question: Examines relationship between high fat foods and breast cancer.
Seierstad SL, Seljeflot I, Johansen O, Hansen R, Haugen M, Rosenlund G, Frøyland L, Arnesen H. Dietary intake of differently fed salmon: The influence on markers of human atherosclerosis. *Eur J Clin Invest.* 2005 Jan; 35(1): 52-59. PMID: 15638820.	Participants diagnosed with T2D.
Shiell AW, Campbell-Brown M, Haselden S, Robinson S, Godfrey KM, Barker DJ. High-meat, low-carbohydrate diet in pregnancy: Relation to adult blood pressure in the offspring. *Hypertension*. 2001 Dec 1; 38(6): 1, 282-1, 288. PMID: 11751704.	Does not answer question: Examines relationship between dietary intake during pregnancy and health of adult offspring.
Sieri S, Krogh V, Muti P, Micheli A, Pala V, Crosignani P, Berrino F. Fat and protein intake and subsequent breast cancer risk in postmenopausal women. *Nutr Cancer.* 2002; 42(1): 10-17. PMID: 12235640.	Study design is case-control study (breast cancer).
Skjelbred CF, Saebø M, Hjartåker A, Grotmol T, Hansteen IL, Tveit KM, Hoff G, Kure EH. Meat, vegetables and genetic polymorphisms and the risk of colorectal carcinomas and adenomas. *BMC Cancer*. 2007 Dec 19; 7: 228. PMID: 18093316; PMCID: PMC2228310.	Study design is case-control study (colorectal cancer).
Smith DR, Wood R, Tseng S, Smith SB. Increased beef consumption increases apolipoprotein A-I but not serum cholesterol of mildly hypercholesterolemic men with different levels of habitual beef intake. *Exp Biol Med (Maywood).* 2002 Apr; 227(4): 266-275. PMID: 11910049.	Participants diagnosed with mild hypercholesterolemia.
SoRelle R. Fish and long-chain omega-3 fatty acids could be lifesavers for diabetic women. *Circulation.* 2003 Apr 22; 107(15): e9, 033-9, 035. PMID: 12707254.	Participants were diagnosed with diabetes.
Sørensen M, Autrup H, Olsen A, Tjønneland A, Overvad K, Raaschou-Nielsen O. Prospective study of NAT1 and NAT2 polymorphisms, tobacco smoking and meat consumption and risk of colorectal cancer. *Cancer Lett.* 2008 Aug 8; 266(2): 186-193. Epub 2008 Mar 26. PMID: 18372103.	Study design is case-control study (colorectal cancer).
Spencer EA, Appleby PN, Davey GK, Key TJ. Diet and body mass index in 38000 EPIC-Oxford meat-eaters, fish-eaters, vegetarians and vegans. *Int J Obes Relat Metab Disord.* 2003 Jun; 27(6): 728-734. PMID: 12833118.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Stewart JW, Kaplan ML, Beitz DC. Pork with a high content of polyunsaturated fatty acids lowers LDL cholesterol in women. *Am J Clin Nutr.* 2001 Aug; 74(2): 179-187. PMID: 11470718.	Intervention consisted of modified pork high in PUFAs.

Tanskanen A, Hibbeln JR, Tuomilehto J, Uutela A, Haukkala A, Viinamäki H, Lehtonen J, Vartiainen E. Fish consumption and depressive symptoms in the general population in Finland. *Psychiatr Serv.* 2001 Apr; 52(4): 529-531. PMID: 11274502.	Does not include health outcome of interest in analyses.
Tapola NS, Lyyra ML, Karvonen HM, Uusitupa MI, Sarkkinen ES. The effect of meat products enriched with plant sterols and minerals on serum lipids and blood pressure. *Int J Food Sci Nutr.* 2004 Aug; 55(5): 389-397. PMID: 15545047.	Intervention consisted of meat products enriched with plant sterols; participants diagnosed with hypercholesterolemia.
Tappel A. Heme of consumed red meat can act as a catalyst of oxidative damage and could initiate colon, breast and prostate cancers, heart disease and other diseases. *Med Hypotheses*. 2007; 68(3): 562-564. Epub 2006 Oct 11. PMID: 17045417.	Study design is narrative review.
Teixeira Rde C, Molina Mdel C, Zandonade E, Mill JG. Cardiovascular risk in vegetarians and omnivores: A comparative study. *Arq Bras Cardiol.* 2007 Oct; 89(4): 237-244. English, Portuguese. PMID: 17992380.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Terry P, Rohan TE, Wolk A, Maehle-Schmidt M, Magnusson C. Fish consumption and breast cancer risk. *Nutr Cancer.* 2002; 44(1): 1-6. PMID: 12672635.	Study design is case-control study (breast cancer).
Thorsdottir I, Birgisdottir B, Kiely M, Martinez J, Bandarra N. Fish consumption among young overweight European adults and compliance to varying seafood content in four weight loss intervention diets. *Public Health Nutr.* 2009 May; 12(5): 592-598. Epub 2008 Jun 19. PMID: 18561865.	Does not answer question: Examined compliance to eating varying types of seafood in weight loss intervention diets.
Thorsdottir I, Tomasson H, Gunnarsdottir I, Gisladottir E, Kiely M, Parra MD, Bandarra NM, Schaafsma G, Martinéz JA. Randomized trial of weight-loss-diets for young adults varying in fish and fish oil content. *Int J Obes* (Lond). 2007 Oct; 31(10): 1, 560-1, 566. Epub 2007 May 15. PMID: 17502874.	Does not answer question: Examined fish intake and weight loss.
Tiemersma EW, Kampman E, Bueno de Mesquita HB, Bunschoten A, van Schothorst EM, Kok FJ, Kromhout D. Meat consumption, cigarette smoking, and genetic susceptibility in the etiology of colorectal cancer: results from a Dutch prospective study. *Cancer Causes Control.* 2002 May; 13(4): 383-393. PMID: 12074508.	Study design is case-control study (colorectal cancer).
Timonen M, Horrobin D, Jokelainen J, Laitinen J, Herva A, Räsänen P. Fish consumption and depression: The Northern Finland 1966 birth cohort study. *J Affect Disord.* 2004 Nov 1; 82(3): 447-452. PMID: 15555697.	Does not include health outcome of interest in analyses.
Tzoulaki I, Brown IJ, Chan Q, Van Horn L, Ueshima H, Zhao L, Stamler J, Elliott P; International Collaborative Research Group on Macro-/Micronutrients and Blood Pressure. Relation of iron and red meat intake to blood pressure: cross sectional epidemiological study. *BMJ.* 2008 Jul 15; 337: a258. doi: 10.1136/bmj.a258. PMID: 18632704; PMCID: PMC2658466.	Study design is cross-sectional epidemiological study.

Umesawa M, Sato S, Imano H, Kitamura A, Shimamoto T, Yamagishi K, Tanigawa T, Iso H. Relations between protein intake and blood pressure in Japanese men and women: the Circulatory Risk in Communities Study (CIRCS). *Am J Clin Nutr.* 2009 Aug; 90(2): 377-384. Epub 2009 Jun 10. PMID: 19515740.	Study design is cross-sectional.
Varraso R, Jiang R, Barr RG, Willett WC, Camargo CA Jr. Prospective study of cured meats consumption and risk of chronic obstructive pulmonary disease in men. *Am J Epidemiol*. 2007 Dec 15; 166(12): 1, 438-1, 445. Epub 2007 Sep 4. PMID: 17785711; PMCID: PMC2573990.	Does not include health outcome of interest in analyses.
Virtanen JK, Mozaffarian D, Chiuve SE, Rimm EB. Fish consumption and risk of major chronic disease in men. *Am J Clin Nutr.* 2008 Dec; 88(6): 1, 618-1, 625. PubMed PMID: 19064523; PMCID: PMC2613199.	Does not answer question: Examined relationship between fish intake and chronic disease.
Wakai K, Tamakoshi K, Date C, Fukui M, Suzuki S, Lin Y, Niwa Y, Nishio K, Yatsuya H, Kondo T, Tokudome S, Yamamoto A, Toyoshima H, Tamakoshi A; JACC Study Group. Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. *Cancer Sci.* 2005 Sep; 96(9): 590-599. PMID: 16128744.	Does not answer question: Examined relationship between breast cancer and fat intake, not animal protein.
Weggemans RM, Zock PL, Katan MB. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: A meta-analysis. *Am J Clin Nutr.* 2001 May; 73(5): 885-891. PMID: 11333841.	Does not examine relationship between intake of animal protein product and health outcome.
Weghuber D, Widhalm K. Effect of 3-month treatment of children and adolescents with familial and polygenic hypercholesterolaemia with a soya-substituted diet. *Br J Nutr.* 2008 Feb; 99(2): 281-286. Epub 2007 Aug 13. PMID: 17697400.	Participants diagnosed with hypercholesterolemia.
Welch AA, Bingham SA, Ive J, Friesen MD, Wareham NJ, Riboli E, Khaw KT. Dietary fish intake and plasma phospholipid n-3 polyunsaturated fatty acid concentrations in men and women in the European Prospective Investigation into Cancer-Norfolk United Kingdom cohort. *Am J Clin Nutr.* 2006 Dec; 84(6): 1, 330-1, 339. PMID: 17158413.	Does not include health outcomes in analyses; fish is the independent variable.
Wu K, Hu FB, Willett WC, Giovannucci E. Dietary patterns and risk of prostate cancer in U.S. men. *Cancer Epidemiol Biomarkers Prev.* 2006 Jan; 15(1): 167-171. PMID: 16434606.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Yoon H, Benamouzig R, Little J, François-Collange M, Tomé D. Systematic review of epidemiological studies on meat, dairy products and egg consumption and risk of colorectal adenomas. *Eur J Cancer Prev*. 2000 Jun; 9(3): 151-164. PMID: 10954254.	Study design is systematic review (colorectal cancer).
Yuan JM, Ross RK, Gao YT, Yu MC. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *Am J Epidemiol.* 2001 Nov 1; 154(9): 809-816. PMID: 11682363.	Does not answer question: Examined relationship between fish intake and myocardial infarction.

CHAPTER 5. ANIMAL PROTEIN PRODUCTS – BODY WEIGHT

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF ANIMAL PROTEIN PRODUCTS AND BODY WEIGHT?

Conclusion statement

Insufficient evidence is available to link animal protein intake and body weight.

Grade

Limited

Evidence summary overview

Three articles (Mahon, 2007; Wagemakers, 2009; Xu, 2007) published since 2000 were identified that examined the relationship between animal protein products and body weight. Inconsistent findings were reported in a cohort of British adults (Wagemakers, 2009) on whether meat intake was associated with body mass index (BMI) and waist circumference (WC) who were studied between 1989 and 1999. Red and processed meat consumed in 1999 was significantly associated with increased BMI in women only. In a cross-sectional study in China (Xu, 2007), red meat consumption was associated with excess body weight. In the only US study found (Mahon, 2007), overweight postmenopausal women were successful in weight loss with either a meat-containing or vegetarian protein intervention. Thus, existing research is sparse and finds little link between meat intake and body weight, and meat-containing diets work as well as calorie-controlled vegetarian diets in enhancing weight loss in intervention studies.

Evidence summary paragraphs

Mahon et al, 2007 (positive quality) used a randomized controlled trial (RCT) to assess the effects of dietary protein intake on energy restriction-induced changes in body mass and body composition. Participants were 54 postmenopausal women aged 58±2 years with a BMI of 29.6±0.8kg/m^2. Participants were assigned to one of four groups: Three groups ate energy-restricted (ER) (1,000kcal per day) lacto-ovo vegetarian basal diet plus 250kcal per day of either beef (BEEF), chicken (CHICKEN) or carbohydrate and fat foods (CARB), while a control group (CON) ate their habitual diets. Basal diet was distributed as a five-day fixed menu that consisted of three meals and two snacks equaling 1,000kcals. BEEF was provided with 250kcal per day of cooked beef; CHICKEN was given 250kcal per day of cooked chicken breast and 10g of butter and the CARB group was provided with shortbread cookies and sugar-coated chocolates. Body composition assessment was taken before and after the nine-week intervention for estimation of percent body fat, fat mass (FM) and fat-free mass (FFM) using DEXA. Energy intake was lower in the ER groups compared to CON (BEEF=1,114±155kcal per day, CHO: PRO: FAT, 46:24:30% of energy intake; CHICKEN=1,098±203kcal per day, 51:25:24; CARB=1,158±341kcal per day, 59:17:24; CON=1,570±633kcal per day, 47:20:33), but did not differ among ER groups. The percent energy intake from protein was lower in CARB compared to BEEF, CHICKEN and CON. Total dietary fiber intake was not different across time or among groups. Compared to CON, the ER groups decreased body mass, BMI, FM, percent body fat

and FFM. These responses were not different among the ER groups, except for a greater change in body mass (CHICKEN -7.9±2.6kg[a]; BEEF -6.6±2.7kg[ab]; CARB -5.6±1.8kg[b]; CON -1.2±1.2kg[c]; values with different superscript differ, P<0.05) and BMI (CHICKEN -3.0±1.2kg/m^{2a}; BEEF -2.5±1.1kg/m^{2ab}; CARB -2.1±0.7kg/m^{2b}; CON -0.3±0.5kg/m^{2c}; P<0.05) for CHICKEN vs. CARB. The authors concluded that overweight postmenopausal women can achieve significant weight loss and comparable short-term improvements in body composition by consuming either a moderate-protein (25% of energy intake) poultry- or beef-containing diet or a lacto-ovo vegetarian protein (17% of energy intake) diet.

Wagemakers et al, 2009 (neutral quality) investigated whether a high consumption of red or processed meat is associated with increased risk of coronary heart disease (CHD) in a cohort of British adults (N=1,152, 55% female, age 43 at baseline) followed from 1989 to 1999. Food intake was self-recorded using five-day diaries in 1989 and 1999. Meat consumption was estimated by adding individual meat portions to the meat fractions of composite dishes. Red meat, processed meat, and combined red and processed meat intake were considered. Height, weight and waist circumference (WC) were measured by study personnel at both time points. Body weight increased more than 5kg for both men and women between 1989 and 1999. No significant differences were observed in BMI or WC in 1999 for thirds of red meat or processed meat consumed in 1989 for men or women. The highest male consumers of red and processed meat combined in 1989 had significantly greater BMI (P=0.027) and WC (P=0.009). Using 1999 dietary data, WC of men only was significantly greater in the highest third of red meat consumption (P=0.013). The highest consumers of processed meat in 1999 had significantly increased WC for men (P=0.009) and women (P=0.001) and BMI for women only (P=0.001). The highest consumers of red and processed meat combined in 1999 had higher WC for men (P<0.001) and women (<0.001) and BMI for women only (P<0.001). A 10g increase in red meat consumption in 1989 was associated with a 0.3cm increase in WC of men (P=0.035) and women (P=0.048) in 1999. A similar association was found for consumption of processed meat. Red and processed meat consumed in 1999 was significantly associated with increased BMI in women only. The authors concluded that significant positive associations were observed between meat consumption measured 10 years earlier or synchronously and BMI and WC.

Xu et al, 2007 (positive quality), a cross-sectional study, examined the association of red meat and vegetable consumption with excess body weight. Participants were 23,316 adults (51% female, age 35-45 years) from a large-scale population-based cross sectional study from Nanjing municipality in China. Diet was assessed through household interviews with a structured questionnaire. Red meat ("mammals' meat") and white meat (seafood and poultry) were included in the interview, but only red meat was considered in the analyses. Height and weight were measured by study personnel. Seventy-seven percent of participants consumed red meat more than six times per week. The prevalence of excess body weight was significantly higher among participants with high and moderate red meat intake than those in the lower level (OR=1.19; 95% CI: 1.09, 1.30 and OR=1.11, 95% CI: 1.03, 1.20) for subjects with high and moderate consumption of red meat, respectively, compared to low consumption after adjusting for multiple confounders. The authors concluded that consumption of red meat was significantly associated with excess body weight.

Overview table

Author, Year, Study Design, Class, Rating	Participants	Description of Study Methodology	Outcomes
Mahon AK, Flynn MG et al, 2007 Study Design: Randomized controlled study. Class: A Positive quality	Initial N: 57 postmenopausal women; Final N: 54. Age: 58±2 years. BMI: 29.6±0.8kg/m2. Caucasian. Location: United States.	Participants were assigned to one of four groups: Three groups ate energy-restricted (ER) (1,000kcal per day) lacto-ovo vegetarian basal diet plus 250kcal per day of either beef (BEEF), chicken (CHICKEN) or CHO/fat foods (CARB), while a control group (CON) ate their habitual diets. Basal diet was distributed as a five-day fixed menu that consisted of three meals and two snacks equaling 1,000kcals. BEEF was provided with 250kcal per day of cooked beef. CHICKEN was given 250kcal per day of cooked chicken breast and 10g butter. CARB group was provided with shortbread cookies and sugar-coated chocolates. Length of treatment: 11 weeks (nine-week intervention and two-week weight maintenance period). Body composition assessment taken pre- and post-intervention for estimation of percent body fat, fat mass (FM) and fat-free mass (FFM) using DEXA.	Energy intake was lower in the ER groups compared to CON (BEEF=1,114±155kcal per day, CHO: PRO: FAT, 46:24:30% of energy intake; CHICKEN=1,098±203kcal per day, 51:25:24; CARB=1,158±341kcal per day, 59:17:24; CON=1,570±633kcal per day, 47:20:33), but did not differ among ER groups. The percent energy intake from protein was lower in CARB compared to BEEF, CHICKEN and CON. Total dietary fiber intake was not different across time or among groups. Compared to CON, the ER groups ↓ body mass, BMI, FM, percent body fat and FFM. These responses were not different among the ER groups, except for a greater Δ in body mass (CHICKEN -7.9±2.6kga; BEEF -6.6±2.7kgab; CARB -5.6±1.8kgb; CON -1.2±1.2kgc; values with different superscript differ, P<0.05) and BMI (CHICKEN -3.0±1.2kg/m2a; BEEF -2.5±1.1kg/m2ab; CARB -2.1±0.7kg/m2b; CON -0.3±0.5kg/m2c; P<0.05) for CHICKEN vs. CARB.

Wagemakers et al 2009 Study Design: Cohort Class: B Neutral quality	N=1,152 (55% women). Age: 43 years at baseline. Medical Research Council National Survey of Health and Development. Location: United Kingdom.	Food intake was self-recorded using five-day diaries at two time periods: 1989 and 1999 (included in analysis if at least three days were recorded). Meat consumption was estimated by adding individual meat portions to the meat fractions of composite dishes. Red meat (beef, lamb, pork, veal and mutton) and processed meat (ham, bacon, sausages, processed meat cuts and processed minced meat). Height, weight and waist circumference (WC) were measured by study personnel in 1989 and 1999.	Body weight ↑ more than 5kg for both men and women between 1989 and 1999. 1989 dietary intake: Red meat and processed meat; NS differences were observed in BMI or WC in 1999 for thirds of red meat or processed meat consumption in 1989 for men or women. Red and processed meat combined; the highest male consumers of these meats in 1989 had significantly greater BMI (P=0.027) and WC (P=0.009). 1999 dietary intake: Red meat; WC of men only was significantly > in the highest third of red meat consumption (P=0.013). NS difference in BMI for men or women. Processed meat; the highest consumers of processed meat had significantly ↑ WC for men (P=0.009) and women (P=0.001) and BMI for women only (P=0.001). Red and processed meat combined; the highest consumers of red and processed meat combined had higher WC for men (P<0.001) and women (P<0.001) and BMI for women only (P<0.001). A 10g ↑ in red meat consumption in 1989 was associated with a 0.3cm ↑ in WC of men (P=0.035) and women (P=0.048) in 1999. A similar association was found for consumption of processed meat. Red and processed meat consumed in 1999 was significantly associated with ↑ BMI in women only.
Xu F, Yin XM et al, 2007 Study Design: Cross-sectional study Class: D Neutral quality	N=23,316 (51% female). Age: 35-45 years. Location: China.	Diet assessed by household interviews with structured questionnaire. Red meat (“mammals’ meat”) and white meat (seafood and poultry) included in interview, but only red meat considered in analyses.	77% of participants consumed red meat more than six times per week. The prevalence of excess body weight was significantly higher among participants with high and moderate red meat intake than those in the lower level (OR=1.19; 95% CI: 1.09, 1.30 and OR=1.11, 95% CI: 1.03, 1.20) for subjects with high and moderate consumption of red meat, respectively, compared to low consumption after adjusting for multiple confounders.

Search plan and results

Inclusion criteria

- January 2000 to September 2009
- Prospective cohort studies on colorectal, breast and prostate cancers
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children two to 18 years; Adults 19 years and older
- *Populations:* Healthy, those with elevated chronic disease risk.

Exclusion criteria

- With the exception of the body weight outcome, cross-sectional studies were excluded from the review
- Systematic reviews and meta-analyses on colorectal, breast and prostate cancers. Only original research studies with prospective cohort design were included in the review
- Studies specifically related to seafood or milk product intake (considered as separate questions)
- Studies that reported on animal protein intake as a component of a dietary pattern and not as an individual variable
- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: (Animal protein* OR meat[mh] OR "Egg Proteins, Dietary"[mh] OR "Fish Proteins"[mh]) AND ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "overweight"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mh:NoExp] OR “heart diseases”[mh] OR "Coronary Disease"[Mesh] OR “blood pressure”[mh] OR “chronic disease”[mh] OR obesity[mh] OR "Body Weights and Measures"[mh] OR "Colorectal Neoplasms"[mesh])
  (Animal protein* OR meat[mh] OR "Egg Proteins, Dietary"[mh] OR "Fish Proteins"[mh] OR seafood[majr] OR crustacea[majr]) AND (systematic[sb] OR Meta-Analysis[ptyp] OR "Cohort Studies"[Mesh]) AND ("Prostatic Neoplasms"[Mesh] OR "Breast Neoplasms"[Mesh])
  eggs [mh] AND ("Diabetes Mellitus, Type 2"[majr] OR "metabolic syndrome X"[majr] OR "overweight"[majr] OR "hypertension"[majr] OR

"dyslipidemias"[majr] OR "cardiovascular diseases"[majr:NoExp] OR “heart diseases”[majr] OR "Coronary Disease"[Mesh] OR “blood pressure”[majr] OR “chronic disease”[majr] OR obesity[majr] OR "Body Weights and Measures"[majr])
(Note: "Cohort Studies"[Mesh]) includes prospective studies)

Date searched: 09/01/2009; update 09/18/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 771
- Total articles identified to review from electronic databases: 166
- Articles identified via handsearch or other means: 2
- Number of Primary Articles Identified: 47
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 47
- Number of Articles Reviewed but Excluded: 121

Included articles (References)

What is the relationship between the intake of animal protein products and cardiovascular disease?

1. Djoussé L, Gaziano JM. Egg consumption in relation to cardiovascular disease and mortality: the Physicians' Health Study.*Am J Clin Nutr.* 2008 Apr; 87(4): 964-969. PMID: 18400720; PMCID: PMC2386667.
2. Halton TL, Willett WC, Liu S, Manson JE, Albert CM, Rexrode K, Hu FB. Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med.* 2006 Nov 9; 355(19): 1, 991-2, 002. PMID: 17093250.
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What is the relationship between the intake of animal protein products and blood pressure?

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1. Alonso A, Beunza JJ, Bes-Rastrollo M, Pajares RM, Martínez-González MA. Vegetable protein and fiber from cereal are inversely associated with the risk of hypertension in a Spanish cohort. *Arch Med Res*. 2006 Aug; 37(6): 778-786. PMID: 16824939.
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What is the relationship between the intake of animal protein products and colorectal cancer?

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Excluded articles

Article	Reason for Exclusion
Alexander DD, Cushing CA, Lowe KA, Sceurman B, Roberts MA. Meta-analysis of animal fat or animal protein intake and colorectal cancer. *Am J Clin Nutr.* 2009 May; 89(5): 1, 402-1, 409. Epub 2009 Mar 4. PMID: 19261724.	Study design is meta-analysis (colorectal cancer).
Appleby PN, Davey GK, Key TJ. Hypertension and blood pressure among meat eaters, fish eaters, vegetarians and vegans in EPIC-Oxford. *Public Health Nutr.* 2002 Oct; 5(5): 645-654. PMID: 12372158.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Augustsson K, Michaud DS, Rimm EB, Leitzmann MF, Stampfer MJ, Willett WC, Giovannucci E. A prospective study of intake of fish and marine fatty acids and prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2003 Jan; 12(1): 64-67. PMID: 12540506.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Azadbakht L, Esmaillzadeh A. Red meat intake is associated with metabolic syndrome and the plasma C-reactive protein concentration in women. *J Nutr.* 2009 Feb; 139(2): 335-339. Epub 2008 Dec 11. PMID: 19074209.	Does not answer question: Examined relationship between red meat intake and metabolic syndrome.

Balder HF, Vogel J, Jansen MC, Weijenberg MP, van den Brandt PA, Westenbrink S, van der Meer R, Goldbohm RA. Heme and chlorophyll intake and risk of colorectal cancer in the Netherlands cohort study. *Cancer Epidemiol Biomarkers Prev.* 2006 Apr; 15(4): 717-725. PMID: 16614114.	Does not answer question: Examined relationship between heme and chlorophyll intake and colorectal cancer.
Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: A systematic literature review and meta-analysis. *Cancer Causes Control.* 2007 Nov; 18(9): 967-988. Epub 2007 Jul 19. Review. PMID: 17638104; PMCID: PMC2592095.	Does not include colorectal, breast, or prostate cancer in analyses.
Barraj L, Tran N, Mink P. A comparison of egg consumption with other modifiable coronary heart disease lifestyle risk factors: a relative risk apportionment study. *Risk Anal*. 2009 Mar; 29(3): 401-415. Epub 2008 Nov 4. PMID: 19000074.	Does not answer question: Used risk apportionment approach to estimate contribution of egg intake to coronary heart disease (CHD) risk at the population level.
Benassi-Evans B, Clifton PM, Noakes M, Keogh JB, Fenech M. High protein-high red meat versus high carbohydrate weight loss diets do not differ in effect on genome stability and cell death in lymphocytes of overweight men. *Mutagenesis.* 2009 May; 24(3): 271-277. Epub 2009 Mar 5. PMID: 19264840.	Does not include animal protein product intake in analyses.
Brink M, Weijenberg MP, de Goeij AF, Roemen GM, Lentjes MH, de Bruïne AP, Goldbohm RA, van den Brandt PA. Meat consumption and K-ras mutations in sporadic colon and rectal cancer in The Netherlands Cohort Study. *Br J Cancer.* 2005 Apr 11; 92(7): 1, 310-1, 320. PMID: 15812479.	Study design is case-cohort.
Cade JE, Burley VJ, Greenwood DC; UK Women's Cohort Study Steering Group. The UK Women's Cohort Study: Comparison of vegetarians, fish-eaters and meat-eaters. *Public Health Nutr.* 2004 Oct; 7(7): 871-878. PMID: 15482612.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Chan AT, Tranah GJ, Giovannucci EL, Willett WC, Hunter DJ, Fuchs CS. Prospective study of N-acetyltransferase-2 genotypes, meat intake, smoking and risk of colorectal cancer. *Int J Cancer.* 2005 Jul 1; 115(4): 648-652. PMID: 15700302.	Study design is case-control study (colorectal cancer).
Chavarro JE, Stampfer MJ, Hall MN, Sesso HD, Ma J. A 22-y prospective study of fish intake in relation to prostate cancer incidence and mortality. *Am J Clin Nutr.* 2008 Nov; 88(5): 1, 297-1, 303. PMID: 18996866.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Chrysohoou C, Panagiotakos DB, Pitsavos C, Skoumas J, Krinos X, Chloptsios Y, Nikolaou V, Stefanadis C. Long-term fish consumption is associated with protection against arrhythmia in healthy persons in a Mediterranean region: The ATTICA study. *Am J Clin Nutr.* 2007 May; 85(5): 1, 385-1, 391. PMID: 17490977.	Does not answer question: Examined relationship between fish intake and arrhythmia.

Cotterchio M, Boucher BA, Manno M, Gallinger S, Okey AB, Harper PA. Red meat intake, doneness, polymorphisms in genes that encode carcinogen-metabolizing enzymes, and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2008 Nov; 17(11): 3, 098-3, 107. PMID: 18990750.	Study design is case-control (colorectal cancer).
Crowe FL, Key TJ, Appleby PN, Travis RC, Overvad K, Jakobsen MU, Johnsen NF, Tjønneland A, Linseisen J, Rohrmann S, Boeing H, Pischon T, Trichopoulou A, Lagiou P, Trichopoulos D, Sacerdote C, Palli D, Tumino R, Krogh V, Bueno-de-Mesquita HB, Kiemeney LA, Chirlaque MD, Ardanaz E, Sánchez MJ, Larrañaga N, González CA, Quirós JR, Manjer J, Wirfält E, Stattin P, Hallmans G, Khaw KT, Bingham S, Ferrari P, Slimani N, Jenab M, Riboli E. Dietary fat intake and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr.* 2008 May; 87(5): 1, 405-1, 413. PMID: 18469265.	Does not answer question: Examined relationship between animal fat intake and prostate cancer.
Dallongeville J, Yarnell J, Ducimetière P, Arveiler D, Ferrières J, Montaye M, Luc G, Evans A, Bingham A, Hass B, Ruidavets JB, Amouyel P. Fish consumption is associated with lower heart rates.*Circulation.* 2003 Aug 19; 108(7): 820-825. Epub 2003 Aug 11. PMID: 12912821.	Does not answer question: Examined relationship between fish intake and heart rates.
Davey GK, Spencer EA, Appleby PN, Allen NE, Knox KH, Key TJ. EPIC-Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33 883 meat-eaters and 31 546 non meat-eaters in the UK. *Public Health Nutr.* 2003 May; 6(3): 259-269. PMID: 12740075.	Does not include health outcomes in analyses.
de Mello VD, Zelmanovitz T, Perassolo MS, Azevedo MJ, Gross JL. Withdrawal of red meat from the usual diet reduces albuminuria and improves serum fatty acid profile in type 2 diabetes patients with macroalbuminuria. *Am J Clin Nutr*. 2006 May; 83(5): 1, 032-1, 038. PMID: 16685043.	Participants diagnosed with type 2 diabetes (T2D).
Dixon LB, Balder HF, Virtanen MJ, Rashidkhani B, Männistö S, Krogh V, van Den Brandt PA, Hartman AM, Pietinen P, Tan F, Virtamo J, Wolk A, Goldbohm RA. Dietary patterns associated with colon and rectal cancer: results from the Dietary Patterns and Cancer (DIETSCAN) Project. *Am J Clin Nutr.* 2004 Oct; 80(4): 1, 003-1, 011. PMID: 15447912.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Djoussé L, Gaziano JM. Egg consumption and risk of heart failure in the Physicians' Health Study. *Circulation.* 2008 Jan 29; 117(4): 512-516. Epub 2008 Jan 14. PMID: 18195171; PMCID: PMC2706003.	Does not answer question: Examined relationship between egg consumption and heart failure.
Egeberg R, Olsen A, Autrup H, Christensen J, Stripp C, Tetens I, Overvad K, Tjønneland A. Meat consumption, N-acetyl transferase 1 and 2 polymorphism and risk of breast cancer in Danish postmenopausal women. *Eur J Cancer Prev.* 2008 Feb; 17(1): 39-47. PMID: 18090909.	Study design is nested case-control study (breast cancer).
Eichholzer M, Bisig B. Daily consumption of (red) meat or meat products in Switzerland: Results of the 1992/93 Swiss Health Survey. *Eur J Clin Nutr.* 2000 Feb; 54(2): 136-142. PMID: 10694784.	Does not include health outcomes in analyses.

Elliott P, Stamler J, Dyer AR, Appel L, Dennis B, Kesteloot H, Ueshima H, Okayama A, Chan Q, Garside DB, Zhou B. Association between protein intake and blood pressure: The INTERMAP Study. *Arch Intern Med.* 2006 Jan 9; 166(1): 79-87. PMID: 16401814.	Study design is cross-sectional epidemiological study.
Engeset D, Andersen V, Hjartåker A, Lund E. Consumption of fish and risk of colon cancer in the Norwegian Women and Cancer (NOWAC) study. *Br J Nutr.* 2007 Sep; 98(3): 576-582. Epub 2007 Apr 10. Erratum in: *Br J Nutr.* 2008 Mar; 99(3): 696. PMID: 17419892.	Does not answer question: Examined relationship between fish intake and colon cancer.
Erkkilä AT, Lichtenstein AH, Mozaffarian D, Herrington DM. Fish intake is associated with a reduced progression of coronary artery atherosclerosis in postmenopausal women with coronary artery disease. *Am J Clin Nutr.* 2004 Sep; 80(3): 626-632. PMID: 15321802.	Participants diagnosed with CHD.
Erkkilä AT, Schwab US, de Mello VD, Lappalainen T, Mussalo H, Lehto S, Kemi V, Lamberg-Allardt C, Uusitupa MI. Effects of fatty and lean fish intake on blood pressure in subjects with coronary heart disease using multiple medications. *Eur J Nutr.* 2008 Sep; 47(6): 319-328. Epub 2008 Jul 29. PMID: 18665413.	Participants diagnosed with CHD.
Faramawi MF, Johnson E, Fry MW, Sall M, Zhou Y. Consumption of different types of meat and the risk of renal cancer: Meta-analysis of case-control studies. *Cancer Causes Control.* 2007 Mar; 18(2): 125-133. Epub 2007 Jan 22. Erratum in: *Cancer Causes Control.* 2007 Jun; 18 (5): 581. Yi, Zhou [corrected to Zhou, Yi]. PMID: 17242980.	Does not include colorectal, breast or prostate cancer in analyses.
Ferrucci LM, Sinha R, Graubard BI, Mayne ST, Ma X, Schatzkin A, Schoenfeld PS, Cash BD, Flood A, Cross AJ. Dietary meat intake in relation to colorectal adenoma in asymptomatic women. *Am J Gastroenterol.* 2009 May; 104(5): 1, 231-1, 140. Epub 2009 Apr 14. PMID: 19367270.	Study design is case-control study (colorectal cancer).
Geelen A, Schouten JM, Kamphuis C, Stam BE, Burema J, Renkema JM, Bakker EJ, van't Veer P, Kampman E. Fish consumption, n-3 fatty acids, and colorectal cancer: a meta-analysis of prospective cohort studies. *Am J Epidemiol*. 2007 Nov 15; 166(10): 1, 116-1, 125. Epub 2007 Sep 6. PMID: 17823383.	Study design is meta-analysis (colorectal cancer).
Gillum RF, Mussolino ME, Madans JH. Fish consumption and hypertension incidence in African Americans and whites: The NHANES I Epidemiologic Follow-up Study. *J Natl Med Assoc.* 2001 Apr; 93(4): 124-128. PMID: 12653399; PMCID: PMC2593988.	Does not answer question: Examined relationship between fish intake and hypertension (HTN).
Goldin BR, Brauner E, Adlercreutz H, Ausman LM, Lichtenstein AH. Hormonal response to diets high in soy or animal protein without and with isoflavones in moderately hypercholesterolemic subjects. *Nutr Cancer.* 2005; 51(1): 1-6. PMID: 15749623.	Does not answer question: Examined hormonal response to diets high in soy or animal protein.
Gonzalez CA, Riboli E. Diet and cancer prevention: Where we are, where we are going. Nutr Cancer. 2006; 56(2): 225-31. Review. PMID: 17474869.	Study design is narrative review.

Grillenberger M, Neumann CG, Murphy SP, Bwibo NO, Weiss RE, Jiang L, Hautvast JG, West CE. Intake of micronutrients high in animal-source foods is associated with better growth in rural Kenyan school children. *Br J Nutr*. 2006 Feb; 95(2): 379-390. PMID: 16469157.	Study population not from a developed country as defined by the Human Development Index (2009).
Gross JL, Zelmanovitz T, Moulin CC, De Mello V, Perassolo M, Leitão C, Hoefel A, Paggi A, Azevedo MJ. Effect of a chicken-based diet on renal function and lipid profile in patients with type 2 diabetes: a randomized crossover trial. *Diabetes Care.* 2002 Apr; 25(4): 645-651. PMID: 11919119.	Participants diagnosed with T2D.
Günther AL, Remer T, Kroke A, Buyken AE. Early protein intake and later obesity risk: which protein sources at which time points throughout infancy and childhood are important for body mass index and body fat percentage at 7 y of age? *Am J Clin Nutr.* 2007 Dec; 86(6): 1, 765-1, 772. PMID: 18065597.	Does not answer question: Examined protein intake during infancy and childhood and body weight outcomes at age seven years.
He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, Greenland P. Accumulated evidence on fish consumption and coronary heart disease mortality: A meta-analysis of cohort studies. *Circulation.* 2004 Jun 8; 109(22): 2, 705-2, 711. PMID: 15184295.	Does not answer question: examined relationship between fish intake and CHD.
High red-meat intake, obesity linked to cancer.*Health News.* 2002 Feb; 8(2): 9. PMID: 11862847.	News article.
Hodgson JM, Burke V, Beilin LJ, Puddey IB. Partial substitution of carbohydrate intake with protein intake from lean red meat lowers blood pressure in hypertensive persons. *Am J Clin Nutr.* 2006 Apr; 83(4): 780-787. PMID: 16600928.	Participants diagnosed with HTN.
Hu FB, Manson JE, Willett WC. Types of dietary fat and risk of coronary heart disease: a critical review.*J Am Coll Nutr.* 2001 Feb; 20(1): 5-19. Review. PMID: 11293467.	Study design is narrative review.
Huncharek M, Kupelnick B, Wheeler L. Dietary cured meat and the risk of adult glioma: A meta-analysis of nine observational studies. *J Environ Pathol Toxicol* Oncol. 2003; 22(2): 129-137. PMID: 14533876.	Does not include colorectal, breast, or prostate cancer in analyses.
Huncharek M, Kupelnick B. A meta-analysis of maternal cured meat consumption during pregnancy and the risk of childhood brain tumors. *Neuroepidemiology.* 2004 Jan-Apr; 23(1-2): 78-84. PMID: 14739572.	Does not include colorectal, breast, or prostate cancer in analyses.
Hunninghake DB, Maki KC, Kwiterovich PO Jr, Davidson MH, Dicklin MR, Kafonek SD. Incorporation of lean red meat into a National Cholesterol Education Program Step I diet: A long-term, randomized clinical trial in free-living persons with hypercholesterolemia. *J Am Coll Nutr.* 2000 Jun; 19(3): 351-360. PMID: 10872897.	Participants diagnosed with hypercholesterolemia.
Iso H, Sato S, Kitamura A, Naito Y, Shimamoto T, Komachi Y. Fat and protein intakes and risk of intraparenchymal hemorrhage among middle-aged Japanese. *Am J Epidemiol.* 2003 Jan 1; 157(1): 32-39. Erratum in: *Am J Epidemiol.* 2004 Feb 1; 159(3): 318. PMID: 12505888.	Does not answer question: examined relationship between protein intake and intraparenchymal hemorrhage.

Järvinen R, Knekt P, Rissanen H, Reunanen A. Intake of fish and long-chain n-3 fatty acids and the risk of coronary heart mortality in men and women. *Br J Nutr.* 2006 Apr; 95(4): 824-829. PMID: 16571163.	Does not answer question: examined relationship between fish intake and CHD.
Jenkins DJ, Wong JM, Kendall CW, Esfahani A, Ng VW, Leong TC, Faulkner DA, Vidgen E, Greaves KA, Paul G, Singer W. The effect of a plant-based low-carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. *Arch Intern Med.* 2009 Jun 8; 169(11): 1, 046-1, 054. PMID: 19506174.	Participants diagnosed hyperlipidemia.
Joshi AD, Corral R, Siegmund KD, Haile RW, Le Marchand L, Martínez ME, Ahnen DJ, Sandler RS, Lance P, Stern MC. Red meat and poultry intake, polymorphisms in the nucleotide excision repair and mismatch repair pathways and colorectal cancer risk. 2009 Mar; 30(3): 472-479. Epub 2008 Nov 24. PMID: 19029193; PMCID: PMC2722151.	Study design is case-control family-based study (colorectal cancer).
Kabat GC, Miller AB, Jain M, Rohan TE. A cohort study of dietary iron and heme iron intake and risk of colorectal cancer in women. *Br J Cancer.* 2007 Jul 2; 97 (1): 118-122. Epub 2007 Jun 5. Erratum in: *Br J Cancer.* 2007 Dec 3; 97(11): 1, 600. PMID: 77551493; PMCID: PMC2359661.	Does not answer question: examined relationship between iron and heme iron intake and colorectal cancer.
König A, Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, Lawrence RS, Savitz DA, Teutsch SM. A quantitative analysis of fish consumption and coronary heart disease mortality. *Am J Prev Med.* 2005 Nov; 29(4): 335-346. PMID: 16242600.	Does not answer question: examined relationship between fish intake and CHD.
Kono S. Secular trend of colon cancer incidence and mortality in relation to fat and meat intake in Japan. *Eur J Cancer Prev*. 2004 Apr; 13(2): 127-132. PMID: 15100579.	Study design is non-comparative, correlational study.
Kontogianni MD, Panagiotakos DB, Pitsavos C, Chrysohoou C, Stefanadis C. Relationship between meat intake and the development of acute coronary syndromes: the CARDIO2000 case-control study. *Eur J Clin Nutr.* 2008 Feb; 62(2): 171-177. Epub 2007 Mar 14. PMID: 17356558.	Does not include health outcome of interest in analyses.
Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation*. 2002 Nov 19; 106(21): 2, 747-2, 757. Erratum in: *Circulation.* 2003 Jan 28; 107 (3): 512. PMID: 12438303.	Expert opinion.
Larsson SC, Orsini N, Wolk A. Processed meat consumption and stomach cancer risk: A meta-analysis. *J Natl Cancer Inst.* 2006 Aug 2; 98(15): 1, 078-1, 087. PMID: 16882945.	Does not include colorectal, breast or prostate cancer in analyses.
Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: A meta-analysis of prospective studies. *Int J Cancer.* 2006 Dec 1; 119(11): 2, 657-2, 664. PMID: 16991129.	Study design is meta-analysis (colorectal cancer).

Lee JE, Spiegelman D, Hunter DJ, Albanes D, Bernstein L, van den Brandt PA, Buring JE, Cho E, English DR, Freudenheim JL, Giles GG, Graham S, Horn-Ross PL, Håkansson N, Leitzmann MF, Männistö S, McCullough ML, Miller AB, Parker AS, Rohan TE, Schatzkin A, Schouten LJ, Sweeney C, Willett WC, Wolk A, Zhang SM, Smith-Warner SA. Fat, protein, and meat consumption and renal cell cancer risk: A pooled analysis of 13 prospective studies. *J Natl Cancer Inst*. 2008 Dec 3; 100(23): 1, 695-1, 706. Epub 2008 Nov 25. PMID: 19033572; PMCID: PMC2727138.	Does not include colorectal, breast or prostate cancer in analyses.
Levitan EB, Wolk A, Mittleman MA. Fish consumption, marine omega-3 fatty acids, and incidence of heart failure: A population-based prospective study of middle-aged and elderly men. *Eur Heart J.* 2009 Jun; 30(12): 1, 495-1, 500. Epub 2009 Apr 21. PMID: 19383731; PMCID: PMC2695952.	Does not answer question: Examined relationship between fish intake and heart failure.
Lichtenstein AH, Jalbert SM, Adlercreutz H, Goldin BR, Rasmussen H, Schaefer EJ, Ausman LM. Lipoprotein response to diets high in soy or animal protein with and without isoflavones in moderately hypercholesterolemic subjects. *Arterioscler Thromb Vasc Biol.* 2002 Nov 1; 22(11): 1, 852-1, 858. PMID: 12426215.	Participants diagnosed with hypercholesterolemia.
Linseisen J, Kesse E, Slimani N; EPIC Working Group on Dietary Pattern, Subgroup Meat. Meat consumption in Europe: Results from the EPIC study.*IARC Sci Publ*. 2002; 156: 211-212. PMID: 12484168.	Does not include health outcomes in analyses.
Liu L, Ikeda K, Yamori Y; WHO-CARDIAC Study Group. Inverse relationship between urinary markers of animal protein intake and blood pressure in Chinese: results from the WHO Cardiovascular Diseases and Alimentary Comparison (CARDIAC) Study. *Int J Epidemiol*. 2002 Feb; 31(1): 227-233. PMID: 11914325.	Does not answer question: Examined the relationship between urinary excretion of 3-methylhistidine (as marker of animal protein intake) and blood pressure (BP).
Lucey AJ, Paschos GK, Cashman KD, Martínéz JA, Thorsdottir I, Kiely M. Influence of moderate energy restriction and seafood consumption on bone turnover in overweight young adults. *Am J Clin Nutr.* 2008 Apr; 87(4): 1, 045-1, 052. PMID: 18400730.	Does not include health outcome of interest in analyses.
Lüchtenborg M, Weijenberg MP, de Goeij AF, Wark PA, Brink M, Roemen GM, Lentjes MH, de Bruïne AP, Goldbohm RA, van 't Veer P, van den Brandt PA. Meat and fish consumption, APC gene mutations and hMLH1 expression in colon and rectal cancer: A prospective cohort study (The Netherlands). *Cancer Causes Control.* 2005 Nov; 16(9): 1, 041-1, 054. PMID: 16184469.	Results reported based on the same dataset as Brink, 2005.
Mamo JC, James AP, Soares MJ, Griffiths DG, Purcell K, Schwenke JL. A low-protein diet exacerbates postprandial chylomicron concentration in moderately dyslipidaemic subjects in comparison to a lean red meat protein-enriched diet. *Eur J Clin Nutr.* 2005 Oct; 59(10): 1, 142-1, 148. PMID: 16015257.	Does not answer question: Examined relationship between protein intake and postprandial response.

Männistö S, Dixon LB, Balder HF, Virtanen MJ, Krogh V, Khani BR, Berrino F, van den Brandt PA, Hartman AM, Pietinen P, Tan F, Wolk A, Goldbohm RA. Dietary patterns and breast cancer risk: Results from three cohort studies in the DIETSCAN project. *Cancer Causes Control.* 2005 Aug; 16(6): 725-733. PMID: 16049811.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Marques-Vidal P, Ravasco P, Ermelinda Camilo M. Foodstuffs and colorectal cancer risk: A review. *Clin Nutr.* 2006 Feb; 25(1): 14-36. Epub 2005 Nov 14. Review. PMID: 16290272.	Study design is systematic review (colorectal cancer).
Matheson EM, Mainous AG 3rd, Hill EG, Carnemolla MA. Shellfish consumption and risk of coronary heart disease. *J Am Diet Assoc.* 2009 Aug; 109(8): 1, 422-1, 426. PMID: 19631050.	Does not answer question: Examined relationship between shellfish intake and CHD.
Matthan NR, Jalbert SM, Ausman LM, Kuvin JT, Karas RH, Lichtenstein AH. Effect of soy protein from differently processed products on cardiovascular disease risk factors and vascular endothelial function in hypercholesterolemic subjects. *Am J Clin Nutr.* 2007 Apr; 85(4): 960-966. Erratum in: *Am J Clin Nutr.* 2007 Aug; 86(2): 525. PMID: 17413093.	Participants were hypercholesterolemic.
McCarty MF. The origins of western obesity: A role for animal protein? *Med Hypotheses.* 2000 Mar; 54(3): 488-494. PMID: 10783494.	Study design is narrative review.
McNaughton SA, Mishra GD, Stephen AM, Wadsworth ME. Dietary patterns throughout adult life are associated with body mass index, waist circumference, blood pressure, and red cell folate. *J Nutr.* 2007 Jan; 137(1): 99-105. PMID: 17182808.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Melanson K, Gootman J, Myrdal A, Kline G, Rippe JM. Weight loss and total lipid profile changes in overweight women consuming beef or chicken as the primary protein source. *Nutrition.* 2003 May; 19(5): 409-414. PMID: 12714091.	Dropout rate is higher than inclusion criteria.
Missmer SA, Smith-Warner SA, Spiegelman D, Yaun SS, Adami HO, Beeson WL, van den Brandt PA, Fraser GE, Freudenheim JL, Goldbohm RA, Graham S, Kushi LH, Miller AB, Potter JD, Rohan TE, Speizer FE, Toniolo P, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Hunter DJ. Meat and dairy food consumption and breast cancer: A pooled analysis of cohort studies. *Int J Epidemiol.* 2002 Feb; 31(1): 78-85. PMID: 11914299.	Study design is meta-analysis (breast cancer).
Möllsten AV, Dahlquist GG, Stattin EL, Rudberg S. Higher intakes of fish protein are related to a lower risk of microalbuminuria in young Swedish type 1 diabetic patients. *Diabetes Care.* 2001 May; 24(5): 805-810. PMID: 11347734.	Participants diagnosed with T2D.
Mortensen LS, Hartvigsen ML, Brader LJ, Astrup A, Schrezenmeir J, Holst JJ, Thomsen C, Hermansen K. Differential effects of protein quality on postprandial lipemia in response to a fat-rich meal in type 2 diabetes: comparison of whey, casein, gluten, and cod protein. *Am J Clin Nutr.* 2009 Jul; 90(1): 41-48. Epub 2009 May 20. PMID: 19458012.	Participants diagnosed with T2D.

Mozaffarian D, Psaty BM, Rimm EB, Lemaitre RN, Burke GL, Lyles MF, Lefkowitz D, Siscovick DS. Fish intake and risk of incident atrial fibrillation. *Circulation.* 2004 Jul 27; 110(4): 368-373. Epub 2004 Jul 19. PMID: 15262826; PMCID: PMC1201400.	Does not answer question: Examined relationship between fish intake and atrial fibrillation.
Nagata C, Shimizu H, Kametani M, Takeyama N, Ohnuma T, Matsushita S. Diet and colorectal adenoma in Japanese males and females. *Dis Colon Rectum.* 2001 Jan; 44(1): 105-111. PMID: 11805576.	Study design is case-control study (colorectal cancer).
Nenseter MS, Østerud B, Larsen T, Strøm E, Bergei C, Hewitt S, Holven KB, Hagve TA, Mjøs SA, Solvang M, Pettersen J, Opstvedt J, Ose L. Effect of Norwegian fish powder on risk factors for coronary heart disease among hypercholesterolemic individuals. *Nutr Metab Cardiovasc Dis.* 2000 Dec; 10(6): 323-330. PMID: 11302007.	Did not answer question: Examined relationship between fish powder and CHD.
Nettleton JA, Steffen LM, Loehr LR, Rosamond WD, Folsom AR. Incident heart failure is associated with lower whole-grain intake and greater high-fat dairy and egg intake in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Diet Assoc*. 2008 Nov; 108(11): 1, 881-1, 887. PMID: 18954578; PMCID: PMC2650810.	Does not answer question: Examined relationship between egg intake and heart failure.
Nkondjock A, Receveur O. Fish-seafood consumption, obesity, and risk of type 2 diabetes: an ecological study. *Diabetes Metab.* 2003 Dec; 29(6): 635-642. PMID: 14707894.	Does not answer question: Examined relationship between fish intake and T2D.
Norat T, Lukanova A, Ferrari P, Riboli E. Meat consumption and colorectal cancer risk: Dose-response meta-analysis of epidemiological studies. *Int J Cancer.* 2002 Mar 10; 98(2): 241-256. PMID: 11857415.	Study design is meta-analysis (colorectal cancer).
Norat T, Riboli E. Meat consumption and colorectal cancer: A review of epidemiologic evidence. *Nutr Rev.* 2001 Feb; 59(2): 37-47. Review. PMID: 11310774.	Study design is meta-analysis (colorectal cancer).
Norat T, Riboli E. Meat consumption and colorectal cancer: A review of epidemiologic evidence. *Nutr Rev.* 2001 Feb; 59(2): 37-47. Review. PMID: 11310774.	Study design is narrative review (colorectal cancer).
Nowson CA, Wattanapenpaiboon N, Pachett A. Low-sodium Dietary Approaches to Stop Hypertension-type diet including lean red meat lowers blood pressure in postmenopausal women. *Nutr Res.* 2009 Jan; 29(1): 8-18. PMID: 19185772.	Does not include animal protein products in analyses.
Olmedilla-Alonso B, Granado-Lorencio F, Herrero-Barbudo C, Blanco-Navarro I, Blázquez-García S, Pérez-Sacristán B. Consumption of restructured meat products with added walnuts has a cholesterol-lowering effect in subjects at high cardiovascular risk: a randomised, crossover, placebo-controlled study. *J Am Coll Nutr.* 2008 Apr; 27(2): 342-348. PMID: 18689569.	Does not answer question: Examined effect of restructured meat product on cholesterol.
Panagiotakos DB, Pitsavos C, Zampelas A, Chrysohoou C, Griffin BA, Stefanadis C, Toutouzas P. Fish consumption and the risk of developing acute coronary syndromes: The CARDIO2000 study. *Int J Cardiol.* 2005 Jul 20; 102(3): 403-409. PMID: 16004884.	Does not answer question: Examined relationship between fish intake and health outcomes.

Panagiotakos DB, Zeimbekis A, Boutziouka V, Economou M, Kourlaba G, Toutouzas P, Polychronopoulos E. Long-term fish intake is associated with better lipid profile, arterial blood pressure, and blood glucose levels in elderly people from Mediterranean islands (MEDIS epidemiological study). *Med Sci Monit.* 2007 Jul; 13(7): CR307-CR312. PMID: 17599024.	Does not answer question: Examined relationship between fish intake and health outcomes.
Pham TM, Fujino Y, Kubo T, Ide R, Tokui N, Mizoue T, Ogimoto I, Matsuda S, Yoshimura T. Fish intake and the risk of fatal prostate cancer: Findings from a cohort study in Japan. *Public Health Nutr.* 2009 May; 12(5): 609-613. Epub 2008 Jul 29. PMID: 18664313.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Pieniak Z, Verbeke W, Perez-Cueto F, Brunsø K, De Henauw S. Fish consumption and its motives in households with versus without self-reported medical history of CVD: A consumer survey from five European countries. *BMC Public Health.* 2008 Sep 10; 8: 306. PMID: 18783593; PMCID: PMC2556335.	Does not include health outcomes in analyses.
Processed meat consumption linked to type 2 diabetes. *Nephrol News Issues.* 2002 Apr; 16(5): 68-69. PMID: 11962157.	News article.
Ramel A, Parra D, Martinéz JA, Kiely M, Thorsdottir I. Effects of seafood consumption and weight loss on fasting leptin and ghrelin concentrations in overweight and obese European young adults. *Eur J Nutr.* 2009 Mar; 48(2): 107-114. Epub 2009 Jan 13. PMID: 19142567.	Does not answer question: Examined relationship between seafood and leptin and ghrelin concentrations.
Rosell M, Appleby P, Spencer E, Key T. Weight gain over 5 years in 21, 966 meat-eating, fish-eating, vegetarian, and vegan men and women in EPIC-Oxford. *Int J Obes (Lond).* 2006 Sep; 30(9): 1, 389-1, 396. Epub 2006 Mar 14. PMID: 16534521.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Sandhu MS, White IR, McPherson K. Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: A meta-analytical approach. *Cancer Epidemiol Biomarkers Prev.* 2001 May; 10(5): 439-446. PMID: 11352852.	Study design is systematic review/meta-analysis (colorectal cancer).
Santarelli RL, Pierre F, Corpet DE. Processed meat and colorectal cancer: A review of epidemiologic and experimental evidence. *Nutr Cancer.* 2008; 60(2): 131-144. Review. PMID: 18444144; PMCID: PMC2661797.	Study design is narrative review.
Satia JA, Tseng M, Galanko JA, Martin C, Sandler RS. Dietary patterns and colon cancer risk in Whites and African Americans in the North Carolina Colon Cancer Study. *Nutr Cancer.* 2009; 61(2): 179-193. PMID: 19235034.	Study design is case-control study (colon cancer).
Schulz M, Hoffmann K, Weikert C, Nöthlings U, Schulze MB, Boeing H. Identification of a dietary pattern characterized by high-fat food choices associated with increased risk of breast cancer: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Br J Nutr.* 2008 Nov; 100(5): 942-946. PMID: 18377685.	Does not answer question: Examines relationship between high fat foods and breast cancer.

Seierstad SL, Seljeflot I, Johansen O, Hansen R, Haugen M, Rosenlund G, Frøyland L, Arnesen H. Dietary intake of differently fed salmon: The influence on markers of human atherosclerosis. *Eur J Clin Invest.* 2005 Jan; 35(1): 52-59. PMID: 15638820.	Participants diagnosed with T2D.
Shiell AW, Campbell-Brown M, Haselden S, Robinson S, Godfrey KM, Barker DJ. High-meat, low-carbohydrate diet in pregnancy: Relation to adult blood pressure in the offspring. *Hypertension*. 2001 Dec 1; 38(6): 1, 282-1, 288. PMID: 11751704.	Does not answer question: Examines relationship between dietary intake during pregnancy and health of adult offspring.
Sieri S, Krogh V, Muti P, Micheli A, Pala V, Crosignani P, Berrino F. Fat and protein intake and subsequent breast cancer risk in postmenopausal women. *Nutr Cancer.* 2002; 42(1): 10-17. PMID: 12235640.	Study design is case-control study (breast cancer).
Skjelbred CF, Saebø M, Hjartåker A, Grotmol T, Hansteen IL, Tveit KM, Hoff G, Kure EH. Meat, vegetables and genetic polymorphisms and the risk of colorectal carcinomas and adenomas. *BMC Cancer*. 2007 Dec 19; 7: 228. PMID: 18093316; PMCID: PMC2228310.	Study design is case-control study (colorectal cancer).
Smith DR, Wood R, Tseng S, Smith SB. Increased beef consumption increases apolipoprotein A-I but not serum cholesterol of mildly hypercholesterolemic men with different levels of habitual beef intake. *Exp Biol Med (Maywood).* 2002 Apr; 227(4): 266-275. PMID: 11910049.	Participants diagnosed with mild hypercholesterolemia.
SoRelle R. Fish and long-chain omega-3 fatty acids could be lifesavers for diabetic women. *Circulation.* 2003 Apr 22; 107(15): e9, 033-9, 035. PMID: 12707254.	Participants were diagnosed with diabetes.
Sørensen M, Autrup H, Olsen A, Tjønneland A, Overvad K, Raaschou-Nielsen O. Prospective study of NAT1 and NAT2 polymorphisms, tobacco smoking and meat consumption and risk of colorectal cancer. *Cancer Lett.* 2008 Aug 8; 266(2): 186-193. Epub 2008 Mar 26. PMID: 18372103.	Study design is case-control study (colorectal cancer).
Spencer EA, Appleby PN, Davey GK, Key TJ. Diet and body mass index in 38000 EPIC-Oxford meat-eaters, fish-eaters, vegetarians and vegans. *Int J Obes Relat Metab Disord.* 2003 Jun; 27(6): 728-734. PMID: 12833118.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Stewart JW, Kaplan ML, Beitz DC. Pork with a high content of polyunsaturated fatty acids lowers LDL cholesterol in women. *Am J Clin Nutr.* 2001 Aug; 74(2): 179-187. PMID: 11470718.	Intervention consisted of modified pork high in PUFAs.
Tanskanen A, Hibbeln JR, Tuomilehto J, Uutela A, Haukkala A, Viinamäki H, Lehtonen J, Vartiainen E. Fish consumption and depressive symptoms in the general population in Finland. *Psychiatr Serv.* 2001 Apr; 52(4): 529-531. PMID: 11274502.	Does not include health outcome of interest in analyses.
Tapola NS, Lyyra ML, Karvonen HM, Uusitupa MI, Sarkkinen ES. The effect of meat products enriched with plant sterols and minerals on serum lipids and blood pressure. *Int J Food Sci Nutr.* 2004 Aug; 55(5): 389-397. PMID: 15545047.	Intervention consisted of meat products enriched with plant sterols; participants diagnosed with hypercholesterolemia.

Tappel A. Heme of consumed red meat can act as a catalyst of oxidative damage and could initiate colon, breast and prostate cancers, heart disease and other diseases. *Med Hypotheses*. 2007; 68(3): 562-564. Epub 2006 Oct 11. PMID: 17045417.	Study design is narrative review.
Teixeira Rde C, Molina Mdel C, Zandonade E, Mill JG. Cardiovascular risk in vegetarians and omnivores: A comparative study. *Arq Bras Cardiol.* 2007 Oct; 89(4): 237-244. English, Portuguese. PMID: 17992380.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Terry P, Rohan TE, Wolk A, Maehle-Schmidt M, Magnusson C. Fish consumption and breast cancer risk. *Nutr Cancer.* 2002; 44(1): 1-6. PMID: 12672635.	Study design is case-control study (breast cancer).
Thorsdottir I, Birgisdottir B, Kiely M, Martinez J, Bandarra N. Fish consumption among young overweight European adults and compliance to varying seafood content in four weight loss intervention diets. *Public Health Nutr.* 2009 May; 12(5): 592-598. Epub 2008 Jun 19. PMID: 18561865.	Does not answer question: Examined compliance to eating varying types of seafood in weight loss intervention diets.
Thorsdottir I, Tomasson H, Gunnarsdottir I, Gisladottir E, Kiely M, Parra MD, Bandarra NM, Schaafsma G, Martinéz JA. Randomized trial of weight-loss-diets for young adults varying in fish and fish oil content. *Int J Obes* (Lond). 2007 Oct; 31(10): 1, 560-1, 566. Epub 2007 May 15. PMID: 17502874.	Does not answer question: Examined fish intake and weight loss.
Tiemersma EW, Kampman E, Bueno de Mesquita HB, Bunschoten A, van Schothorst EM, Kok FJ, Kromhout D. Meat consumption, cigarette smoking, and genetic susceptibility in the etiology of colorectal cancer: results from a Dutch prospective study. *Cancer Causes Control.* 2002 May; 13(4): 383-393. PMID: 12074508.	Study design is case-control study (colorectal cancer).
Timonen M, Horrobin D, Jokelainen J, Laitinen J, Herva A, Räsänen P. Fish consumption and depression: The Northern Finland 1966 birth cohort study. *J Affect Disord.* 2004 Nov 1; 82(3): 447-452. PMID: 15555697.	Does not include health outcome of interest in analyses.
Tzoulaki I, Brown IJ, Chan Q, Van Horn L, Ueshima H, Zhao L, Stamler J, Elliott P; International Collaborative Research Group on Macro-/Micronutrients and Blood Pressure. Relation of iron and red meat intake to blood pressure: cross sectional epidemiological study. *BMJ.* 2008 Jul 15; 337: a258. doi: 10.1136/bmj.a258. PMID: 18632704; PMCID: PMC2658466.	Study design is cross-sectional epidemiological study.
Umesawa M, Sato S, Imano H, Kitamura A, Shimamoto T, Yamagishi K, Tanigawa T, Iso H. Relations between protein intake and blood pressure in Japanese men and women: the Circulatory Risk in Communities Study (CIRCS). *Am J Clin Nutr.* 2009 Aug; 90(2): 377-384. Epub 2009 Jun 10. PMID: 19515740.	Study design is cross-sectional.
Varraso R, Jiang R, Barr RG, Willett WC, Camargo CA Jr. Prospective study of cured meats consumption and risk of chronic obstructive pulmonary disease in men. *Am J Epidemiol*. 2007 Dec 15; 166(12): 1, 438-1, 445. Epub 2007 Sep 4. PMID: 17785711; PMCID: PMC2573990.	Does not include health outcome of interest in analyses.

Virtanen JK, Mozaffarian D, Chiuve SE, Rimm EB. Fish consumption and risk of major chronic disease in men. *Am J Clin Nutr.* 2008 Dec; 88(6): 1, 618-1, 625. PubMed PMID: 19064523; PMCID: PMC2613199.	Does not answer question: Examined relationship between fish intake and chronic disease.
Wakai K, Tamakoshi K, Date C, Fukui M, Suzuki S, Lin Y, Niwa Y, Nishio K, Yatsuya H, Kondo T, Tokudome S, Yamamoto A, Toyoshima H, Tamakoshi A; JACC Study Group. Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. *Cancer Sci.* 2005 Sep; 96(9): 590-599. PMID: 16128744.	Does not answer question: Examined relationship between breast cancer and fat intake, not animal protein.
Weggemans RM, Zock PL, Katan MB. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: A meta-analysis. *Am J Clin Nutr.* 2001 May; 73(5): 885-891. PMID: 11333841.	Does not examine relationship between intake of animal protein product and health outcome.
Weghuber D, Widhalm K. Effect of 3-month treatment of children and adolescents with familial and polygenic hypercholesterolaemia with a soya-substituted diet. *Br J Nutr.* 2008 Feb; 99(2): 281-286. Epub 2007 Aug 13. PMID: 17697400.	Participants diagnosed with hypercholesterolemia.
Welch AA, Bingham SA, Ive J, Friesen MD, Wareham NJ, Riboli E, Khaw KT. Dietary fish intake and plasma phospholipid n-3 polyunsaturated fatty acid concentrations in men and women in the European Prospective Investigation into Cancer-Norfolk United Kingdom cohort. *Am J Clin Nutr.* 2006 Dec; 84(6): 1, 330-1, 339. PMID: 17158413.	Does not include health outcomes in analyses; fish is the independent variable.
Wu K, Hu FB, Willett WC, Giovannucci E. Dietary patterns and risk of prostate cancer in U.S. men. *Cancer Epidemiol Biomarkers Prev.* 2006 Jan; 15(1): 167-171. PMID: 16434606.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Yoon H, Benamouzig R, Little J, François-Collange M, Tomé D. Systematic review of epidemiological studies on meat, dairy products and egg consumption and risk of colorectal adenomas. *Eur J Cancer Prev*. 2000 Jun; 9(3): 151-164. PMID: 10954254.	Study design is systematic review (colorectal cancer).
Yuan JM, Ross RK, Gao YT, Yu MC. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *Am J Epidemiol.* 2001 Nov 1; 154(9): 809-816. PMID: 11682363.	Does not answer question: Examined relationship between fish intake and myocardial infarction.

CHAPTER 6. ANIMAL PROTEIN PRODUCTS – COLORECTAL CANCER

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF ANIMAL PROTEIN PRODUCTS AND COLORECTAL CANCER?

Conclusion statement

Moderate evidence reports inconsistent positive associations between colorectal cancer and the intake of certain animal protein products, mainly red and processed meat.

Grade

Moderate

Evidence summary overview

This review included 13 studies (Chao, 2005; Cross, 2007; English, 2004; Flood, 2003; Jarvinen, 2001; Kojima, 2004; Larsson, 2005; Lee, 2009b; Norat, 2005; Oba, 2006; Sato, 2006; Wei, 2004; Wu, 2006) representing prospective cohorts from the US, Europe, Australia, Finland, Japan, China and Sweden published since 2000. In studies examining total meat intake, none reported a relationship with overall colorectal cancer risk (Flood, 2003; Jarvinen, 2001; Lee, 2009b; Oba, 2006; Sato, 2006) or risk associated with specific subsites (Lee, 2009b; Sato, 2006; Wu, 2006).

However, more varied results were reported for red and processed meats. For example, in the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study, positive associations between red meat and processed meat and colorectal cancer were observed (Cross, 2007). However, no associations were observed between red or processed meats and colorectal cancer in the Breast Cancer Detection Demonstration Project (Flood, 2003). The European Prospective Investigation into Cancer and Nutrition (EPIC) study observed no association between red meat and colorectal cancer, but did observe a positive association for processed meat. Further risk may vary depending on subsite. Some studies found a relationship with rectal cancer and red meat intake (Chao, 2005; English, 2004), while others found no association (Kojima, 2004; Larsson, 2005; Lee, 2009b; Wei, 2004; Wu, 2006).

Studies also report inconsistent results for the intake of poultry and colorectal cancer at various subsites, with studies reporting a positive association (Jarvinen, 2001; Kojima, 2004; Sato, 2006), no association (Flood, 2003; Lee, 2009b; Norat, 2005; Wu, 2006) or an inverse association (Chao, 2005; English, 2004; Larsson, 2005).

In general, the studies showed no consistent findings on type of meat or meat product and colorectal cancer. Little information also is available about how much meat is consumed, and the association may differ depending on amount as well as the way it is cooked. Further, although it has been suggested that animal protein products have a different effect in different sites of the colon and rectum, no consistent findings are available. Future studies should consider the subsite of the cancer.

Evidence summary paragraphs

Chao et al, 2005 (positive quality) used data from the Cancer Prevention Study II

(CPS II) Nutrition Cohort (N=148,610; aged 50 to 74 years) to examine the relationship between recent and long-term meat consumption and the risk of incident colon and rectal cancer in the United States. Dietary intake was assessed using a 68-item modified Block food frequency questionnaire (FFQ). Intake of red meat, poultry and fish, and processed meat (grams per week) was computed by summing across meat items that contributed to each meat group and categorizing by quintile. Long-term consumption was examined by considering consumption reported in 1982 and in 1992 to 1993. Consumption at each time point was categorized into tertiles (low, moderate, high) and participants were classified as low intake in 1982 and 1992 to 1993 (referent group), high intake in 1982 and 1992 to 1993 and all other combinations of intake over time. Follow-up from time of enrollment in 1992/1993 through August 31, 2001, identified 1,667 incident colorectal cancers. Eighty percent of cancer cases were self-reported and verified by medical record or linkage with state cancer registries, 3% were identified while verifying a different reported cancer and 17% were identified using death certificates. High intake of red and processed meat reported in 1992 to 1993 was associated with higher risk of colon cancer after adjusting for age and energy intake but not after further adjustment for body mass index (BMI), cigarette smoking and other covariates. When long-term consumption was considered, persons in the highest tertile of consumption in both 1982 and 1992 to 1993 had higher risk of distal colon cancer associated with processed meat (RR=1.50; 95% CI: 1.04, 2.17), and ratio of red meat to poultry and fish (RR=1.53; 95% CI: 1.08 to 2.18) relative to those persons in the lowest tertile at both time points. Long-term consumption of poultry and fish was inversely associated with risk of both proximal and distal colon cancer. High consumption of red meat reported in 1992 to 1993 was associated with higher risk of rectal cancer (RR=1.71; 95% CI: 1.15, 2.52; P=0.007), as was high consumption reported in both 1982 and 1992 to 1993 (RR=1.43; 95% CI: 1.00, 2.05). The authors concluded that prolonged high consumption of red and processed meat may increase the risk of cancer in the distal portion of the large intestine.

Cross et al, 2007 (positive quality) investigated whether red or processed meat intake increases cancer risk using data from the NIH-AARP Diet and Health Study (N=494,036; aged 50 to 71 years) in the US. Cancer cases were identified by linkage to state cancer registries and the National Death Index Plus. A 124-item FFQ based on the Diet History Questionnaire developed at the National Cancer Institute (NCI) was completed at baseline. Red meat intake included all types of beef, pork and lamb (i.e., bacon, beef, cold cuts, ham, hamburger, hot dogs, liver, pork, sausage and steak). The processed meat variable included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham, regular hot dogs and low-fat hot dogs made from poultry. The meat variables also included meats added to complex food mixtures, such as pizza, chili, lasagna and stew. Follow-up for these analyses was calculated from baseline (1995 to 1996) until the end of 2003. During a mean follow-up of 6.8 years, 5,107 cases of colorectal cancer were observed. Individuals in the highest quintile of red meat intake, compared with those in lowest, had a statistically significant elevated risk of colorectal cancer (multivariate HR=1.24; 95% CI: 1.12, 1.36; P<0.001). Individuals in the highest quintile, compared with those in the lowest quintile, of processed meat intake were at elevated risk for colorectal cancer (multivariate HR=1.20; 95% CI: 1.09, 1.32; P<0.001). The authors concluded that both red and processed meat intakes were positively associated with colorectal cancer.

English et al, 2004 (positive quality) investigated the relationship between red meat, chicken and fish consumption and the risk of colorectal cancer using data from the Melbourne Collaborative Cohort Study (N=37,112; aged 27 to 75 years) in Australia. Cancer cases were identified from the Victorian Cancer Registry. Participants completed a 121-item FFQ including 22 items on intake of fresh red meat, processed meat, chicken and fish. Follow-up was conducted from baseline (1990 to 1994) to June 30, 2002. Over an average of nine years of follow-up per person, 451 incident colorectal cancer cases were observed, including 283 colon and 169 rectal tumors (one subject had a colon and rectal tumor). For rectal cancer, the hazard ratios (HR) in the highest quartile of consumption of fresh red meat and processed meat were 2.3 (95% CI: 1.2, 4.2; P=0.07) and 2.0 (95% CI: 1.1, 3.4; P=0.09), respectively. The corresponding HRs for colon cancer were 1.1 (0.7 to 1.6; P=0.9) and 1.3 (0.9 to 1.9; P=0.06). Chicken consumption was weakly negatively associated with colorectal cancer (HR for the highest quartile = 0.7; 95% CI: 0.6, 1.0; P=0.03), whereas hazard ratios for fish consumption were close to unity. The authors concluded that consumption of fresh red meat and processed meat seemed to be associated with an increased risk of rectal cancer. Consumption of chicken and fish did not increase risk.

Flood et al, 2003 (positive quality) investigated the association of intakes of total meat, red meat, white meat and processed meat, as well as for total fat, saturated fat and unsaturated fat with colorectal cancer in a prospective cohort of women in the United States from the Breast Cancer Detection Demonstration Project (BCDDP) (N=45,496). Questionnaires were completed at three time points: 1987 to 1989, 1992 to 1995 and 1995 to 1998. Colorectal case ascertainment was from self-reports on 1992 to 1995 and 1995 to 1998 questionnaires, state-wide cancer registries, and the National Death Index (through 1997). A 62-item National Cancer Institute/ Block FFQ was used to assess usual dietary intake over the previous year. The FFQ had 17 line items containing meat. During an average of 8.5 years of follow-up, there were 487 incident cases of colorectal cancer. For total meat, no association between increased consumption and colorectal cancer was observed, with the relative risk in the top quintile being 1.05 (95% CI: 0.80, 1.38; P=0.28). Similarly, no significant (NS) associations between colorectal cancer and red meat, white meat or processed meat were observed in energy-adjusted or energy- and total meat-adjusted models. The authors concluded that this study provided no evidence of an association between either meat or fat (or any subtypes) and colorectal cancer incidence.

Jarvinen et al, 2001 (positive quality) investigated the relationships between consumption of total fat, major dietary fatty acids, cholesterol, consumption of meat and eggs and the incidence of colorectal cancers in a cohort (N=9,959) based on the Finnish Mobile Clinic Health Examination Survey in Finland. Cancer incidence was ascertained through the national Finnish Cancer Registry. Habitual food consumption during the preceding year was obtained through interview. A structured questionnaire listing more than 100 foods and mixed dishes was used to guide the interview. The average daily consumption of food items was computed utilizing a software package specifically developed for this study. From 1967 to 1972 to 1999, 109 new colorectal cancer cases (63 in colon and 46 in rectum) were ascertained. Total consumption of meat (all), red meat or liver was not significantly associated with the incidence of colorectal cancers. The RR between extreme quartiles for colorectal cancer and meat (all) and red meat were 1.52 (95% CI: 0.78, 2.96) and 1.50 (95% CI: 0.77, 2.94),

respectively. Poultry intake was analyzed as a dichotomous variable (yes/no). Those who consumed poultry meat had an increased risk for colorectal cancers mainly due to an increased risk for colon cancer (RR=1.93; 95% CI: 1.12–3.35). Egg consumption was not significantly related to colorectal cancer risk. The authors concluded that non-significant associations between consumption of meat and eggs and colorectal cancer risk were found.

Kojima et al, 2004 (positive quality) used data from a prospective cohort study to investigate the association between diet and colorectal cancer risk in Japanese adults participating in the Japan Collaborative Cohort Study. Subjects (N=107,824, 58% women, ages 40 to 79 years) completed a FFQ containing 33 foods typical in the Japanese diet, recorded three-day diet records every three months for a year, and then filled out the FFQ again. Fatal deaths due to colon cancer were determined using resident registration records of municipalities. Cause of death was confirmed by death certificates. Over an average follow-up period of 9.9±2.2 years or 1,064,448 person-years at risk, there were 284 cases of death from colon cancer and 173 deaths from rectal cancer. Colon cancer mortality risk was significantly higher among men with a high intake of chicken compared with men with a low intake of chicken (adjusted HR=1.7; 95% CI: 1.1, 2.6). No other significant association between meat (including beef, pork and ham and sausage) and colon or rectal cancer mortality in men or women was observed. Egg consumption was significantly associated with colon cancer mortality only in men (HR for high vs. low intake = 1.5; 95% CI: 1.0, 2.4; P=0.04). However, the authors caution that the study lacked statistical power due to small sample size and the measurement error in the FFQ, so that results should be interpreted with caution.

Larson et al, 2005 (positive quality) examined the association of red meat consumption with cancer risk by subsite within the large bowel. Participants were 61,433 women from the Swedish Mammography Cohort (aged 40 to 75 years). Colon and rectal cancer cases were identified by linkages to the National Swedish Cancer Registry (from March 1987 through December 21, 2002) and the Regional Cancer Registry in the study area (from January 1, 2003 through June 30,2003). Dietary intake during the past six months was assessed by a self-administered FFQ with 67 food items (including nine items about red and processed meats). Over a mean follow-up of 13.9 years, 234 proximal colon cancers, 155 distal colon cancers and 230 rectal cancers were identified. A significant positive association between red meat consumption and risk of distal colon cancer (P=0.001), but not of cancers of the proximal colon (P=0.95) or rectum (P=0.32) was observed. The multivariate rate ratio for women who consumed ≥94g per day of red meat compared to those who consumed <50g per day was 2.22 (95% CI: 1.34, 3.68) for distal colon, 1.03 (95% CI: 0.67, 1.60) for proximal colon and 1.28 (95% CI: 0.83, 1.98) for rectal cancer. Multivariate RR of overall colorectal cancer according to red meat intake was 1.32 (95% CI: 1.03, 1.68; P=0.03) among extreme quartiles. No significant association between processed meat intake and colorectal cancer at any subsite was observed. Poultry consumption was weakly inversely related to risk of total colorectal cancer; multivariate RR of colorectal cancer for women who consumed on average one serving of poultry per week was 0.75 (95% CI: 0.55, 1.02; P=0.04) compared to women who rarely or never consumed poultry. The authors concluded that high consumption of red meat may substantially increase the risk of distal colon cancer, and

future investigations on red meat and colorectal cancer risk should consider cancer subsites separately.

Lee et al, 2009 (positive quality) used prospective cohort data to describe the association between consumption of animal-origin foods and colorectal cancer among 73,224 women (40 to 70 years of age) participating in the Shanghai Women's Health Study (China). A validated, quantitative FFQ was administered by in-person interviews. Participants were asked how often, on average, during the past year they had consumed a specific food or food group and were also asked about the cooking methods used. Colorectal cancer cases were identified by in-person follow-up surveys, annual record linkage with the Shanghai Cancer Registry and death certificate registry. Cases were verified through home visits, medical charts and pathological evidence. Adjustments were made for age, education, income, season of recruitment, tea consumption, nonsteroidal anti-inflammatory drug use, total energy intake and fiber intake. After a mean follow-up of 7.4 years, 394 incident cases of colorectal (236 colon, 158 rectal) cancer were observed. Total meat intake was not associated with risk of colorectal cancer (P=0.30) nor was red meat (P=0.53), poultry intake (P=0.23) or eggs (P=0.57). Similarly, no significant (NS) associations were observed when colon and rectal cancer were considered separately. The authors concluded that they did not find an association between total consumption of animal origin food and colorectal cancer.

Norat et al, 2005 (positive quality) examined the relationship between intakes of red and processed meat, poultry and fish and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study (N=478,040; aged 35 to 70 years at baseline). Colorectal cancer cases were identified from population cancer registries, health insurance records, cancer and pathology registries, and active follow-up of study subjects and their next-of-kin. Diet over 12 months before enrollment was measured by country-specific validated questionnaires. Most centers used a self-administered dietary questionnaire of 88 to 266 food items. In Greece, all centers in Spain and Ragusa, Italy, the questionnaire was administered at a personal interview. In Sweden, a questionnaire method combined with a food record was used. Meats were grouped into red meat, processed meat and poultry. After a mean follow-up of 4.8 years, 1,329 incident colorectal cancers were documented. Colorectal cancer risk was positively associated with intake of red and processed meat [highest (>160g per day) vs. lowest (<20g per day) intake, HR=1.35; 95% CI: 0.96, 1.88; P=0.03], but was not related to poultry intake. In separate analyses, intake of red meat was positively but not significantly associated with colorectal cancer (HR for highest vs. lowest intake = 1.17; 95% CI: 0.92, 1.49, P=0.08), whereas intake of processed meat was significantly associated with increased colorectal cancer risk (HR for highest vs. lowest intake = 1.42, 95% CI: 1.09, 1.86; P=0.02). The authors concluded that their results confirm that colorectal cancer risk is positively associated with high consumption of red and processed meat.

Oba et al, 2006 (positive quality) used data from a Japanese prospective cohort study to determine the relationship between a western diet, characterized by high fat intake and meat consumption, and the risk of developing colon cancer. Analyses included 30,221 subjects, 54% women, ages 35 to 101 years with a mean BMI of approximately 22.0kg/m^2. Dietary intake data was collected using a validated, 169-item, semi-quantitative FFQ. For this study "red meat" included beef and pork, and "processed

meat" included ham, sausage, bacon and yakibuta (Chinese-style roasted pork). Mean red meat intake was 32.3±2.06g per day for men and 22.1±2.30g per day for women; mean processed meat intake was 9.21±2.28g per day for men and 7.42±2.31g per day for women. From January 1, 1993 to December 31, 2000, 111 men and 102 women were diagnosed with colon cancer. Total meat and red meat intake was unrelated to the risk of colon cancer in men and women. Processed meat intake was significantly, positively associated with the risk of colon cancer in men only (RR in the highest tertile vs. the lowest tertile = 1.98; 95% CI: 1.24, 3.16; P<0.01). The authors concluded that they provided evidence to suggest a possible linkage between a western diet and risk of colon cancer.

Sato et al, 2006 (positive quality) conducted a prospective cohort study to examine the association between total meat consumption and the risk of colorectal cancer in Japanese adults participating in the Miyagi Cohort Study. A self-administered 40-item FFQ, with five items assessing meat intake (beef, pork, ham or sausage, chicken and liver) was used to calculate the total weight of each type of meat consumed per day. Colon cancer cases were identified by the linkage of computerized records with the Miyagi Prefectural Cancer Registry. The final sample consisted of 41,835 adult subjects, age 40 to 64 years at baseline. There were 474 incident cases of colorectal cancer during 11 years of follow-up, to March 2001, and median intake of total meat in the cohort was 52.1g per day. The age-adjusted and sex-adjusted relative risks (RR) for the highest vs. the lowest quartiles of meat consumption were non-significant for colorectal cancer (1.15; 95% CI: 0.89, 1.49; P=0.14), colon cancer (1.23; 95% CI: 0.87, 1.73; P=0.11), and rectal cancer (1.01; 95% CI: 0.68, 1.50; P=0.86). Multivariate analyses did not substantially change these estimates. Intake of chicken had a significant dose-response relationship to the risk of colon cancer only (multivariate RR = 1.58; 95% CI: 0.84, 2.95; P=0.03). Analyses of beef, pork, ham or sausage and liver as individual meat sources were not significant. The authors concluded that their data do not support the hypothesis that meat consumption is a risk factor for colorectal cancer.

Wei et al, 2004 (positive quality) examined established risk factors to determine whether they were differentially associated with colon and rectal cancer using data from the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). Participants were 87,733 women from the NHS (aged 30 to 55 years) and 46,632 men from the HPFS (aged 40 to 75 years). Colon or rectal cancer was reported on questionnaires and verified by review of hospital records and pathology reports. Dietary intake was assessed using FFQs. Baseline values of "beef, pork or lamb as a main dish" and "processed meat" were included in analyses. The combined cohort had 1,139 colon cancer cases and 339 rectal cancer cases over 2,302,712 person years. In the pooled analyses of the two cohorts, the multivariate RR of colon cancer was 1.43 (95% CI: 1.00, 2.05; P=0.25) for those who consumed five or more servings per day of beef, pork or lamb as a main dish compared to those who consumed none; the combined cohort multivariate RR of rectal cancer was 0.90 (95% CI: 0.47, 1.75; P=0.55). A significant association between processed meat and colon cancer was observed in the combined cohorts (multivariate RR=1.33; 95% CI: 1.04, 1.70; P=0.008) between those who consumed five or more servings per day of processed meats, compared to those who consumed none. The multivariate RR of colon cancer was 1.32 (95% CI: 0.95, 1.83; P=0.02) for women in the NHS who consumed five or

more servings per day of processed meats compared to those who consumed none. However, no significant (NS) association was observed in the HPFS. For processed meat, the pooled multivariate RR of rectal cancer was 0.90 (95% CI: 0.52, 1.57; P=0.93). The authors concluded that beef, pork or lamb as a main dish and processed meat were related to colon cancer, but not rectal cancer. In addition, they stated that future investigations into risk for colorectal cancer should ideally be done differentially by subsite.

Wu et al, 2006 (positive quality) conducted a cohort study to prospectively examine the associations between heterocyclic amine and meat-derived mutagenicity and risk of developing colon cancer in a group of men participating in Health Professionals Follow-up Study (N=14,032). Distal colon adenoma diagnosis was self-reported by participants on the biennial follow-up questionnaire, and medical records were reviewed and cases were confirmed by pathology reports. Food frequency questionnaires were used to assess meat intake and cooking methods and the Charred Database was used to determine the amount of heterocyclic amines and meat-derived mutagenicity in meats. Cumulative average intake from 1986, 1990, 1994 and 1998 assessments were used to estimate long-term dietary intake. Total red meat; hamburger; beef, lamb or pork as main dish; processed meat; and chicken or turkey were included in analyses. Between 1996 and 2002, 581 distal colon adenoma cases were identified. Total red meat; hamburger; beef, lamb or pork as main dish; and chicken or turkey were not associated with distal colon adenoma before or after adjusting for MDM or MeIQx (meat mutagens). There was a positive association between higher intake of processed meat and risk of adenoma (multivariate OR of extreme quintiles = 1.52; 95% CI: 1.12, 2.08; P=0.02). This association was 1.46 (95% CI: 1.06, 1.99; P=0.04) and 1.47 (95% CI: 1.06, 2.04; P=0.05) after adjusting for MDM and MeIQx, respectively. The authors concluded that higher consumption of mutagens from meats cooked at higher temperature and longer duration may be associated with higher risk of distal colon adenoma independent of overall meat intake.

Overview table

Author, Year, Study Design, Class, Rating	Study Name/Location	Total Meat Association (Pos, Neg, None)	Red Meat Association (Pos, Neg, None)	Processed Meat Association (Pos, Neg, None)	Poultry Association (Pos, Neg, None)
Chao et al 2005 Study Design: prospective cohort Class: B Positive quality	Cancer Prevention Study II Nutrition Cohort. Location: US.	Not examined.	(+) Rectal. (+) Distal (Ratio of red meat to poultry or fish).	(+) Distal.	Poultry and fish: (-) Proximal and distal.
Cross et al 2007 Study Design: Prospective Cohort Study Class: B Positive quality	NIH-AARP Diet and Health Study. Location: US.	Not examined.	(+) CRC.	(+) CRC.	Not examined.
English et al 2004 Study Design: Prospective Cohort Study Class: B Positive quality	Melbourne Collaborative Cohort Study. Location: Australia.	Not examined.	(+) Rectal. (+) Colon.	(+) Rectal. (+) Colon.	Chicken: (-) CRC.

Flood et al 2003 Study Design: Prospective Cohort Study Class: B Positive quality	Breast Cancer Detection Demonstration Project (BCDDP). Location: US.	Ø CRC.	Ø CRC.	Ø CRC.	White meat: Ø CRC.
Jarvinen et al 2001 Study Design: Prospective cohort design Class: B Positive quality	Finnish Mobile Clinic Health Examination Survey. Location: Finland.	Ø CRC.	Ø CRC.	Not examined.	Poultry (intake = yes or no): (+) CRC. Egg: Ø CRC.
Kojima M, Wakai K et al, 2004 Study Design: Prospective cohort study Class: B Positive quality	Japan Collaborative Cohort Study. Location: Japan.	Not examined.	Beef or pork: Ø Colon or rectal cancer mortality.	Ham and sausage: Ø Colon or rectal cancer mortality.	Chicken: (+) Colon cancer mortality. Egg: (+) Colon cancer mortality (men only).

Larsson et al 2005 Study Design: Prospective cohort study Class: B Positive quality	Swedish Mammography Cohort. Location: Sweden.	Not examined.	(+) CRC and distal. Ø Proximal and rectal	Ø CRC or any subsite.	Poultry: (-) CRC.
Lee SA, Shu XO et al, 2009 Study Design: Prospective Cohort Study Class: B Positive quality	Shanghai Women's Health Study. Location: China.	Ø CRC, colon or rectal.	Ø CRC, colon or rectal.	Not examined.	Poultry: Ø CRC, colon or rectal. Eggs: Ø CRC, colon or rectal.
Norat et al 2005 Study Design: prospective cohort study Class: B Positive quality	European Prospective Investigation into Cancer and Nutrition (EPIC). Location: Europe.	Red and processed meat: (+) CRC.	Ø CRC.	(+) CRC.	Poultry: Ø CRC.

Oba S, Shimizu N et al, 2006 Study Design: Prospective cohort study Class: B Positive quality	Location: Japan.	Ø CRC.	Ø CRC.	Not examined.	(+) Colon in men only.
Sato Y, Nakaya N et al, 2006 Study Design: Prospective cohort Class: B Positive quality	Miyagi Cohort Study. Location: Japan.	Ø CRC, colon or rectal.	Beef: Ø CRC. Pork: Ø CRC.	Ham: Ø CRC. Sausage: Ø CRC.	Chicken: (+) Colon only.
Wei et al 2004 Study Design: prospective cohorts (pooled) Class: B Positive quality	Nurses' Health and Health Professionals Follow Up Studies. Location: US.	Not examined.	Beef, pork or lamb as main dish: (+) Colon, Ø Rectal.	(+) Colon (pooled analyses and women only), Ø Rectal.	Not examined.

Wu K, Giovannucci E et al, 2006 Study Design: Prospective Cohort Study Class: B Positive quality	Health Professionals Follow-up Study. Location: US.	Ø Distal.	Hamburger: Ø Distal. Beef, pork or lamb main dish: Ø Distal.	(+) Distal.	Chicken or turkey: Ø Distal.

Search plan and results

Inclusion criteria

- January 2000 to September 2009
- Prospective cohort studies on colorectal, breast and prostate cancers
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children two to 18 years; Adults 19 years and older
- *Populations:* Healthy, those with elevated chronic disease risk.

Exclusion criteria

- With the exception of the body weight outcome, cross-sectional studies were excluded from the review
- Systematic reviews and meta-analyses on colorectal, breast and prostate cancers. Only original research studies with prospective cohort design were included in the review
- Studies specifically related to seafood or milk product intake (considered as separate questions)
- Studies that reported on animal protein intake as a component of a dietary pattern and not as an individual variable
- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: (Animal protein* OR meat[mh] OR "Egg Proteins, Dietary"[mh] OR "Fish Proteins"[mh]) AND ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "overweight"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mh:NoExp] OR “heart diseases”[mh] OR "Coronary Disease"[Mesh] OR “blood pressure”[mh] OR “chronic disease”[mh] OR obesity[mh] OR "Body Weights and Measures"[mh] OR "Colorectal Neoplasms"[mesh])
  (Animal protein* OR meat[mh] OR "Egg Proteins, Dietary"[mh] OR "Fish Proteins"[mh] OR seafood[majr] OR crustacea[majr]) AND (systematic[sb] OR Meta-Analysis[ptyp] OR "Cohort Studies"[Mesh]) AND ("Prostatic Neoplasms"[Mesh] OR "Breast Neoplasms"[Mesh])
  eggs [mh] AND ("Diabetes Mellitus, Type 2"[majr] OR "metabolic syndrome X"[majr] OR "overweight"[majr] OR "hypertension"[majr] OR "dyslipidemias"[majr] OR "cardiovascular diseases"[majr:NoExp] OR “heart diseases”[majr] OR "Coronary Disease"[Mesh] OR “blood pressure”[majr] OR “chronic disease”[majr] OR obesity[majr] OR "Body Weights and Measures"[majr])
  (Note: "Cohort Studies"[Mesh]) includes prospective studies)

Date searched: 09/01/2009; update 09/18/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 771
- Total articles identified to review from electronic databases: 166
- Articles identified via handsearch or other means: 2
- Number of Primary Articles Identified: 47
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 47
- Number of Articles Reviewed but Excluded: 121

Included articles (References)

What is the relationship between the intake of animal protein products and cardiovascular disease?

1. Djoussé L, Gaziano JM. Egg consumption in relation to cardiovascular disease and mortality: the Physicians' Health Study.*Am J Clin Nutr.* 2008 Apr; 87(4): 964-969. PMID: 18400720; PMCID: PMC2386667.
2. Halton TL, Willett WC, Liu S, Manson JE, Albert CM, Rexrode K, Hu FB. Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med.* 2006 Nov 9; 355(19): 1, 991-2, 002. PMID: 17093250.
3. Kelemen LE, Kushi LH, Jacobs DR Jr, Cerhan JR. Associations of dietary protein with disease and mortality in a prospective study of postmenopausal women. *Am J Epidemiol.* 2005 Feb 1; 161(3): 239-249. PMID: 15671256.
4. Nakamura Y, Iso H, Kita Y, Ueshima H, Okada K, Konishi M, Inoue M, Tsugane S. Egg consumption, serum total cholesterol concentrations and coronary heart disease incidence: Japan Public Health Center-based prospective study. *Br J Nutr.* 2006 Nov; 96(5): 921-928. PMID: 17092383.
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serum cholesterol, and cause-specific and all-cause mortality: The National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980 (NIPPON DATA80).*Am J Clin Nutr.* 2004 Jul; 80(1): 58-63. PMID: 15213028.

6. Qureshi AI, Suri FK, Ahmed S, Nasar A, Divani AA, Kirmani JF. Regular egg consumption does not increase the risk of stroke and cardiovascular diseases. *Med Sci Monit.* 2007 Jan; 13(1): CR1-8. Epub 2006 Dec 18. PMID: 17179903.
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What is the relationship between the intake of animal protein products and blood pressure?

Primary Citations

1. Alonso A, Beunza JJ, Bes-Rastrollo M, Pajares RM, Martínez-González MA. Vegetable protein and fiber from cereal are inversely associated with the risk of hypertension in a Spanish cohort. *Arch Med Res*. 2006 Aug; 37(6): 778-786. PMID: 16824939.
2. Miura K, Greenland P, Stamler J, Liu K, Daviglus ML, Nakagawa H. Relation of vegetable, fruit, and meat intake to 7-year blood pressure change in middle-aged men: The Chicago Western Electric Study. *Am J Epidemiol.* 2004 Mar 15; 159(6): 572-580. PMID: 15003961.
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4. Wagemakers JJ, Prynne CJ, Stephen AM, Wadsworth ME. Consumption of red or processed meat does not predict risk factors for coronary heart disease; results from a cohort of British adults in 1989 and 1999. *Eur J Clin Nutr.* 2009 Mar; 63(3): 303-311. Epub 2007 Nov 14. PMID: 18000518.
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What is the relationship between the intake of animal protein products and type 2 diabetes?

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3. Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. *Am J Clin Nutr.* 2008 Feb; 87(2): 339-346. PMID: 18258623.

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What is the relationship between the intake of animal protein products and body weight?

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What is the relationship between the intake of animal protein products and colorectal cancer?

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What is the relationship between the intake of animal protein products and prostate cancer?

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What is the relationship between the intake of animal protein products and breast cancer?

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Excluded articles

Article	Reason for Exclusion
Alexander DD, Cushing CA, Lowe KA, Sceurman B, Roberts MA. Meta-analysis of animal fat or animal protein intake and colorectal cancer. *Am J Clin Nutr.* 2009 May; 89(5): 1, 402-1, 409. Epub 2009 Mar 4. PMID: 19261724.	Study design is meta-analysis (colorectal cancer).

Appleby PN, Davey GK, Key TJ. Hypertension and blood pressure among meat eaters, fish eaters, vegetarians and vegans in EPIC-Oxford. *Public Health Nutr.* 2002 Oct; 5(5): 645-654. PMID: 12372158.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Augustsson K, Michaud DS, Rimm EB, Leitzmann MF, Stampfer MJ, Willett WC, Giovannucci E. A prospective study of intake of fish and marine fatty acids and prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2003 Jan; 12(1): 64-67. PMID: 12540506.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Azadbakht L, Esmaillzadeh A. Red meat intake is associated with metabolic syndrome and the plasma C-reactive protein concentration in women. *J Nutr.* 2009 Feb; 139(2): 335-339. Epub 2008 Dec 11. PMID: 19074209.	Does not answer question: Examined relationship between red meat intake and metabolic syndrome.
Balder HF, Vogel J, Jansen MC, Weijenberg MP, van den Brandt PA, Westenbrink S, van der Meer R, Goldbohm RA. Heme and chlorophyll intake and risk of colorectal cancer in the Netherlands cohort study. *Cancer Epidemiol Biomarkers Prev.* 2006 Apr; 15(4): 717-725. PMID: 16614114.	Does not answer question: Examined relationship between heme and chlorophyll intake and colorectal cancer.
Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: A systematic literature review and meta-analysis. *Cancer Causes Control.* 2007 Nov; 18(9): 967-988. Epub 2007 Jul 19. Review. PMID: 17638104; PMCID: PMC2592095.	Does not include colorectal, breast, or prostate cancer in analyses.
Barraj L, Tran N, Mink P. A comparison of egg consumption with other modifiable coronary heart disease lifestyle risk factors: a relative risk apportionment study. *Risk Anal*. 2009 Mar; 29(3): 401-415. Epub 2008 Nov 4. PMID: 19000074.	Does not answer question: Used risk apportionment approach to estimate contribution of egg intake to coronary heart disease (CHD) risk at the population level.
Benassi-Evans B, Clifton PM, Noakes M, Keogh JB, Fenech M. High protein-high red meat versus high carbohydrate weight loss diets do not differ in effect on genome stability and cell death in lymphocytes of overweight men. *Mutagenesis.* 2009 May; 24(3): 271-277. Epub 2009 Mar 5. PMID: 19264840.	Does not include animal protein product intake in analyses.
Brink M, Weijenberg MP, de Goeij AF, Roemen GM, Lentjes MH, de Bruïne AP, Goldbohm RA, van den Brandt PA. Meat consumption and K-ras mutations in sporadic colon and rectal cancer in The Netherlands Cohort Study. *Br J Cancer.* 2005 Apr 11; 92(7): 1, 310-1, 320. PMID: 15812479.	Study design is case-cohort.
Cade JE, Burley VJ, Greenwood DC; UK Women's Cohort Study Steering Group. The UK Women's Cohort Study: Comparison of vegetarians, fish-eaters and meat-eaters. *Public Health Nutr.* 2004 Oct; 7(7): 871-878. PMID: 15482612.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.

Chan AT, Tranah GJ, Giovannucci EL, Willett WC, Hunter DJ, Fuchs CS. Prospective study of N-acetyltransferase-2 genotypes, meat intake, smoking and risk of colorectal cancer. *Int J Cancer.* 2005 Jul 1; 115(4): 648-652. PMID: 15700302.	Study design is case-control study (colorectal cancer).
Chavarro JE, Stampfer MJ, Hall MN, Sesso HD, Ma J. A 22-y prospective study of fish intake in relation to prostate cancer incidence and mortality. *Am J Clin Nutr.* 2008 Nov; 88(5): 1, 297-1, 303. PMID: 18996866.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Chrysohoou C, Panagiotakos DB, Pitsavos C, Skoumas J, Krinos X, Chloptsios Y, Nikolaou V, Stefanadis C. Long-term fish consumption is associated with protection against arrhythmia in healthy persons in a Mediterranean region: The ATTICA study. *Am J Clin Nutr.* 2007 May; 85(5): 1, 385-1, 391. PMID: 17490977.	Does not answer question: Examined relationship between fish intake and arrhythmia.
Cotterchio M, Boucher BA, Manno M, Gallinger S, Okey AB, Harper PA. Red meat intake, doneness, polymorphisms in genes that encode carcinogen-metabolizing enzymes, and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2008 Nov; 17(11): 3, 098-3, 107. PMID: 18990750.	Study design is case-control (colorectal cancer).
Crowe FL, Key TJ, Appleby PN, Travis RC, Overvad K, Jakobsen MU, Johnsen NF, Tjønneland A, Linseisen J, Rohrmann S, Boeing H, Pischon T, Trichopoulou A, Lagiou P, Trichopoulos D, Sacerdote C, Palli D, Tumino R, Krogh V, Bueno-de-Mesquita HB, Kiemeney LA, Chirlaque MD, Ardanaz E, Sánchez MJ, Larrañaga N, González CA, Quirós JR, Manjer J, Wirfält E, Stattin P, Hallmans G, Khaw KT, Bingham S, Ferrari P, Slimani N, Jenab M, Riboli E. Dietary fat intake and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr.* 2008 May; 87(5): 1, 405-1, 413. PMID: 18469265.	Does not answer question: Examined relationship between animal fat intake and prostate cancer.
Dallongeville J, Yarnell J, Ducimetière P, Arveiler D, Ferrières J, Montaye M, Luc G, Evans A, Bingham A, Hass B, Ruidavets JB, Amouyel P. Fish consumption is associated with lower heart rates.*Circulation.* 2003 Aug 19; 108(7): 820-825. Epub 2003 Aug 11. PMID: 12912821.	Does not answer question: Examined relationship between fish intake and heart rates.
Davey GK, Spencer EA, Appleby PN, Allen NE, Knox KH, Key TJ. EPIC-Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33 883 meat-eaters and 31 546 non meat-eaters in the UK. *Public Health Nutr.* 2003 May; 6(3): 259-269. PMID: 12740075.	Does not include health outcomes in analyses.
de Mello VD, Zelmanovitz T, Perassolo MS, Azevedo MJ, Gross JL. Withdrawal of red meat from the usual diet reduces albuminuria and improves serum fatty acid profile in type 2 diabetes patients with macroalbuminuria. *Am J Clin Nutr*. 2006 May; 83(5): 1, 032-1, 038. PMID: 16685043.	Participants diagnosed with type 2 diabetes (T2D).
Dixon LB, Balder HF, Virtanen MJ, Rashidkhani B, Männistö S, Krogh V, van Den Brandt PA, Hartman AM, Pietinen P, Tan F, Virtamo J, Wolk A, Goldbohm RA. Dietary patterns associated with colon and rectal cancer: results from the Dietary Patterns and Cancer (DIETSCAN) Project. *Am J Clin Nutr.* 2004 Oct; 80(4): 1, 003-1, 011. PMID: 15447912.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.

Djoussé L, Gaziano JM. Egg consumption and risk of heart failure in the Physicians' Health Study. *Circulation.* 2008 Jan 29; 117(4): 512-516. Epub 2008 Jan 14. PMID: 18195171; PMCID: PMC2706003.	Does not answer question: Examined relationship between egg consumption and heart failure.
Egeberg R, Olsen A, Autrup H, Christensen J, Stripp C, Tetens I, Overvad K, Tjønneland A. Meat consumption, N-acetyl transferase 1 and 2 polymorphism and risk of breast cancer in Danish postmenopausal women. *Eur J Cancer Prev.* 2008 Feb; 17(1): 39-47. PMID: 18090909.	Study design is nested case-control study (breast cancer).
Eichholzer M, Bisig B. Daily consumption of (red) meat or meat products in Switzerland: Results of the 1992/93 Swiss Health Survey. *Eur J Clin Nutr.* 2000 Feb; 54(2): 136-142. PMID: 10694784.	Does not include health outcomes in analyses.
Elliott P, Stamler J, Dyer AR, Appel L, Dennis B, Kesteloot H, Ueshima H, Okayama A, Chan Q, Garside DB, Zhou B. Association between protein intake and blood pressure: The INTERMAP Study. *Arch Intern Med.* 2006 Jan 9; 166(1): 79-87. PMID: 16401814.	Study design is cross-sectional epidemiological study.
Engeset D, Andersen V, Hjartåker A, Lund E. Consumption of fish and risk of colon cancer in the Norwegian Women and Cancer (NOWAC) study. *Br J Nutr.* 2007 Sep; 98(3): 576-582. Epub 2007 Apr 10. Erratum in: *Br J Nutr.* 2008 Mar; 99(3): 696. PMID: 17419892.	Does not answer question: Examined relationship between fish intake and colon cancer.
Erkkilä AT, Lichtenstein AH, Mozaffarian D, Herrington DM. Fish intake is associated with a reduced progression of coronary artery atherosclerosis in postmenopausal women with coronary artery disease. *Am J Clin Nutr.* 2004 Sep; 80(3): 626-632. PMID: 15321802.	Participants diagnosed with CHD.
Erkkilä AT, Schwab US, de Mello VD, Lappalainen T, Mussalo H, Lehto S, Kemi V, Lamberg-Allardt C, Uusitupa MI. Effects of fatty and lean fish intake on blood pressure in subjects with coronary heart disease using multiple medications. *Eur J Nutr.* 2008 Sep; 47(6): 319-328. Epub 2008 Jul 29. PMID: 18665413.	Participants diagnosed with CHD.
Faramawi MF, Johnson E, Fry MW, Sall M, Zhou Y. Consumption of different types of meat and the risk of renal cancer: Meta-analysis of case-control studies. *Cancer Causes Control.* 2007 Mar; 18(2): 125-133. Epub 2007 Jan 22. Erratum in: *Cancer Causes Control.* 2007 Jun; 18 (5): 581. Yi, Zhou [corrected to Zhou, Yi]. PMID: 17242980.	Does not include colorectal, breast or prostate cancer in analyses.
Ferrucci LM, Sinha R, Graubard BI, Mayne ST, Ma X, Schatzkin A, Schoenfeld PS, Cash BD, Flood A, Cross AJ. Dietary meat intake in relation to colorectal adenoma in asymptomatic women. *Am J Gastroenterol.* 2009 May; 104(5): 1, 231-1, 140. Epub 2009 Apr 14. PMID: 19367270.	Study design is case-control study (colorectal cancer).
Geelen A, Schouten JM, Kamphuis C, Stam BE, Burema J, Renkema JM, Bakker EJ, van't Veer P, Kampman E. Fish consumption, n-3 fatty acids, and colorectal cancer: a meta-analysis of prospective cohort studies. *Am J Epidemiol*. 2007 Nov 15; 166(10): 1, 116-1, 125. Epub 2007 Sep 6. PMID: 17823383.	Study design is meta-analysis (colorectal cancer).

Gillum RF, Mussolino ME, Madans JH. Fish consumption and hypertension incidence in African Americans and whites: The NHANES I Epidemiologic Follow-up Study. *J Natl Med Assoc.* 2001 Apr; 93(4): 124-128. PMID: 12653399; PMCID: PMC2593988.	Does not answer question: Examined relationship between fish intake and hypertension (HTN).
Goldin BR, Brauner E, Adlercreutz H, Ausman LM, Lichtenstein AH. Hormonal response to diets high in soy or animal protein without and with isoflavones in moderately hypercholesterolemic subjects. *Nutr Cancer.* 2005; 51(1): 1-6. PMID: 15749623.	Does not answer question: Examined hormonal response to diets high in soy or animal protein.
Gonzalez CA, Riboli E. Diet and cancer prevention: Where we are, where we are going. Nutr Cancer. 2006; 56(2): 225-31. Review. PMID: 17474869.	Study design is narrative review.
Grillenberger M, Neumann CG, Murphy SP, Bwibo NO, Weiss RE, Jiang L, Hautvast JG, West CE. Intake of micronutrients high in animal-source foods is associated with better growth in rural Kenyan school children. *Br J Nutr*. 2006 Feb; 95(2): 379-390. PMID: 16469157.	Study population not from a developed country as defined by the Human Development Index (2009).
Gross JL, Zelmanovitz T, Moulin CC, De Mello V, Perassolo M, Leitão C, Hoefel A, Paggi A, Azevedo MJ. Effect of a chicken-based diet on renal function and lipid profile in patients with type 2 diabetes: a randomized crossover trial. *Diabetes Care.* 2002 Apr; 25(4): 645-651. PMID: 11919119.	Participants diagnosed with T2D.
Günther AL, Remer T, Kroke A, Buyken AE. Early protein intake and later obesity risk: which protein sources at which time points throughout infancy and childhood are important for body mass index and body fat percentage at 7 y of age? *Am J Clin Nutr.* 2007 Dec; 86(6): 1, 765-1, 772. PMID: 18065597.	Does not answer question: Examined protein intake during infancy and childhood and body weight outcomes at age seven years.
He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, Greenland P. Accumulated evidence on fish consumption and coronary heart disease mortality: A meta-analysis of cohort studies. *Circulation.* 2004 Jun 8; 109(22): 2, 705-2, 711. PMID: 15184295.	Does not answer question: examined relationship between fish intake and CHD.
High red-meat intake, obesity linked to cancer.*Health News.* 2002 Feb; 8(2): 9. PMID: 11862847.	News article.
Hodgson JM, Burke V, Beilin LJ, Puddey IB. Partial substitution of carbohydrate intake with protein intake from lean red meat lowers blood pressure in hypertensive persons. *Am J Clin Nutr.* 2006 Apr; 83(4): 780-787. PMID: 16600928.	Participants diagnosed with HTN.
Hu FB, Manson JE, Willett WC. Types of dietary fat and risk of coronary heart disease: a critical review.*J Am Coll Nutr.* 2001 Feb; 20(1): 5-19. Review. PMID: 11293467.	Study design is narrative review.
Huncharek M, Kupelnick B, Wheeler L. Dietary cured meat and the risk of adult glioma: A meta-analysis of nine observational studies. *J Environ Pathol Toxicol* Oncol. 2003; 22(2): 129-137. PMID: 14533876.	Does not include colorectal, breast, or prostate cancer in analyses.

Huncharek M, Kupelnick B. A meta-analysis of maternal cured meat consumption during pregnancy and the risk of childhood brain tumors. *Neuroepidemiology.* 2004 Jan-Apr; 23(1-2): 78-84. PMID: 14739572.	Does not include colorectal, breast, or prostate cancer in analyses.
Hunninghake DB, Maki KC, Kwiterovich PO Jr, Davidson MH, Dicklin MR, Kafonek SD. Incorporation of lean red meat into a National Cholesterol Education Program Step I diet: A long-term, randomized clinical trial in free-living persons with hypercholesterolemia. *J Am Coll Nutr.* 2000 Jun; 19(3): 351-360. PMID: 10872897.	Participants diagnosed with hypercholesterolemia.
Iso H, Sato S, Kitamura A, Naito Y, Shimamoto T, Komachi Y. Fat and protein intakes and risk of intraparenchymal hemorrhage among middle-aged Japanese. *Am J Epidemiol.* 2003 Jan 1; 157(1): 32-39. Erratum in: *Am J Epidemiol.* 2004 Feb 1; 159(3): 318. PMID: 12505888.	Does not answer question: examined relationship between protein intake and intraparenchymal hemorrhage.
Järvinen R, Knekt P, Rissanen H, Reunanen A. Intake of fish and long-chain n-3 fatty acids and the risk of coronary heart mortality in men and women. *Br J Nutr.* 2006 Apr; 95(4): 824-829. PMID: 16571163.	Does not answer question: examined relationship between fish intake and CHD.
Jenkins DJ, Wong JM, Kendall CW, Esfahani A, Ng VW, Leong TC, Faulkner DA, Vidgen E, Greaves KA, Paul G, Singer W. The effect of a plant-based low-carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. *Arch Intern Med.* 2009 Jun 8; 169(11): 1, 046-1, 054. PMID: 19506174.	Participants diagnosed hyperlipidemia.
Joshi AD, Corral R, Siegmund KD, Haile RW, Le Marchand L, Martínez ME, Ahnen DJ, Sandler RS, Lance P, Stern MC. Red meat and poultry intake, polymorphisms in the nucleotide excision repair and mismatch repair pathways and colorectal cancer risk. 2009 Mar; 30(3): 472-479. Epub 2008 Nov 24. PMID: 19029193; PMCID: PMC2722151.	Study design is case-control family-based study (colorectal cancer).
Kabat GC, Miller AB, Jain M, Rohan TE. A cohort study of dietary iron and heme iron intake and risk of colorectal cancer in women. *Br J Cancer.* 2007 Jul 2; 97 (1): 118-122. Epub 2007 Jun 5. Erratum in: *Br J Cancer.* 2007 Dec 3; 97(11): 1, 600. PMID: 77551493; PMCID: PMC2359661.	Does not answer question: examined relationship between iron and heme iron intake and colorectal cancer.
König A, Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, Lawrence RS, Savitz DA, Teutsch SM. A quantitative analysis of fish consumption and coronary heart disease mortality. *Am J Prev Med.* 2005 Nov; 29(4): 335-346. PMID: 16242600.	Does not answer question: examined relationship between fish intake and CHD.
Kono S. Secular trend of colon cancer incidence and mortality in relation to fat and meat intake in Japan. *Eur J Cancer Prev*. 2004 Apr; 13(2): 127-132. PMID: 15100579.	Study design is non-comparative, correlational study.
Kontogianni MD, Panagiotakos DB, Pitsavos C, Chrysohoou C, Stefanadis C. Relationship between meat intake and the development of acute coronary syndromes: the CARDIO2000 case-control study. *Eur J Clin Nutr.* 2008 Feb; 62(2): 171-177. Epub 2007 Mar 14. PMID: 17356558.	Does not include health outcome of interest in analyses.

Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation*. 2002 Nov 19; 106(21): 2, 747-2, 757. Erratum in: *Circulation.* 2003 Jan 28; 107 (3): 512. PMID: 12438303.	Expert opinion.
Larsson SC, Orsini N, Wolk A. Processed meat consumption and stomach cancer risk: A meta-analysis. *J Natl Cancer Inst.* 2006 Aug 2; 98(15): 1, 078-1, 087. PMID: 16882945.	Does not include colorectal, breast or prostate cancer in analyses.
Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: A meta-analysis of prospective studies. *Int J Cancer.* 2006 Dec 1; 119(11): 2, 657-2, 664. PMID: 16991129.	Study design is meta-analysis (colorectal cancer).
Lee JE, Spiegelman D, Hunter DJ, Albanes D, Bernstein L, van den Brandt PA, Buring JE, Cho E, English DR, Freudenheim JL, Giles GG, Graham S, Horn-Ross PL, Håkansson N, Leitzmann MF, Männistö S, McCullough ML, Miller AB, Parker AS, Rohan TE, Schatzkin A, Schouten LJ, Sweeney C, Willett WC, Wolk A, Zhang SM, Smith-Warner SA. Fat, protein, and meat consumption and renal cell cancer risk: A pooled analysis of 13 prospective studies. *J Natl Cancer Inst*. 2008 Dec 3; 100(23): 1, 695-1, 706. Epub 2008 Nov 25. PMID: 19033572; PMCID: PMC2727138.	Does not include colorectal, breast or prostate cancer in analyses.
Levitan EB, Wolk A, Mittleman MA. Fish consumption, marine omega-3 fatty acids, and incidence of heart failure: A population-based prospective study of middle-aged and elderly men. *Eur Heart J.* 2009 Jun; 30(12): 1, 495-1, 500. Epub 2009 Apr 21. PMID: 19383731; PMCID: PMC2695952.	Does not answer question: Examined relationship between fish intake and heart failure.
Lichtenstein AH, Jalbert SM, Adlercreutz H, Goldin BR, Rasmussen H, Schaefer EJ, Ausman LM. Lipoprotein response to diets high in soy or animal protein with and without isoflavones in moderately hypercholesterolemic subjects. *Arterioscler Thromb Vasc Biol.* 2002 Nov 1; 22(11): 1, 852-1, 858. PMID: 12426215.	Participants diagnosed with hypercholesterolemia.
Linseisen J, Kesse E, Slimani N; EPIC Working Group on Dietary Pattern, Subgroup Meat. Meat consumption in Europe: Results from the EPIC study.*IARC Sci Publ*. 2002; 156: 211-212. PMID: 12484168.	Does not include health outcomes in analyses.
Liu L, Ikeda K, Yamori Y; WHO-CARDIAC Study Group. Inverse relationship between urinary markers of animal protein intake and blood pressure in Chinese: results from the WHO Cardiovascular Diseases and Alimentary Comparison (CARDIAC) Study. *Int J Epidemiol*. 2002 Feb; 31(1): 227-233. PMID: 11914325.	Does not answer question: Examined the relationship between urinary excretion of 3-methylhistidine (as marker of animal protein intake) and blood pressure (BP).
Lucey AJ, Paschos GK, Cashman KD, Martínéz JA, Thorsdottir I, Kiely M. Influence of moderate energy restriction and seafood consumption on bone turnover in overweight young adults. *Am J Clin Nutr.* 2008 Apr; 87(4): 1, 045-1, 052. PMID: 18400730.	Does not include health outcome of interest in analyses.

Lüchtenborg M, Weijenberg MP, de Goeij AF, Wark PA, Brink M, Roemen GM, Lentjes MH, de Bruïne AP, Goldbohm RA, van 't Veer P, van den Brandt PA. Meat and fish consumption, APC gene mutations and hMLH1 expression in colon and rectal cancer: A prospective cohort study (The Netherlands). *Cancer Causes Control.* 2005 Nov; 16(9): 1, 041-1, 054. PMID: 16184469.	Results reported based on the same dataset as Brink, 2005.
Mamo JC, James AP, Soares MJ, Griffiths DG, Purcell K, Schwenke JL. A low-protein diet exacerbates postprandial chylomicron concentration in moderately dyslipidaemic subjects in comparison to a lean red meat protein-enriched diet. *Eur J Clin Nutr.* 2005 Oct; 59(10): 1, 142-1, 148. PMID: 16015257.	Does not answer question: Examined relationship between protein intake and postprandial response.
Männistö S, Dixon LB, Balder HF, Virtanen MJ, Krogh V, Khani BR, Berrino F, van den Brandt PA, Hartman AM, Pietinen P, Tan F, Wolk A, Goldbohm RA. Dietary patterns and breast cancer risk: Results from three cohort studies in the DIETSCAN project. *Cancer Causes Control.* 2005 Aug; 16(6): 725-733. PMID: 16049811.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Marques-Vidal P, Ravasco P, Ermelinda Camilo M. Foodstuffs and colorectal cancer risk: A review. *Clin Nutr.* 2006 Feb; 25(1): 14-36. Epub 2005 Nov 14. Review. PMID: 16290272.	Study design is systematic review (colorectal cancer).
Matheson EM, Mainous AG 3rd, Hill EG, Carnemolla MA. Shellfish consumption and risk of coronary heart disease. *J Am Diet Assoc.* 2009 Aug; 109(8): 1, 422-1, 426. PMID: 19631050.	Does not answer question: Examined relationship between shellfish intake and CHD.
Matthan NR, Jalbert SM, Ausman LM, Kuvin JT, Karas RH, Lichtenstein AH. Effect of soy protein from differently processed products on cardiovascular disease risk factors and vascular endothelial function in hypercholesterolemic subjects. *Am J Clin Nutr.* 2007 Apr; 85(4): 960-966. Erratum in: *Am J Clin Nutr.* 2007 Aug; 86(2): 525. PMID: 17413093.	Participants were hypercholesterolemic.
McCarty MF. The origins of western obesity: A role for animal protein? *Med Hypotheses.* 2000 Mar; 54(3): 488-494. PMID: 10783494.	Study design is narrative review.
McNaughton SA, Mishra GD, Stephen AM, Wadsworth ME. Dietary patterns throughout adult life are associated with body mass index, waist circumference, blood pressure, and red cell folate. *J Nutr.* 2007 Jan; 137(1): 99-105. PMID: 17182808.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Melanson K, Gootman J, Myrdal A, Kline G, Rippe JM. Weight loss and total lipid profile changes in overweight women consuming beef or chicken as the primary protein source. *Nutrition.* 2003 May; 19(5): 409-414. PMID: 12714091.	Dropout rate is higher than inclusion criteria.
Missmer SA, Smith-Warner SA, Spiegelman D, Yaun SS, Adami HO, Beeson WL, van den Brandt PA, Fraser GE, Freudenheim JL, Goldbohm RA, Graham S, Kushi LH, Miller AB, Potter JD, Rohan TE, Speizer FE, Toniolo P, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Hunter DJ. Meat and dairy food consumption and breast cancer: A pooled analysis of cohort studies. *Int J Epidemiol.* 2002 Feb; 31(1): 78-85. PMID: 11914299.	Study design is meta-analysis (breast cancer).

Möllsten AV, Dahlquist GG, Stattin EL, Rudberg S. Higher intakes of fish protein are related to a lower risk of microalbuminuria in young Swedish type 1 diabetic patients. *Diabetes Care.* 2001 May; 24(5): 805-810. PMID: 11347734.	Participants diagnosed with T2D.
Mortensen LS, Hartvigsen ML, Brader LJ, Astrup A, Schrezenmeir J, Holst JJ, Thomsen C, Hermansen K. Differential effects of protein quality on postprandial lipemia in response to a fat-rich meal in type 2 diabetes: comparison of whey, casein, gluten, and cod protein. *Am J Clin Nutr.* 2009 Jul; 90(1): 41-48. Epub 2009 May 20. PMID: 19458012.	Participants diagnosed with T2D.
Mozaffarian D, Psaty BM, Rimm EB, Lemaitre RN, Burke GL, Lyles MF, Lefkowitz D, Siscovick DS. Fish intake and risk of incident atrial fibrillation. *Circulation.* 2004 Jul 27; 110(4): 368-373. Epub 2004 Jul 19. PMID: 15262826; PMCID: PMC1201400.	Does not answer question: Examined relationship between fish intake and atrial fibrillation.
Nagata C, Shimizu H, Kametani M, Takeyama N, Ohnuma T, Matsushita S. Diet and colorectal adenoma in Japanese males and females. *Dis Colon Rectum.* 2001 Jan; 44(1): 105-111. PMID: 11805576.	Study design is case-control study (colorectal cancer).
Nenseter MS, Østerud B, Larsen T, Strøm E, Bergei C, Hewitt S, Holven KB, Hagve TA, Mjøs SA, Solvang M, Pettersen J, Opstvedt J, Ose L. Effect of Norwegian fish powder on risk factors for coronary heart disease among hypercholesterolemic individuals. *Nutr Metab Cardiovasc Dis.* 2000 Dec; 10(6): 323-330. PMID: 11302007.	Did not answer question: Examined relationship between fish powder and CHD.
Nettleton JA, Steffen LM, Loehr LR, Rosamond WD, Folsom AR. Incident heart failure is associated with lower whole-grain intake and greater high-fat dairy and egg intake in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Diet Assoc*. 2008 Nov; 108(11): 1, 881-1, 887. PMID: 18954578; PMCID: PMC2650810.	Does not answer question: Examined relationship between egg intake and heart failure.
Nkondjock A, Receveur O. Fish-seafood consumption, obesity, and risk of type 2 diabetes: an ecological study. *Diabetes Metab.* 2003 Dec; 29(6): 635-642. PMID: 14707894.	Does not answer question: Examined relationship between fish intake and T2D.
Norat T, Lukanova A, Ferrari P, Riboli E. Meat consumption and colorectal cancer risk: Dose-response meta-analysis of epidemiological studies. *Int J Cancer.* 2002 Mar 10; 98(2): 241-256. PMID: 11857415.	Study design is meta-analysis (colorectal cancer).
Norat T, Riboli E. Meat consumption and colorectal cancer: A review of epidemiologic evidence. *Nutr Rev.* 2001 Feb; 59(2): 37-47. Review. PMID: 11310774.	Study design is meta-analysis (colorectal cancer).
Norat T, Riboli E. Meat consumption and colorectal cancer: A review of epidemiologic evidence. *Nutr Rev.* 2001 Feb; 59(2): 37-47. Review. PMID: 11310774.	Study design is narrative review (colorectal cancer).
Nowson CA, Wattanapenpaiboon N, Pachett A. Low-sodium Dietary Approaches to Stop Hypertension-type diet including lean red meat lowers blood pressure in postmenopausal women. *Nutr Res.* 2009 Jan; 29(1): 8-18. PMID: 19185772.	Does not include animal protein products in analyses.

Olmedilla-Alonso B, Granado-Lorencio F, Herrero-Barbudo C, Blanco-Navarro I, Blázquez-García S, Pérez-Sacristán B. Consumption of restructured meat products with added walnuts has a cholesterol-lowering effect in subjects at high cardiovascular risk: a randomised, crossover, placebo-controlled study. *J Am Coll Nutr.* 2008 Apr; 27(2): 342-348. PMID: 18689569.	Does not answer question: Examined effect of restructured meat product on cholesterol.
Panagiotakos DB, Pitsavos C, Zampelas A, Chrysohoou C, Griffin BA, Stefanadis C, Toutouzas P. Fish consumption and the risk of developing acute coronary syndromes: The CARDIO2000 study. *Int J Cardiol.* 2005 Jul 20; 102(3): 403-409. PMID: 16004884.	Does not answer question: Examined relationship between fish intake and health outcomes.
Panagiotakos DB, Zeimbekis A, Boutziouka V, Economou M, Kourlaba G, Toutouzas P, Polychronopoulos E. Long-term fish intake is associated with better lipid profile, arterial blood pressure, and blood glucose levels in elderly people from Mediterranean islands (MEDIS epidemiological study). *Med Sci Monit.* 2007 Jul; 13(7): CR307-CR312. PMID: 17599024.	Does not answer question: Examined relationship between fish intake and health outcomes.
Pham TM, Fujino Y, Kubo T, Ide R, Tokui N, Mizoue T, Ogimoto I, Matsuda S, Yoshimura T. Fish intake and the risk of fatal prostate cancer: Findings from a cohort study in Japan. *Public Health Nutr.* 2009 May; 12(5): 609-613. Epub 2008 Jul 29. PMID: 18664313.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Pieniak Z, Verbeke W, Perez-Cueto F, Brunsø K, De Henauw S. Fish consumption and its motives in households with versus without self-reported medical history of CVD: A consumer survey from five European countries. *BMC Public Health.* 2008 Sep 10; 8: 306. PMID: 18783593; PMCID: PMC2556335.	Does not include health outcomes in analyses.
Processed meat consumption linked to type 2 diabetes. *Nephrol News Issues.* 2002 Apr; 16(5): 68-69. PMID: 11962157.	News article.
Ramel A, Parra D, Martinéz JA, Kiely M, Thorsdottir I. Effects of seafood consumption and weight loss on fasting leptin and ghrelin concentrations in overweight and obese European young adults. *Eur J Nutr.* 2009 Mar; 48(2): 107-114. Epub 2009 Jan 13. PMID: 19142567.	Does not answer question: Examined relationship between seafood and leptin and ghrelin concentrations.
Rosell M, Appleby P, Spencer E, Key T. Weight gain over 5 years in 21, 966 meat-eating, fish-eating, vegetarian, and vegan men and women in EPIC-Oxford. *Int J Obes (Lond).* 2006 Sep; 30(9): 1, 389-1, 396. Epub 2006 Mar 14. PMID: 16534521.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Sandhu MS, White IR, McPherson K. Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: A meta-analytical approach. *Cancer Epidemiol Biomarkers Prev.* 2001 May; 10(5): 439-446. PMID: 11352852.	Study design is systematic review/meta-analysis (colorectal cancer).
Santarelli RL, Pierre F, Corpet DE. Processed meat and colorectal cancer: A review of epidemiologic and experimental evidence. *Nutr Cancer.* 2008; 60(2): 131-144. Review. PMID: 18444144; PMCID: PMC2661797.	Study design is narrative review.

Satia JA, Tseng M, Galanko JA, Martin C, Sandler RS. Dietary patterns and colon cancer risk in Whites and African Americans in the North Carolina Colon Cancer Study. *Nutr Cancer.* 2009; 61(2): 179-193. PMID: 19235034.	Study design is case-control study (colon cancer).
Schulz M, Hoffmann K, Weikert C, Nöthlings U, Schulze MB, Boeing H. Identification of a dietary pattern characterized by high-fat food choices associated with increased risk of breast cancer: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Br J Nutr.* 2008 Nov; 100(5): 942-946. PMID: 18377685.	Does not answer question: Examines relationship between high fat foods and breast cancer.
Seierstad SL, Seljeflot I, Johansen O, Hansen R, Haugen M, Rosenlund G, Frøyland L, Arnesen H. Dietary intake of differently fed salmon: The influence on markers of human atherosclerosis. *Eur J Clin Invest.* 2005 Jan; 35(1): 52-59. PMID: 15638820.	Participants diagnosed with T2D.
Shiell AW, Campbell-Brown M, Haselden S, Robinson S, Godfrey KM, Barker DJ. High-meat, low-carbohydrate diet in pregnancy: Relation to adult blood pressure in the offspring. *Hypertension*. 2001 Dec 1; 38(6): 1, 282-1, 288. PMID: 11751704.	Does not answer question: Examines relationship between dietary intake during pregnancy and health of adult offspring.
Sieri S, Krogh V, Muti P, Micheli A, Pala V, Crosignani P, Berrino F. Fat and protein intake and subsequent breast cancer risk in postmenopausal women. *Nutr Cancer.* 2002; 42(1): 10-17. PMID: 12235640.	Study design is case-control study (breast cancer).
Skjelbred CF, Saebø M, Hjartåker A, Grotmol T, Hansteen IL, Tveit KM, Hoff G, Kure EH. Meat, vegetables and genetic polymorphisms and the risk of colorectal carcinomas and adenomas. *BMC Cancer*. 2007 Dec 19; 7: 228. PMID: 18093316; PMCID: PMC2228310.	Study design is case-control study (colorectal cancer).
Smith DR, Wood R, Tseng S, Smith SB. Increased beef consumption increases apolipoprotein A-I but not serum cholesterol of mildly hypercholesterolemic men with different levels of habitual beef intake. *Exp Biol Med (Maywood).* 2002 Apr; 227(4): 266-275. PMID: 11910049.	Participants diagnosed with mild hypercholesterolemia.
SoRelle R. Fish and long-chain omega-3 fatty acids could be lifesavers for diabetic women. *Circulation.* 2003 Apr 22; 107(15): e9, 033-9, 035. PMID: 12707254.	Participants were diagnosed with diabetes.
Sørensen M, Autrup H, Olsen A, Tjønneland A, Overvad K, Raaschou-Nielsen O. Prospective study of NAT1 and NAT2 polymorphisms, tobacco smoking and meat consumption and risk of colorectal cancer. *Cancer Lett.* 2008 Aug 8; 266(2): 186-193. Epub 2008 Mar 26. PMID: 18372103.	Study design is case-control study (colorectal cancer).
Spencer EA, Appleby PN, Davey GK, Key TJ. Diet and body mass index in 38000 EPIC-Oxford meat-eaters, fish-eaters, vegetarians and vegans. *Int J Obes Relat Metab Disord.* 2003 Jun; 27(6): 728-734. PMID: 12833118.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Stewart JW, Kaplan ML, Beitz DC. Pork with a high content of polyunsaturated fatty acids lowers LDL cholesterol in women. *Am J Clin Nutr.* 2001 Aug; 74(2): 179-187. PMID: 11470718.	Intervention consisted of modified pork high in PUFAs.

Tanskanen A, Hibbeln JR, Tuomilehto J, Uutela A, Haukkala A, Viinamäki H, Lehtonen J, Vartiainen E. Fish consumption and depressive symptoms in the general population in Finland. *Psychiatr Serv.* 2001 Apr; 52(4): 529-531. PMID: 11274502.	Does not include health outcome of interest in analyses.
Tapola NS, Lyyra ML, Karvonen HM, Uusitupa MI, Sarkkinen ES. The effect of meat products enriched with plant sterols and minerals on serum lipids and blood pressure. *Int J Food Sci Nutr.* 2004 Aug; 55(5): 389-397. PMID: 15545047.	Intervention consisted of meat products enriched with plant sterols; participants diagnosed with hypercholesterolemia.
Tappel A. Heme of consumed red meat can act as a catalyst of oxidative damage and could initiate colon, breast and prostate cancers, heart disease and other diseases. *Med Hypotheses*. 2007; 68(3): 562-564. Epub 2006 Oct 11. PMID: 17045417.	Study design is narrative review.
Teixeira Rde C, Molina Mdel C, Zandonade E, Mill JG. Cardiovascular risk in vegetarians and omnivores: A comparative study. *Arq Bras Cardiol.* 2007 Oct; 89(4): 237-244. English, Portuguese. PMID: 17992380.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Terry P, Rohan TE, Wolk A, Maehle-Schmidt M, Magnusson C. Fish consumption and breast cancer risk. *Nutr Cancer.* 2002; 44(1): 1-6. PMID: 12672635.	Study design is case-control study (breast cancer).
Thorsdottir I, Birgisdottir B, Kiely M, Martinez J, Bandarra N. Fish consumption among young overweight European adults and compliance to varying seafood content in four weight loss intervention diets. *Public Health Nutr.* 2009 May; 12(5): 592-598. Epub 2008 Jun 19. PMID: 18561865.	Does not answer question: Examined compliance to eating varying types of seafood in weight loss intervention diets.
Thorsdottir I, Tomasson H, Gunnarsdottir I, Gisladottir E, Kiely M, Parra MD, Bandarra NM, Schaafsma G, Martinéz JA. Randomized trial of weight-loss-diets for young adults varying in fish and fish oil content. *Int J Obes* (Lond). 2007 Oct; 31(10): 1, 560-1, 566. Epub 2007 May 15. PMID: 17502874.	Does not answer question: Examined fish intake and weight loss.
Tiemersma EW, Kampman E, Bueno de Mesquita HB, Bunschoten A, van Schothorst EM, Kok FJ, Kromhout D. Meat consumption, cigarette smoking, and genetic susceptibility in the etiology of colorectal cancer: results from a Dutch prospective study. *Cancer Causes Control.* 2002 May; 13(4): 383-393. PMID: 12074508.	Study design is case-control study (colorectal cancer).
Timonen M, Horrobin D, Jokelainen J, Laitinen J, Herva A, Räsänen P. Fish consumption and depression: The Northern Finland 1966 birth cohort study. *J Affect Disord.* 2004 Nov 1; 82(3): 447-452. PMID: 15555697.	Does not include health outcome of interest in analyses.
Tzoulaki I, Brown IJ, Chan Q, Van Horn L, Ueshima H, Zhao L, Stamler J, Elliott P; International Collaborative Research Group on Macro-/Micronutrients and Blood Pressure. Relation of iron and red meat intake to blood pressure: cross sectional epidemiological study. *BMJ.* 2008 Jul 15; 337: a258. doi: 10.1136/bmj.a258. PMID: 18632704; PMCID: PMC2658466.	Study design is cross-sectional epidemiological study.

Umesawa M, Sato S, Imano H, Kitamura A, Shimamoto T, Yamagishi K, Tanigawa T, Iso H. Relations between protein intake and blood pressure in Japanese men and women: the Circulatory Risk in Communities Study (CIRCS). *Am J Clin Nutr.* 2009 Aug; 90(2): 377-384. Epub 2009 Jun 10. PMID: 19515740.	Study design is cross-sectional.
Varraso R, Jiang R, Barr RG, Willett WC, Camargo CA Jr. Prospective study of cured meats consumption and risk of chronic obstructive pulmonary disease in men. *Am J Epidemiol*. 2007 Dec 15; 166(12): 1, 438-1, 445. Epub 2007 Sep 4. PMID: 17785711; PMCID: PMC2573990.	Does not include health outcome of interest in analyses.
Virtanen JK, Mozaffarian D, Chiuve SE, Rimm EB. Fish consumption and risk of major chronic disease in men. *Am J Clin Nutr.* 2008 Dec; 88(6): 1, 618-1, 625. PubMed PMID: 19064523; PMCID: PMC2613199.	Does not answer question: Examined relationship between fish intake and chronic disease.
Wakai K, Tamakoshi K, Date C, Fukui M, Suzuki S, Lin Y, Niwa Y, Nishio K, Yatsuya H, Kondo T, Tokudome S, Yamamoto A, Toyoshima H, Tamakoshi A; JACC Study Group. Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. *Cancer Sci.* 2005 Sep; 96(9): 590-599. PMID: 16128744.	Does not answer question: Examined relationship between breast cancer and fat intake, not animal protein.
Weggemans RM, Zock PL, Katan MB. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: A meta-analysis. *Am J Clin Nutr.* 2001 May; 73(5): 885-891. PMID: 11333841.	Does not examine relationship between intake of animal protein product and health outcome.
Weghuber D, Widhalm K. Effect of 3-month treatment of children and adolescents with familial and polygenic hypercholesterolaemia with a soya-substituted diet. *Br J Nutr.* 2008 Feb; 99(2): 281-286. Epub 2007 Aug 13. PMID: 17697400.	Participants diagnosed with hypercholesterolemia.
Welch AA, Bingham SA, Ive J, Friesen MD, Wareham NJ, Riboli E, Khaw KT. Dietary fish intake and plasma phospholipid n-3 polyunsaturated fatty acid concentrations in men and women in the European Prospective Investigation into Cancer-Norfolk United Kingdom cohort. *Am J Clin Nutr.* 2006 Dec; 84(6): 1, 330-1, 339. PMID: 17158413.	Does not include health outcomes in analyses; fish is the independent variable.
Wu K, Hu FB, Willett WC, Giovannucci E. Dietary patterns and risk of prostate cancer in U.S. men. *Cancer Epidemiol Biomarkers Prev.* 2006 Jan; 15(1): 167-171. PMID: 16434606.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Yoon H, Benamouzig R, Little J, François-Collange M, Tomé D. Systematic review of epidemiological studies on meat, dairy products and egg consumption and risk of colorectal adenomas. *Eur J Cancer Prev*. 2000 Jun; 9(3): 151-164. PMID: 10954254.	Study design is systematic review (colorectal cancer).
Yuan JM, Ross RK, Gao YT, Yu MC. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *Am J Epidemiol.* 2001 Nov 1; 154(9): 809-816. PMID: 11682363.	Does not answer question: Examined relationship between fish intake and myocardial infarction.

CHAPTER 7. ANIMAL PROTEIN PRODUCTS – PROSTATE CANCER

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF ANIMAL PROTEIN PRODUCTS AND PROSTATE CANCER?

Conclusion statement

Limited evidence shows that animal protein products are associated with prostate cancer incidence.

Grade

Limited

Evidence summary overview

The Committee reviewed six articles (Cross, 2005; Koutros, 2008; Michaud, 2001; Park, 2007; Rodriguez, 2006; Rohrmann, 2007) examining the relationship between animal protein products and incidence of prostate cancer published since 2000. All of the studies represented prospective cohorts from the US. Most studies reported no association between total, red, processed or white meat consumption, meat-cooking method and risk of total prostate cancer, incident cancer or advanced disease. However, in the Health Professionals Follow-Up Study (Michaud, 2001), positive associations between metastatic prostate cancer and red and processed meats were observed. Also, in the Cancer Prevention Study (Rodriguez, 2006), red meat (including processed red meat) and cooked processed meats were positively associated with prostate cancer in Black, but not White, men. Rohrmann and colleagues (2007) reported a positive association between the intake of processed meat and total and advanced prostate cancer, but did not observe relationships between cancer and other animal protein products.

Mixed results were observed regarding the level of doneness of meat. Well and very well done meat were associated with prostate cancer in the Prostate, Lung, and Colorectal and Ovarian (PLCO) Screening Trial (Cross, 2005) and the Agricultural Health Study (Koutros, 2008), but level of doneness was not related to cancer risk in the Multi-ethnic Cohort Study (Park, 2007) or Cancer Prevention Study (Rodriguez, 2006). Thus, cohort studies of animal protein products and prostate cancer since 2000 show little link between total meat intake and prostate cancer, although there may be a link between processed meat products, as well as well-done meat and prostate cancer.

Evidence summary paragraphs

Cross et al, 2005 (positive quality) investigated whether meat intake or meat-related mutagens was associated with an increased risk for prostate cancer. Participants were 29,361 men (aged 55-74 years) in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (United States). All prostate cancers were pathologically confirmed. Dietary intake was assessed at baseline using a 137-item food frequency questionnaire (FFQ) and a detailed meat-cooking and doneness questionnaire; meat categories included in analyses were red meat, white meat, processed meat, barbecued meat, pan-fried meat and very well done meat. During follow-up, 1,338

prostate cancer cases were recorded; of these, 868 were incident cases and 520 were advanced cases. There was no association between total, red, processed or white meat consumption, meat-cooking method, or for meats cooked rare, medium or well-done and risk of total prostate cancer, incident cancer or advanced disease. For very well-done meat, there was an elevated risk for total prostate cancer (RR=1.42; 95% CI: 1.05, 1.92; P for trend=0.02) and for incident disease (RR=1.69; 95% CI: 1.19, 2.40; P for trend=0.003), comparing men who consumed>10g per day to non-consumers. However, no association was evident for advanced disease (RR=1.23; 95% CI: 0.73, 2.06; P for trend=0.44). The authors concluded that the study does not support the hypothesis that red meat intake per se is a risk factor for prostate cancer; however, very well-done meat was positively associated with prostate cancer risk.

Koutros et al, 2008 (positive quality) investigated the association between meat types, cooking methods, doneness and mutagens on the risk of prostate cancer in the Agricultural Health Study (US). Participants were 23,080 male licensed pesticide applicators. Cancer diagnosis was obtained through linkage to cancer registries and to the state death registries and the National Death Index. Dietary intake was assessed with questionnaires that included questions about the frequency of intake of hamburgers, beef steaks, chicken, pork chops or ham steaks and bacon or sausage in the last 12 months. Additional questions were asked on ‘‘doneness’’ of hamburgers and beef steaks (rare, medium, well-done and very well-done) and bacon or sausage (just until done, well-done, charred or blackened) and cooking methods (pan-fried, broiled and grilled) for all meats. During 197,017 person-years of follow-up, 668 incident prostate cancer cases were identified (613 of these were diagnosed after the first year of follow-up and 140 were advanced cases). There was no association between total meat intake and prostate cancer risk among all cases, incident cases, or advanced cases when the highest quintile of intake was compared with the lowest (RR=1.04; 95% CI: 0.80, 1.35; P for trend=0.93, RR=1.06; 95% CI: 0.81, 1.38; P for trend=0.71 and RR=0.93; 95% CI: 0.51, 1.70; P for trend=0.80, respectively). Similarly, no association was observed for any of the following meat items: Total meat, red meat, chicken, bacon or sausage, beef steaks, pork chops or ham steaks and hamburgers. Increased intake of grilled meat, pan-fried meat or broiled meat was not associated with an increased risk of prostate cancer. Well- and very well-done total meat was significantly associated with prostate cancer in all cases (RR=1.22; 95% CI: 1.00, 1.49; P for trend=0.06), incident cases (RR=1.26; 95% CI: 1.02, 1.54; P for trend=0.03), and advanced cases (RR=1.97; 95% CI: 1.26, 3.08; P for trend=0.004) when the highest tertile was compared with the lowest. The authors concluded that well- and very well-done meat was associated with an increased risk for prostate cancer in this cohort.

Michaud et al, 2001 (positive quality) used prospective cohort data from the Health Professionals Follow-up Study to examine whether specific types of animal products or different components of animal products (e.g., calcium and types of fats) are associated with prostate cancer risk in 47,780 men from the US (aged 40-75 years). Prostate cancer status was self-reported on biennial questionnaires with medical record confirmation. Dietary intake over the previous year was estimated in 1986, 1990 and 1994 using a 131-item self-administered, mailed FFQ. Between 1986 and 1996, 1897 total cases of prostate cancer (excluding stage A1) were identified; of these, 536 were advanced and 249 were metastatic cancers. Intakes of total and red meat were not associated with risk of total or advanced prostate cancer. An elevated risk of

metastatic prostate cancer was observed with intake of red meat, which was slightly attenuated after controlling for saturated fat and alpha-linoleic fatty acids (RR=1.5, 95% CI: 0.88, 2.5; P for trend=0.20). Processed meats, bacon and beef, pork or lamb as a main dish each contributed to an elevated risk of metastatic prostate cancer. Men who consumed processed meats twice or more per week had a relative risk of 1.4 (95% CI: 0.94, 2.1; P for trend=0.08), compared to men who did not eat processed meat, after controlling for saturated fat and alpha-linolenic acid. Similar risks were observed among men consuming bacon twice or more a week (P for trend=0.08). An elevated risk of metastatic prostate cancer was also observed among high consumers of beef, pork or lamb (five or more per week), eaten as a main dish (RR=1.4, 95% CI: 0.72, 2.5; P for trend=0.24). Intakes of hamburgers, hot dogs and chicken (with or without skin) were not associated with increased risk of metastatic prostate cancer. There was a two-fold increase in the risk of metastatic prostate cancer when those who had high intakes of both red meat and dairy products were compared to those with low intakes of both products, but this association was attenuated after controlling for potential confounders. The authors concluded that intakes of red meat appear to be related to increased risk of metastatic prostate cancer.

Park et al, 2007 (positive quality) examined the association between prostate cancer risk and the intake of fat, cholesterol, meat, fish and fats from meat in the Multiethnic Cohort Study (N=82,483 men, ≥45 years) in the US. Incident cases of prostate cancer were identified by linkage to three population-based cancer registries. Dietary intake was assessed using self-administered FFQ with 180 items at baseline. Intake of meat was calculated as the sum of grams from single food items of meat and relevant portions of mixed dishes, estimated from recipes. Total meat, poultry and processed meat as well as individual meat groups (beef, pork, red meat, poultry and processed meat) were examined. During the follow-up period of eight years, a total of 4,404 incident cases, including 1,278 non-localized or high-grade cancer cases, were identified. Intakes of total, red, and processed meat and individual meat items did not show a statistically significant association with risk. No association between meat preparation and prostate cancer risk was observed: RR of well-done vs. rare or medium=1.10; 95% CI: 0.91, 1.33. The authors concluded that intake of different types of fat and meat showed no strong association with overall prostate cancer risk.

Rodriguez et al, 2006 (positive quality) examined the association between unprocessed red meat, processed meats and poultry intake among White and Black men in relation to prostate cancer incidence in the Cancer Prevention Study II Nutrition Cohort (N=692 Black and 64,856 White men) in the US. Cancer incidence was initially identified through self-report on follow-up questionnaires and subsequently verified by medical records or by linkage to state cancer registries and the National Death Index. Dietary intake over the past year was assessed at baseline using a 68-item modified Block FFQ. The analyses considered intake of total red meat, unprocessed red meat, processed meat (which was further categorized as cooked processed or lunch meats) and poultry, computed by summing across all items that contribute to each group. “Doneness” was also considered. From 1992 to 2001, 85 and 5,028 cases of incident prostate cancer were observed among Black and White men, respectively. Total red meat (processed plus unprocessed red meat) consumption was associated with higher incidence of prostate cancer among Black men (rate ratio [RR]=2.0; 95% CI: 1.0, 4.2, for highest vs. lowest quartiles; P for trend=0.05). However, among White men, no

association was seen between total red meat consumption and either the overall incidence of prostate cancer (RR=1.0; 95% CI: 0.9, 1.0) or metastatic (RR=0.8; 95% CI: 0.5, 1.3) prostate cancer. Black men in the highest category of processed meat consumption had higher risk of total incident prostate cancer than those in the lowest quartile (RR=2.4; 95% CI: 1.2, 4.9; P for trend=0.008). This increased risk of prostate cancer among Black men was associated solely with consumption of cooked processed meat (bacon, hot dogs and sausages; RR=2.7; 95% CI: 1.3, 5.3 for the highest vs. lowest quartiles; P for trend=0.008) and not with consumption of lunch meats. The risk of metastatic prostate cancer was associated with consumption of cooked processed meats (P for trend=0.04) among White men in analyses adjusted only for age, but this association was attenuated by further adjustment. No other measure of meat intake was associated with risk of prostate cancer. Reported preference for red meat doneness was not associated with risk of prostate cancer among White or Black men. The authors concluded that that high consumption of cooked processed meats may contribute to prostate cancer risk among Black men in the US.

Rohrmann et al, 2007 (positive quality) conducted a prospective cohort study in men to evaluate the association of the intake of total meat, specific types of meat, dairy foods and others rich in calcium and total dietary supplemental calcium intake with prostate cancer. Subjects were men (N=3,892; 53.8 years of age; BMI of 26.5kg/m^2) who were participating in the CLUE II study based in Washington County, MD, which began in 1989. Meat intake was assessed at baseline using an abbreviated version of the Block FFQ that was administered by mail to assess the frequency and portion size of consumption of 60 food items. Items included in analyses were total meat, beef, processed meat, red meat and poultry. Prostate cancer diagnosis was assessed using the Washington County Cancer Registry and Maryland Cancer Registry in October 2004. From 1989 through October 2004, 199 incident prostate cancer cases were ascertained. Results showed no significant (NS) relationships between total meat, red meat or poultry intake with total, low-stage or high-stage prostate cancer. Processed meat consumption was associated with a non-statistically significant higher risk of total (5+ vs. less than one serving per week: HR=1.53, 95% CI: 0.98, 2.39; P for trend=0.20) and advanced (HR=2.24; 95% CI: 0.90, 5.59; P for trend=0.22) prostate cancer. The authors concluded that consumption of processed meat, but not total meat or red meat, was associated with a possible increased risk of total prostate cancer in this prospective study.

Overview table

Author, Year, Study Design, Class, Rating	Study Name/Location	Total Meat Association (Pos, Neg, None)	Read Meat Association (Pos, Neg, None)	Processed Meat Association (Pos, Neg, None)	Poultry Association (Pos, Neg, None)
Cross et al 2005; Cancer Res Study Design: Prospective Cohort Study Class: B Positive quality	Prostate, Lung, Colorectal and Ovarian (PLCO) Screening Trial. Location: US.	Ø Total, incident or advanced. Very well-done meat: (+) Total and incident, Ø Advanced.	Ø Total, incident or advanced.	Ø Total, incident or advanced.	White meat: Ø Total, incident or advanced.
Koutros S et al 2008 Study Design: Prospective cohort design Class: B Positive quality	Agricultural Health Study. Location: US.	Ø Total, incident or advanced. Well- and very well-done meat: (+) Total, incident, and advanced.	Ø Total, incident or advanced.	Bacon/sausage: Ø Total, incident or advanced.	Chicken: Ø Total, incident or advanced.

Michaud DS, Augustsson K et al, 2001 Study Design: Prospective Cohort Study Class: B Positive quality	Health Professionals Follow Up Study. Location: US.	Ø Total or advanced.	Ø Total or advanced. (+) Metastatic.	(+) Metastatic.	Chicken: Ø Metastatic.
Park et al 2007; Int J Cancer Study Design: Prospective cohort design Class: B Positive quality	Multiethnic Cohort Study. Location: US.	Ø; Doneness: Ø.	Not examined.	Ø.	Poultry: Ø.
Rodriguez et al 2006 Study Design: Prospective cohort study Class: B Positive quality	Cancer Prevention Study II Nutrition Cohort. Location: US.	Red plus processed red meat: + Black men, Ø White men. Doneness: Ø.	Not examined.	Cooked processed meat: (+) Black men only. Lunchmeats: Ø.	Not examined.

Rohrmann S, Platz EA et al, 2007 Study Design: Prospective cohort study Class: B Positive quality	CLUE II. Location: US.	Ø Total, low-, or high-stage.	Ø Total, low-, or high-stage.	(+) Total and advanced.	Poultry: Ø Total, low-, or high-stage.

Search plan and results

Inclusion criteria

- January 2000 to September 2009
- Prospective cohort studies on colorectal, breast and prostate cancers
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children two to 18 years; Adults 19 years and older
- *Populations:* Healthy, those with elevated chronic disease risk.

Exclusion criteria

- With the exception of the body weight outcome, cross-sectional studies were excluded from the review
- Systematic reviews and meta-analyses on colorectal, breast and prostate cancers. Only original research studies with prospective cohort design were included in the review
- Studies specifically related to seafood or milk product intake (considered as separate questions)
- Studies that reported on animal protein intake as a component of a dietary pattern and not as an individual variable
- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: (Animal protein* OR meat[mh] OR "Egg Proteins, Dietary"[mh] OR "Fish Proteins"[mh]) AND ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "overweight"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mh:NoExp] OR “heart diseases”[mh] OR "Coronary Disease"[Mesh] OR “blood pressure”[mh] OR “chronic disease”[mh] OR obesity[mh] OR "Body Weights and Measures"[mh] OR "Colorectal Neoplasms"[mesh])
  (Animal protein* OR meat[mh] OR "Egg Proteins, Dietary"[mh] OR "Fish Proteins"[mh] OR seafood[majr] OR crustacea[majr]) AND (systematic[sb] OR Meta-Analysis[ptyp] OR "Cohort Studies"[Mesh]) AND ("Prostatic Neoplasms"[Mesh] OR "Breast Neoplasms"[Mesh])
  eggs [mh] AND ("Diabetes Mellitus, Type 2"[majr] OR "metabolic syndrome X"[majr] OR "overweight"[majr] OR "hypertension"[majr] OR "dyslipidemias"[majr] OR "cardiovascular diseases"[majr:NoExp] OR “heart diseases”[majr] OR "Coronary Disease"[Mesh] OR “blood pressure”[majr] OR “chronic disease”[majr] OR obesity[majr] OR "Body Weights and Measures"[majr])
  (Note: "Cohort Studies"[Mesh]) includes prospective studies)

Date searched: 09/01/2009; update 09/18/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 771
- Total articles identified to review from electronic databases: 166
- Articles identified via handsearch or other means: 2
- Number of Primary Articles Identified: 47
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 47
- Number of Articles Reviewed but Excluded: 121

Included articles (References)

What is the relationship between the intake of animal protein products and cardiovascular disease?

1. Djoussé L, Gaziano JM. Egg consumption in relation to cardiovascular disease and mortality: the Physicians' Health Study.*Am J Clin Nutr.* 2008 Apr; 87(4): 964-969. PMID: 18400720; PMCID: PMC2386667.
2. Halton TL, Willett WC, Liu S, Manson JE, Albert CM, Rexrode K, Hu FB. Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med.* 2006 Nov 9; 355(19): 1, 991-2, 002. PMID: 17093250.
3. Kelemen LE, Kushi LH, Jacobs DR Jr, Cerhan JR. Associations of dietary protein with disease and mortality in a prospective study of postmenopausal women. *Am J Epidemiol.* 2005 Feb 1; 161(3): 239-249. PMID: 15671256.
4. Nakamura Y, Iso H, Kita Y, Ueshima H, Okada K, Konishi M, Inoue M, Tsugane S. Egg consumption, serum total cholesterol concentrations and coronary heart disease incidence: Japan Public Health Center-based prospective study. *Br J Nutr.* 2006 Nov; 96(5): 921-928. PMID: 17092383.
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serum cholesterol, and cause-specific and all-cause mortality: The National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980 (NIPPON DATA80).*Am J Clin Nutr.* 2004 Jul; 80(1): 58-63. PMID: 15213028.

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What is the relationship between the intake of animal protein products and blood pressure?

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What is the relationship between the intake of animal protein products and colorectal cancer?

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What is the relationship between the intake of animal protein products and prostate cancer?

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What is the relationship between the intake of animal protein products and breast cancer?

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Excluded articles

Article	Reason for Exclusion
Alexander DD, Cushing CA, Lowe KA, Sceurman B, Roberts MA. Meta-analysis of animal fat or animal protein intake and colorectal cancer. *Am J Clin Nutr.* 2009 May; 89(5): 1, 402-1, 409. Epub 2009 Mar 4. PMID: 19261724.	Study design is meta-analysis (colorectal cancer).

Appleby PN, Davey GK, Key TJ. Hypertension and blood pressure among meat eaters, fish eaters, vegetarians and vegans in EPIC-Oxford. *Public Health Nutr.* 2002 Oct; 5(5): 645-654. PMID: 12372158.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Augustsson K, Michaud DS, Rimm EB, Leitzmann MF, Stampfer MJ, Willett WC, Giovannucci E. A prospective study of intake of fish and marine fatty acids and prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2003 Jan; 12(1): 64-67. PMID: 12540506.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Azadbakht L, Esmaillzadeh A. Red meat intake is associated with metabolic syndrome and the plasma C-reactive protein concentration in women. *J Nutr.* 2009 Feb; 139(2): 335-339. Epub 2008 Dec 11. PMID: 19074209.	Does not answer question: Examined relationship between red meat intake and metabolic syndrome.
Balder HF, Vogel J, Jansen MC, Weijenberg MP, van den Brandt PA, Westenbrink S, van der Meer R, Goldbohm RA. Heme and chlorophyll intake and risk of colorectal cancer in the Netherlands cohort study. *Cancer Epidemiol Biomarkers Prev.* 2006 Apr; 15(4): 717-725. PMID: 16614114.	Does not answer question: Examined relationship between heme and chlorophyll intake and colorectal cancer.
Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: A systematic literature review and meta-analysis. *Cancer Causes Control.* 2007 Nov; 18(9): 967-988. Epub 2007 Jul 19. Review. PMID: 17638104; PMCID: PMC2592095.	Does not include colorectal, breast, or prostate cancer in analyses.
Barraj L, Tran N, Mink P. A comparison of egg consumption with other modifiable coronary heart disease lifestyle risk factors: a relative risk apportionment study. *Risk Anal*. 2009 Mar; 29(3): 401-415. Epub 2008 Nov 4. PMID: 19000074.	Does not answer question: Used risk apportionment approach to estimate contribution of egg intake to coronary heart disease (CHD) risk at the population level.
Benassi-Evans B, Clifton PM, Noakes M, Keogh JB, Fenech M. High protein-high red meat versus high carbohydrate weight loss diets do not differ in effect on genome stability and cell death in lymphocytes of overweight men. *Mutagenesis.* 2009 May; 24(3): 271-277. Epub 2009 Mar 5. PMID: 19264840.	Does not include animal protein product intake in analyses.
Brink M, Weijenberg MP, de Goeij AF, Roemen GM, Lentjes MH, de Bruïne AP, Goldbohm RA, van den Brandt PA. Meat consumption and K-ras mutations in sporadic colon and rectal cancer in The Netherlands Cohort Study. *Br J Cancer.* 2005 Apr 11; 92(7): 1, 310-1, 320. PMID: 15812479.	Study design is case-cohort.
Cade JE, Burley VJ, Greenwood DC; UK Women's Cohort Study Steering Group. The UK Women's Cohort Study: Comparison of vegetarians, fish-eaters and meat-eaters. *Public Health Nutr.* 2004 Oct; 7(7): 871-878. PMID: 15482612.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.

Chan AT, Tranah GJ, Giovannucci EL, Willett WC, Hunter DJ, Fuchs CS. Prospective study of N-acetyltransferase-2 genotypes, meat intake, smoking and risk of colorectal cancer. *Int J Cancer.* 2005 Jul 1; 115(4): 648-652. PMID: 15700302.	Study design is case-control study (colorectal cancer).
Chavarro JE, Stampfer MJ, Hall MN, Sesso HD, Ma J. A 22-y prospective study of fish intake in relation to prostate cancer incidence and mortality. *Am J Clin Nutr.* 2008 Nov; 88(5): 1, 297-1, 303. PMID: 18996866.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Chrysohoou C, Panagiotakos DB, Pitsavos C, Skoumas J, Krinos X, Chloptsios Y, Nikolaou V, Stefanadis C. Long-term fish consumption is associated with protection against arrhythmia in healthy persons in a Mediterranean region: The ATTICA study. *Am J Clin Nutr.* 2007 May; 85(5): 1, 385-1, 391. PMID: 17490977.	Does not answer question: Examined relationship between fish intake and arrhythmia.
Cotterchio M, Boucher BA, Manno M, Gallinger S, Okey AB, Harper PA. Red meat intake, doneness, polymorphisms in genes that encode carcinogen-metabolizing enzymes, and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2008 Nov; 17(11): 3, 098-3, 107. PMID: 18990750.	Study design is case-control (colorectal cancer).
Crowe FL, Key TJ, Appleby PN, Travis RC, Overvad K, Jakobsen MU, Johnsen NF, Tjønneland A, Linseisen J, Rohrmann S, Boeing H, Pischon T, Trichopoulou A, Lagiou P, Trichopoulos D, Sacerdote C, Palli D, Tumino R, Krogh V, Bueno-de-Mesquita HB, Kiemeney LA, Chirlaque MD, Ardanaz E, Sánchez MJ, Larrañaga N, González CA, Quirós JR, Manjer J, Wirfält E, Stattin P, Hallmans G, Khaw KT, Bingham S, Ferrari P, Slimani N, Jenab M, Riboli E. Dietary fat intake and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr.* 2008 May; 87(5): 1, 405-1, 413. PMID: 18469265.	Does not answer question: Examined relationship between animal fat intake and prostate cancer.
Dallongeville J, Yarnell J, Ducimetière P, Arveiler D, Ferrières J, Montaye M, Luc G, Evans A, Bingham A, Hass B, Ruidavets JB, Amouyel P. Fish consumption is associated with lower heart rates.*Circulation.* 2003 Aug 19; 108(7): 820-825. Epub 2003 Aug 11. PMID: 12912821.	Does not answer question: Examined relationship between fish intake and heart rates.
Davey GK, Spencer EA, Appleby PN, Allen NE, Knox KH, Key TJ. EPIC-Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33 883 meat-eaters and 31 546 non meat-eaters in the UK. *Public Health Nutr.* 2003 May; 6(3): 259-269. PMID: 12740075.	Does not include health outcomes in analyses.
de Mello VD, Zelmanovitz T, Perassolo MS, Azevedo MJ, Gross JL. Withdrawal of red meat from the usual diet reduces albuminuria and improves serum fatty acid profile in type 2 diabetes patients with macroalbuminuria. *Am J Clin Nutr*. 2006 May; 83(5): 1, 032-1, 038. PMID: 16685043.	Participants diagnosed with type 2 diabetes (T2D).
Dixon LB, Balder HF, Virtanen MJ, Rashidkhani B, Männistö S, Krogh V, van Den Brandt PA, Hartman AM, Pietinen P, Tan F, Virtamo J, Wolk A, Goldbohm RA. Dietary patterns associated with colon and rectal cancer: results from the Dietary Patterns and Cancer (DIETSCAN) Project. *Am J Clin Nutr.* 2004 Oct; 80(4): 1, 003-1, 011. PMID: 15447912.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.

Djoussé L, Gaziano JM. Egg consumption and risk of heart failure in the Physicians' Health Study. *Circulation.* 2008 Jan 29; 117(4): 512-516. Epub 2008 Jan 14. PMID: 18195171; PMCID: PMC2706003.	Does not answer question: Examined relationship between egg consumption and heart failure.
Egeberg R, Olsen A, Autrup H, Christensen J, Stripp C, Tetens I, Overvad K, Tjønneland A. Meat consumption, N-acetyl transferase 1 and 2 polymorphism and risk of breast cancer in Danish postmenopausal women. *Eur J Cancer Prev.* 2008 Feb; 17(1): 39-47. PMID: 18090909.	Study design is nested case-control study (breast cancer).
Eichholzer M, Bisig B. Daily consumption of (red) meat or meat products in Switzerland: Results of the 1992/93 Swiss Health Survey. *Eur J Clin Nutr.* 2000 Feb; 54(2): 136-142. PMID: 10694784.	Does not include health outcomes in analyses.
Elliott P, Stamler J, Dyer AR, Appel L, Dennis B, Kesteloot H, Ueshima H, Okayama A, Chan Q, Garside DB, Zhou B. Association between protein intake and blood pressure: The INTERMAP Study. *Arch Intern Med.* 2006 Jan 9; 166(1): 79-87. PMID: 16401814.	Study design is cross-sectional epidemiological study.
Engeset D, Andersen V, Hjartåker A, Lund E. Consumption of fish and risk of colon cancer in the Norwegian Women and Cancer (NOWAC) study. *Br J Nutr.* 2007 Sep; 98(3): 576-582. Epub 2007 Apr 10. Erratum in: *Br J Nutr.* 2008 Mar; 99(3): 696. PMID: 17419892.	Does not answer question: Examined relationship between fish intake and colon cancer.
Erkkilä AT, Lichtenstein AH, Mozaffarian D, Herrington DM. Fish intake is associated with a reduced progression of coronary artery atherosclerosis in postmenopausal women with coronary artery disease. *Am J Clin Nutr.* 2004 Sep; 80(3): 626-632. PMID: 15321802.	Participants diagnosed with CHD.
Erkkilä AT, Schwab US, de Mello VD, Lappalainen T, Mussalo H, Lehto S, Kemi V, Lamberg-Allardt C, Uusitupa MI. Effects of fatty and lean fish intake on blood pressure in subjects with coronary heart disease using multiple medications. *Eur J Nutr.* 2008 Sep; 47(6): 319-328. Epub 2008 Jul 29. PMID: 18665413.	Participants diagnosed with CHD.
Faramawi MF, Johnson E, Fry MW, Sall M, Zhou Y. Consumption of different types of meat and the risk of renal cancer: Meta-analysis of case-control studies. *Cancer Causes Control.* 2007 Mar; 18(2): 125-133. Epub 2007 Jan 22. Erratum in: *Cancer Causes Control.* 2007 Jun; 18 (5): 581. Yi, Zhou [corrected to Zhou, Yi]. PMID: 17242980.	Does not include colorectal, breast or prostate cancer in analyses.
Ferrucci LM, Sinha R, Graubard BI, Mayne ST, Ma X, Schatzkin A, Schoenfeld PS, Cash BD, Flood A, Cross AJ. Dietary meat intake in relation to colorectal adenoma in asymptomatic women. *Am J Gastroenterol.* 2009 May; 104(5): 1, 231-1, 140. Epub 2009 Apr 14. PMID: 19367270.	Study design is case-control study (colorectal cancer).
Geelen A, Schouten JM, Kamphuis C, Stam BE, Burema J, Renkema JM, Bakker EJ, van't Veer P, Kampman E. Fish consumption, n-3 fatty acids, and colorectal cancer: a meta-analysis of prospective cohort studies. *Am J Epidemiol*. 2007 Nov 15; 166(10): 1, 116-1, 125. Epub 2007 Sep 6. PMID: 17823383.	Study design is meta-analysis (colorectal cancer).

Gillum RF, Mussolino ME, Madans JH. Fish consumption and hypertension incidence in African Americans and whites: The NHANES I Epidemiologic Follow-up Study. *J Natl Med Assoc.* 2001 Apr; 93(4): 124-128. PMID: 12653399; PMCID: PMC2593988.	Does not answer question: Examined relationship between fish intake and hypertension (HTN).
Goldin BR, Brauner E, Adlercreutz H, Ausman LM, Lichtenstein AH. Hormonal response to diets high in soy or animal protein without and with isoflavones in moderately hypercholesterolemic subjects. *Nutr Cancer.* 2005; 51(1): 1-6. PMID: 15749623.	Does not answer question: Examined hormonal response to diets high in soy or animal protein.
Gonzalez CA, Riboli E. Diet and cancer prevention: Where we are, where we are going. Nutr Cancer. 2006; 56(2): 225-31. Review. PMID: 17474869.	Study design is narrative review.
Grillenberger M, Neumann CG, Murphy SP, Bwibo NO, Weiss RE, Jiang L, Hautvast JG, West CE. Intake of micronutrients high in animal-source foods is associated with better growth in rural Kenyan school children. *Br J Nutr*. 2006 Feb; 95(2): 379-390. PMID: 16469157.	Study population not from a developed country as defined by the Human Development Index (2009).
Gross JL, Zelmanovitz T, Moulin CC, De Mello V, Perassolo M, Leitão C, Hoefel A, Paggi A, Azevedo MJ. Effect of a chicken-based diet on renal function and lipid profile in patients with type 2 diabetes: a randomized crossover trial. *Diabetes Care.* 2002 Apr; 25(4): 645-651. PMID: 11919119.	Participants diagnosed with T2D.
Günther AL, Remer T, Kroke A, Buyken AE. Early protein intake and later obesity risk: which protein sources at which time points throughout infancy and childhood are important for body mass index and body fat percentage at 7 y of age? *Am J Clin Nutr.* 2007 Dec; 86(6): 1, 765-1, 772. PMID: 18065597.	Does not answer question: Examined protein intake during infancy and childhood and body weight outcomes at age seven years.
He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, Greenland P. Accumulated evidence on fish consumption and coronary heart disease mortality: A meta-analysis of cohort studies. *Circulation.* 2004 Jun 8; 109(22): 2, 705-2, 711. PMID: 15184295.	Does not answer question: examined relationship between fish intake and CHD.
High red-meat intake, obesity linked to cancer.*Health News.* 2002 Feb; 8(2): 9. PMID: 11862847.	News article.
Hodgson JM, Burke V, Beilin LJ, Puddey IB. Partial substitution of carbohydrate intake with protein intake from lean red meat lowers blood pressure in hypertensive persons. *Am J Clin Nutr.* 2006 Apr; 83(4): 780-787. PMID: 16600928.	Participants diagnosed with HTN.
Hu FB, Manson JE, Willett WC. Types of dietary fat and risk of coronary heart disease: a critical review.*J Am Coll Nutr.* 2001 Feb; 20(1): 5-19. Review. PMID: 11293467.	Study design is narrative review.
Huncharek M, Kupelnick B, Wheeler L. Dietary cured meat and the risk of adult glioma: A meta-analysis of nine observational studies. *J Environ Pathol Toxicol* Oncol. 2003; 22(2): 129-137. PMID: 14533876.	Does not include colorectal, breast, or prostate cancer in analyses.

Huncharek M, Kupelnick B. A meta-analysis of maternal cured meat consumption during pregnancy and the risk of childhood brain tumors. *Neuroepidemiology.* 2004 Jan-Apr; 23(1-2): 78-84. PMID: 14739572.	Does not include colorectal, breast, or prostate cancer in analyses.
Hunninghake DB, Maki KC, Kwiterovich PO Jr, Davidson MH, Dicklin MR, Kafonek SD. Incorporation of lean red meat into a National Cholesterol Education Program Step I diet: A long-term, randomized clinical trial in free-living persons with hypercholesterolemia. *J Am Coll Nutr.* 2000 Jun; 19(3): 351-360. PMID: 10872897.	Participants diagnosed with hypercholesterolemia.
Iso H, Sato S, Kitamura A, Naito Y, Shimamoto T, Komachi Y. Fat and protein intakes and risk of intraparenchymal hemorrhage among middle-aged Japanese. *Am J Epidemiol.* 2003 Jan 1; 157(1): 32-39. Erratum in: *Am J Epidemiol.* 2004 Feb 1; 159(3): 318. PMID: 12505888.	Does not answer question: examined relationship between protein intake and intraparenchymal hemorrhage.
Järvinen R, Knekt P, Rissanen H, Reunanen A. Intake of fish and long-chain n-3 fatty acids and the risk of coronary heart mortality in men and women. *Br J Nutr.* 2006 Apr; 95(4): 824-829. PMID: 16571163.	Does not answer question: examined relationship between fish intake and CHD.
Jenkins DJ, Wong JM, Kendall CW, Esfahani A, Ng VW, Leong TC, Faulkner DA, Vidgen E, Greaves KA, Paul G, Singer W. The effect of a plant-based low-carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. *Arch Intern Med.* 2009 Jun 8; 169(11): 1, 046-1, 054. PMID: 19506174.	Participants diagnosed hyperlipidemia.
Joshi AD, Corral R, Siegmund KD, Haile RW, Le Marchand L, Martínez ME, Ahnen DJ, Sandler RS, Lance P, Stern MC. Red meat and poultry intake, polymorphisms in the nucleotide excision repair and mismatch repair pathways and colorectal cancer risk. 2009 Mar; 30(3): 472-479. Epub 2008 Nov 24. PMID: 19029193; PMCID: PMC2722151.	Study design is case-control family-based study (colorectal cancer).
Kabat GC, Miller AB, Jain M, Rohan TE. A cohort study of dietary iron and heme iron intake and risk of colorectal cancer in women. *Br J Cancer.* 2007 Jul 2; 97 (1): 118-122. Epub 2007 Jun 5. Erratum in: *Br J Cancer.* 2007 Dec 3; 97(11): 1, 600. PMID: 77551493; PMCID: PMC2359661.	Does not answer question: examined relationship between iron and heme iron intake and colorectal cancer.
König A, Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, Lawrence RS, Savitz DA, Teutsch SM. A quantitative analysis of fish consumption and coronary heart disease mortality. *Am J Prev Med.* 2005 Nov; 29(4): 335-346. PMID: 16242600.	Does not answer question: examined relationship between fish intake and CHD.
Kono S. Secular trend of colon cancer incidence and mortality in relation to fat and meat intake in Japan. *Eur J Cancer Prev*. 2004 Apr; 13(2): 127-132. PMID: 15100579.	Study design is non-comparative, correlational study.
Kontogianni MD, Panagiotakos DB, Pitsavos C, Chrysohoou C, Stefanadis C. Relationship between meat intake and the development of acute coronary syndromes: the CARDIO2000 case-control study. *Eur J Clin Nutr.* 2008 Feb; 62(2): 171-177. Epub 2007 Mar 14. PMID: 17356558.	Does not include health outcome of interest in analyses.

Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation*. 2002 Nov 19; 106(21): 2, 747-2, 757. Erratum in: *Circulation.* 2003 Jan 28; 107 (3): 512. PMID: 12438303.	Expert opinion.
Larsson SC, Orsini N, Wolk A. Processed meat consumption and stomach cancer risk: A meta-analysis. *J Natl Cancer Inst.* 2006 Aug 2; 98(15): 1, 078-1, 087. PMID: 16882945.	Does not include colorectal, breast or prostate cancer in analyses.
Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: A meta-analysis of prospective studies. *Int J Cancer.* 2006 Dec 1; 119(11): 2, 657-2, 664. PMID: 16991129.	Study design is meta-analysis (colorectal cancer).
Lee JE, Spiegelman D, Hunter DJ, Albanes D, Bernstein L, van den Brandt PA, Buring JE, Cho E, English DR, Freudenheim JL, Giles GG, Graham S, Horn-Ross PL, Håkansson N, Leitzmann MF, Männistö S, McCullough ML, Miller AB, Parker AS, Rohan TE, Schatzkin A, Schouten LJ, Sweeney C, Willett WC, Wolk A, Zhang SM, Smith-Warner SA. Fat, protein, and meat consumption and renal cell cancer risk: A pooled analysis of 13 prospective studies. *J Natl Cancer Inst*. 2008 Dec 3; 100(23): 1, 695-1, 706. Epub 2008 Nov 25. PMID: 19033572; PMCID: PMC2727138.	Does not include colorectal, breast or prostate cancer in analyses.
Levitan EB, Wolk A, Mittleman MA. Fish consumption, marine omega-3 fatty acids, and incidence of heart failure: A population-based prospective study of middle-aged and elderly men. *Eur Heart J.* 2009 Jun; 30(12): 1, 495-1, 500. Epub 2009 Apr 21. PMID: 19383731; PMCID: PMC2695952.	Does not answer question: Examined relationship between fish intake and heart failure.
Lichtenstein AH, Jalbert SM, Adlercreutz H, Goldin BR, Rasmussen H, Schaefer EJ, Ausman LM. Lipoprotein response to diets high in soy or animal protein with and without isoflavones in moderately hypercholesterolemic subjects. *Arterioscler Thromb Vasc Biol.* 2002 Nov 1; 22(11): 1, 852-1, 858. PMID: 12426215.	Participants diagnosed with hypercholesterolemia.
Linseisen J, Kesse E, Slimani N; EPIC Working Group on Dietary Pattern, Subgroup Meat. Meat consumption in Europe: Results from the EPIC study.*IARC Sci Publ*. 2002; 156: 211-212. PMID: 12484168.	Does not include health outcomes in analyses.
Liu L, Ikeda K, Yamori Y; WHO-CARDIAC Study Group. Inverse relationship between urinary markers of animal protein intake and blood pressure in Chinese: results from the WHO Cardiovascular Diseases and Alimentary Comparison (CARDIAC) Study. *Int J Epidemiol*. 2002 Feb; 31(1): 227-233. PMID: 11914325.	Does not answer question: Examined the relationship between urinary excretion of 3-methylhistidine (as marker of animal protein intake) and blood pressure (BP).
Lucey AJ, Paschos GK, Cashman KD, Martínéz JA, Thorsdottir I, Kiely M. Influence of moderate energy restriction and seafood consumption on bone turnover in overweight young adults. *Am J Clin Nutr.* 2008 Apr; 87(4): 1, 045-1, 052. PMID: 18400730.	Does not include health outcome of interest in analyses.

Lüchtenborg M, Weijenberg MP, de Goeij AF, Wark PA, Brink M, Roemen GM, Lentjes MH, de Bruïne AP, Goldbohm RA, van 't Veer P, van den Brandt PA. Meat and fish consumption, APC gene mutations and hMLH1 expression in colon and rectal cancer: A prospective cohort study (The Netherlands). *Cancer Causes Control.* 2005 Nov; 16(9): 1, 041-1, 054. PMID: 16184469.	Results reported based on the same dataset as Brink, 2005.
Mamo JC, James AP, Soares MJ, Griffiths DG, Purcell K, Schwenke JL. A low-protein diet exacerbates postprandial chylomicron concentration in moderately dyslipidaemic subjects in comparison to a lean red meat protein-enriched diet. *Eur J Clin Nutr.* 2005 Oct; 59(10): 1, 142-1, 148. PMID: 16015257.	Does not answer question: Examined relationship between protein intake and postprandial response.
Männistö S, Dixon LB, Balder HF, Virtanen MJ, Krogh V, Khani BR, Berrino F, van den Brandt PA, Hartman AM, Pietinen P, Tan F, Wolk A, Goldbohm RA. Dietary patterns and breast cancer risk: Results from three cohort studies in the DIETSCAN project. *Cancer Causes Control.* 2005 Aug; 16(6): 725-733. PMID: 16049811.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Marques-Vidal P, Ravasco P, Ermelinda Camilo M. Foodstuffs and colorectal cancer risk: A review. *Clin Nutr.* 2006 Feb; 25(1): 14-36. Epub 2005 Nov 14. Review. PMID: 16290272.	Study design is systematic review (colorectal cancer).
Matheson EM, Mainous AG 3rd, Hill EG, Carnemolla MA. Shellfish consumption and risk of coronary heart disease. *J Am Diet Assoc.* 2009 Aug; 109(8): 1, 422-1, 426. PMID: 19631050.	Does not answer question: Examined relationship between shellfish intake and CHD.
Matthan NR, Jalbert SM, Ausman LM, Kuvin JT, Karas RH, Lichtenstein AH. Effect of soy protein from differently processed products on cardiovascular disease risk factors and vascular endothelial function in hypercholesterolemic subjects. *Am J Clin Nutr.* 2007 Apr; 85(4): 960-966. Erratum in: *Am J Clin Nutr.* 2007 Aug; 86(2): 525. PMID: 17413093.	Participants were hypercholesterolemic.
McCarty MF. The origins of western obesity: A role for animal protein? *Med Hypotheses.* 2000 Mar; 54(3): 488-494. PMID: 10783494.	Study design is narrative review.
McNaughton SA, Mishra GD, Stephen AM, Wadsworth ME. Dietary patterns throughout adult life are associated with body mass index, waist circumference, blood pressure, and red cell folate. *J Nutr.* 2007 Jan; 137(1): 99-105. PMID: 17182808.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Melanson K, Gootman J, Myrdal A, Kline G, Rippe JM. Weight loss and total lipid profile changes in overweight women consuming beef or chicken as the primary protein source. *Nutrition.* 2003 May; 19(5): 409-414. PMID: 12714091.	Dropout rate is higher than inclusion criteria.
Missmer SA, Smith-Warner SA, Spiegelman D, Yaun SS, Adami HO, Beeson WL, van den Brandt PA, Fraser GE, Freudenheim JL, Goldbohm RA, Graham S, Kushi LH, Miller AB, Potter JD, Rohan TE, Speizer FE, Toniolo P, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Hunter DJ. Meat and dairy food consumption and breast cancer: A pooled analysis of cohort studies. *Int J Epidemiol.* 2002 Feb; 31(1): 78-85. PMID: 11914299.	Study design is meta-analysis (breast cancer).

Möllsten AV, Dahlquist GG, Stattin EL, Rudberg S. Higher intakes of fish protein are related to a lower risk of microalbuminuria in young Swedish type 1 diabetic patients. *Diabetes Care.* 2001 May; 24(5): 805-810. PMID: 11347734.	Participants diagnosed with T2D.
Mortensen LS, Hartvigsen ML, Brader LJ, Astrup A, Schrezenmeir J, Holst JJ, Thomsen C, Hermansen K. Differential effects of protein quality on postprandial lipemia in response to a fat-rich meal in type 2 diabetes: comparison of whey, casein, gluten, and cod protein. *Am J Clin Nutr.* 2009 Jul; 90(1): 41-48. Epub 2009 May 20. PMID: 19458012.	Participants diagnosed with T2D.
Mozaffarian D, Psaty BM, Rimm EB, Lemaitre RN, Burke GL, Lyles MF, Lefkowitz D, Siscovick DS. Fish intake and risk of incident atrial fibrillation. *Circulation.* 2004 Jul 27; 110(4): 368-373. Epub 2004 Jul 19. PMID: 15262826; PMCID: PMC1201400.	Does not answer question: Examined relationship between fish intake and atrial fibrillation.
Nagata C, Shimizu H, Kametani M, Takeyama N, Ohnuma T, Matsushita S. Diet and colorectal adenoma in Japanese males and females. *Dis Colon Rectum.* 2001 Jan; 44(1): 105-111. PMID: 11805576.	Study design is case-control study (colorectal cancer).
Nenseter MS, Østerud B, Larsen T, Strøm E, Bergei C, Hewitt S, Holven KB, Hagve TA, Mjøs SA, Solvang M, Pettersen J, Opstvedt J, Ose L. Effect of Norwegian fish powder on risk factors for coronary heart disease among hypercholesterolemic individuals. *Nutr Metab Cardiovasc Dis.* 2000 Dec; 10(6): 323-330. PMID: 11302007.	Did not answer question: Examined relationship between fish powder and CHD.
Nettleton JA, Steffen LM, Loehr LR, Rosamond WD, Folsom AR. Incident heart failure is associated with lower whole-grain intake and greater high-fat dairy and egg intake in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Diet Assoc*. 2008 Nov; 108(11): 1, 881-1, 887. PMID: 18954578; PMCID: PMC2650810.	Does not answer question: Examined relationship between egg intake and heart failure.
Nkondjock A, Receveur O. Fish-seafood consumption, obesity, and risk of type 2 diabetes: an ecological study. *Diabetes Metab.* 2003 Dec; 29(6): 635-642. PMID: 14707894.	Does not answer question: Examined relationship between fish intake and T2D.
Norat T, Lukanova A, Ferrari P, Riboli E. Meat consumption and colorectal cancer risk: Dose-response meta-analysis of epidemiological studies. *Int J Cancer.* 2002 Mar 10; 98(2): 241-256. PMID: 11857415.	Study design is meta-analysis (colorectal cancer).
Norat T, Riboli E. Meat consumption and colorectal cancer: A review of epidemiologic evidence. *Nutr Rev.* 2001 Feb; 59(2): 37-47. Review. PMID: 11310774.	Study design is meta-analysis (colorectal cancer).
Norat T, Riboli E. Meat consumption and colorectal cancer: A review of epidemiologic evidence. *Nutr Rev.* 2001 Feb; 59(2): 37-47. Review. PMID: 11310774.	Study design is narrative review (colorectal cancer).
Nowson CA, Wattanapenpaiboon N, Pachett A. Low-sodium Dietary Approaches to Stop Hypertension-type diet including lean red meat lowers blood pressure in postmenopausal women. *Nutr Res.* 2009 Jan; 29(1): 8-18. PMID: 19185772.	Does not include animal protein products in analyses.

Olmedilla-Alonso B, Granado-Lorencio F, Herrero-Barbudo C, Blanco-Navarro I, Blázquez-García S, Pérez-Sacristán B. Consumption of restructured meat products with added walnuts has a cholesterol-lowering effect in subjects at high cardiovascular risk: a randomised, crossover, placebo-controlled study. *J Am Coll Nutr.* 2008 Apr; 27(2): 342-348. PMID: 18689569.	Does not answer question: Examined effect of restructured meat product on cholesterol.
Panagiotakos DB, Pitsavos C, Zampelas A, Chrysohoou C, Griffin BA, Stefanadis C, Toutouzas P. Fish consumption and the risk of developing acute coronary syndromes: The CARDIO2000 study. *Int J Cardiol.* 2005 Jul 20; 102(3): 403-409. PMID: 16004884.	Does not answer question: Examined relationship between fish intake and health outcomes.
Panagiotakos DB, Zeimbekis A, Boutziouka V, Economou M, Kourlaba G, Toutouzas P, Polychronopoulos E. Long-term fish intake is associated with better lipid profile, arterial blood pressure, and blood glucose levels in elderly people from Mediterranean islands (MEDIS epidemiological study). *Med Sci Monit.* 2007 Jul; 13(7): CR307-CR312. PMID: 17599024.	Does not answer question: Examined relationship between fish intake and health outcomes.
Pham TM, Fujino Y, Kubo T, Ide R, Tokui N, Mizoue T, Ogimoto I, Matsuda S, Yoshimura T. Fish intake and the risk of fatal prostate cancer: Findings from a cohort study in Japan. *Public Health Nutr.* 2009 May; 12(5): 609-613. Epub 2008 Jul 29. PMID: 18664313.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Pieniak Z, Verbeke W, Perez-Cueto F, Brunsø K, De Henauw S. Fish consumption and its motives in households with versus without self-reported medical history of CVD: A consumer survey from five European countries. *BMC Public Health.* 2008 Sep 10; 8: 306. PMID: 18783593; PMCID: PMC2556335.	Does not include health outcomes in analyses.
Processed meat consumption linked to type 2 diabetes. *Nephrol News Issues.* 2002 Apr; 16(5): 68-69. PMID: 11962157.	News article.
Ramel A, Parra D, Martinéz JA, Kiely M, Thorsdottir I. Effects of seafood consumption and weight loss on fasting leptin and ghrelin concentrations in overweight and obese European young adults. *Eur J Nutr.* 2009 Mar; 48(2): 107-114. Epub 2009 Jan 13. PMID: 19142567.	Does not answer question: Examined relationship between seafood and leptin and ghrelin concentrations.
Rosell M, Appleby P, Spencer E, Key T. Weight gain over 5 years in 21, 966 meat-eating, fish-eating, vegetarian, and vegan men and women in EPIC-Oxford. *Int J Obes (Lond).* 2006 Sep; 30(9): 1, 389-1, 396. Epub 2006 Mar 14. PMID: 16534521.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Sandhu MS, White IR, McPherson K. Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: A meta-analytical approach. *Cancer Epidemiol Biomarkers Prev.* 2001 May; 10(5): 439-446. PMID: 11352852.	Study design is systematic review/meta-analysis (colorectal cancer).
Santarelli RL, Pierre F, Corpet DE. Processed meat and colorectal cancer: A review of epidemiologic and experimental evidence. *Nutr Cancer.* 2008; 60(2): 131-144. Review. PMID: 18444144; PMCID: PMC2661797.	Study design is narrative review.

Satia JA, Tseng M, Galanko JA, Martin C, Sandler RS. Dietary patterns and colon cancer risk in Whites and African Americans in the North Carolina Colon Cancer Study. *Nutr Cancer.* 2009; 61(2): 179-193. PMID: 19235034.	Study design is case-control study (colon cancer).
Schulz M, Hoffmann K, Weikert C, Nöthlings U, Schulze MB, Boeing H. Identification of a dietary pattern characterized by high-fat food choices associated with increased risk of breast cancer: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Br J Nutr.* 2008 Nov; 100(5): 942-946. PMID: 18377685.	Does not answer question: Examines relationship between high fat foods and breast cancer.
Seierstad SL, Seljeflot I, Johansen O, Hansen R, Haugen M, Rosenlund G, Frøyland L, Arnesen H. Dietary intake of differently fed salmon: The influence on markers of human atherosclerosis. *Eur J Clin Invest.* 2005 Jan; 35(1): 52-59. PMID: 15638820.	Participants diagnosed with T2D.
Shiell AW, Campbell-Brown M, Haselden S, Robinson S, Godfrey KM, Barker DJ. High-meat, low-carbohydrate diet in pregnancy: Relation to adult blood pressure in the offspring. *Hypertension*. 2001 Dec 1; 38(6): 1, 282-1, 288. PMID: 11751704.	Does not answer question: Examines relationship between dietary intake during pregnancy and health of adult offspring.
Sieri S, Krogh V, Muti P, Micheli A, Pala V, Crosignani P, Berrino F. Fat and protein intake and subsequent breast cancer risk in postmenopausal women. *Nutr Cancer.* 2002; 42(1): 10-17. PMID: 12235640.	Study design is case-control study (breast cancer).
Skjelbred CF, Saebø M, Hjartåker A, Grotmol T, Hansteen IL, Tveit KM, Hoff G, Kure EH. Meat, vegetables and genetic polymorphisms and the risk of colorectal carcinomas and adenomas. *BMC Cancer*. 2007 Dec 19; 7: 228. PMID: 18093316; PMCID: PMC2228310.	Study design is case-control study (colorectal cancer).
Smith DR, Wood R, Tseng S, Smith SB. Increased beef consumption increases apolipoprotein A-I but not serum cholesterol of mildly hypercholesterolemic men with different levels of habitual beef intake. *Exp Biol Med (Maywood).* 2002 Apr; 227(4): 266-275. PMID: 11910049.	Participants diagnosed with mild hypercholesterolemia.
SoRelle R. Fish and long-chain omega-3 fatty acids could be lifesavers for diabetic women. *Circulation.* 2003 Apr 22; 107(15): e9, 033-9, 035. PMID: 12707254.	Participants were diagnosed with diabetes.
Sørensen M, Autrup H, Olsen A, Tjønneland A, Overvad K, Raaschou-Nielsen O. Prospective study of NAT1 and NAT2 polymorphisms, tobacco smoking and meat consumption and risk of colorectal cancer. *Cancer Lett.* 2008 Aug 8; 266(2): 186-193. Epub 2008 Mar 26. PMID: 18372103.	Study design is case-control study (colorectal cancer).
Spencer EA, Appleby PN, Davey GK, Key TJ. Diet and body mass index in 38000 EPIC-Oxford meat-eaters, fish-eaters, vegetarians and vegans. *Int J Obes Relat Metab Disord.* 2003 Jun; 27(6): 728-734. PMID: 12833118.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Stewart JW, Kaplan ML, Beitz DC. Pork with a high content of polyunsaturated fatty acids lowers LDL cholesterol in women. *Am J Clin Nutr.* 2001 Aug; 74(2): 179-187. PMID: 11470718.	Intervention consisted of modified pork high in PUFAs.

Tanskanen A, Hibbeln JR, Tuomilehto J, Uutela A, Haukkala A, Viinamäki H, Lehtonen J, Vartiainen E. Fish consumption and depressive symptoms in the general population in Finland. *Psychiatr Serv.* 2001 Apr; 52(4): 529-531. PMID: 11274502.	Does not include health outcome of interest in analyses.
Tapola NS, Lyyra ML, Karvonen HM, Uusitupa MI, Sarkkinen ES. The effect of meat products enriched with plant sterols and minerals on serum lipids and blood pressure. *Int J Food Sci Nutr.* 2004 Aug; 55(5): 389-397. PMID: 15545047.	Intervention consisted of meat products enriched with plant sterols; participants diagnosed with hypercholesterolemia.
Tappel A. Heme of consumed red meat can act as a catalyst of oxidative damage and could initiate colon, breast and prostate cancers, heart disease and other diseases. *Med Hypotheses*. 2007; 68(3): 562-564. Epub 2006 Oct 11. PMID: 17045417.	Study design is narrative review.
Teixeira Rde C, Molina Mdel C, Zandonade E, Mill JG. Cardiovascular risk in vegetarians and omnivores: A comparative study. *Arq Bras Cardiol.* 2007 Oct; 89(4): 237-244. English, Portuguese. PMID: 17992380.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Terry P, Rohan TE, Wolk A, Maehle-Schmidt M, Magnusson C. Fish consumption and breast cancer risk. *Nutr Cancer.* 2002; 44(1): 1-6. PMID: 12672635.	Study design is case-control study (breast cancer).
Thorsdottir I, Birgisdottir B, Kiely M, Martinez J, Bandarra N. Fish consumption among young overweight European adults and compliance to varying seafood content in four weight loss intervention diets. *Public Health Nutr.* 2009 May; 12(5): 592-598. Epub 2008 Jun 19. PMID: 18561865.	Does not answer question: Examined compliance to eating varying types of seafood in weight loss intervention diets.
Thorsdottir I, Tomasson H, Gunnarsdottir I, Gisladottir E, Kiely M, Parra MD, Bandarra NM, Schaafsma G, Martinéz JA. Randomized trial of weight-loss-diets for young adults varying in fish and fish oil content. *Int J Obes* (Lond). 2007 Oct; 31(10): 1, 560-1, 566. Epub 2007 May 15. PMID: 17502874.	Does not answer question: Examined fish intake and weight loss.
Tiemersma EW, Kampman E, Bueno de Mesquita HB, Bunschoten A, van Schothorst EM, Kok FJ, Kromhout D. Meat consumption, cigarette smoking, and genetic susceptibility in the etiology of colorectal cancer: results from a Dutch prospective study. *Cancer Causes Control.* 2002 May; 13(4): 383-393. PMID: 12074508.	Study design is case-control study (colorectal cancer).
Timonen M, Horrobin D, Jokelainen J, Laitinen J, Herva A, Räsänen P. Fish consumption and depression: The Northern Finland 1966 birth cohort study. *J Affect Disord.* 2004 Nov 1; 82(3): 447-452. PMID: 15555697.	Does not include health outcome of interest in analyses.
Tzoulaki I, Brown IJ, Chan Q, Van Horn L, Ueshima H, Zhao L, Stamler J, Elliott P; International Collaborative Research Group on Macro-/Micronutrients and Blood Pressure. Relation of iron and red meat intake to blood pressure: cross sectional epidemiological study. *BMJ.* 2008 Jul 15; 337: a258. doi: 10.1136/bmj.a258. PMID: 18632704; PMCID: PMC2658466.	Study design is cross-sectional epidemiological study.

Umesawa M, Sato S, Imano H, Kitamura A, Shimamoto T, Yamagishi K, Tanigawa T, Iso H. Relations between protein intake and blood pressure in Japanese men and women: the Circulatory Risk in Communities Study (CIRCS). *Am J Clin Nutr.* 2009 Aug; 90(2): 377-384. Epub 2009 Jun 10. PMID: 19515740.	Study design is cross-sectional.
Varraso R, Jiang R, Barr RG, Willett WC, Camargo CA Jr. Prospective study of cured meats consumption and risk of chronic obstructive pulmonary disease in men. *Am J Epidemiol*. 2007 Dec 15; 166(12): 1, 438-1, 445. Epub 2007 Sep 4. PMID: 17785711; PMCID: PMC2573990.	Does not include health outcome of interest in analyses.
Virtanen JK, Mozaffarian D, Chiuve SE, Rimm EB. Fish consumption and risk of major chronic disease in men. *Am J Clin Nutr.* 2008 Dec; 88(6): 1, 618-1, 625. PubMed PMID: 19064523; PMCID: PMC2613199.	Does not answer question: Examined relationship between fish intake and chronic disease.
Wakai K, Tamakoshi K, Date C, Fukui M, Suzuki S, Lin Y, Niwa Y, Nishio K, Yatsuya H, Kondo T, Tokudome S, Yamamoto A, Toyoshima H, Tamakoshi A; JACC Study Group. Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. *Cancer Sci.* 2005 Sep; 96(9): 590-599. PMID: 16128744.	Does not answer question: Examined relationship between breast cancer and fat intake, not animal protein.
Weggemans RM, Zock PL, Katan MB. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: A meta-analysis. *Am J Clin Nutr.* 2001 May; 73(5): 885-891. PMID: 11333841.	Does not examine relationship between intake of animal protein product and health outcome.
Weghuber D, Widhalm K. Effect of 3-month treatment of children and adolescents with familial and polygenic hypercholesterolaemia with a soya-substituted diet. *Br J Nutr.* 2008 Feb; 99(2): 281-286. Epub 2007 Aug 13. PMID: 17697400.	Participants diagnosed with hypercholesterolemia.
Welch AA, Bingham SA, Ive J, Friesen MD, Wareham NJ, Riboli E, Khaw KT. Dietary fish intake and plasma phospholipid n-3 polyunsaturated fatty acid concentrations in men and women in the European Prospective Investigation into Cancer-Norfolk United Kingdom cohort. *Am J Clin Nutr.* 2006 Dec; 84(6): 1, 330-1, 339. PMID: 17158413.	Does not include health outcomes in analyses; fish is the independent variable.
Wu K, Hu FB, Willett WC, Giovannucci E. Dietary patterns and risk of prostate cancer in U.S. men. *Cancer Epidemiol Biomarkers Prev.* 2006 Jan; 15(1): 167-171. PMID: 16434606.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Yoon H, Benamouzig R, Little J, François-Collange M, Tomé D. Systematic review of epidemiological studies on meat, dairy products and egg consumption and risk of colorectal adenomas. *Eur J Cancer Prev*. 2000 Jun; 9(3): 151-164. PMID: 10954254.	Study design is systematic review (colorectal cancer).
Yuan JM, Ross RK, Gao YT, Yu MC. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *Am J Epidemiol.* 2001 Nov 1; 154(9): 809-816. PMID: 11682363.	Does not answer question: Examined relationship between fish intake and myocardial infarction.

CHAPTER 8. ANIMAL PROTEIN PRODUCTS – BREAST CANCER

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF ANIMAL PROTEIN PRODUCTS AND BREAST CANCER?

Conclusion statement

Limited evidence from cohort studies shows there is no association between the intake of animal protein products and overall breast cancer risk. However in sub-groups of breast cancer patients, limited evidence suggested a relationship between the intake of animal protein products and risk of developing breast cancer.

Grade

Limited

Evidence summary overview

This review included six studies published since 2000 (Cho, 2006; Ferrucci, 2009; Fung, 2005; Kabat, 2009; Linos, 2008; Taylor, 2007) representing prospective cohorts from the US and United Kingdom. Results were often reported based on menopausal status (pre-menopausal or post-menopausal) and estrogen receptor status (positive or negative). In the Nurses' Health Study (Cho, 2006), overall, there was no association between total meat intake and risk of breast cancer. However, there was a positive association for ER (estrogen receptor)+/PR (progesterone receptor)+ breast cancer and no association for ER-/PR-. Similarly, they reported positive associations between ER+/PR+ breast cancer and individual red and processed meats, but not for ER-/PR-. Ferrucii et al, 2009, found a stronger association between red meat intake and ER+/PR+ breast cancer compared to negative receptor status in the PLCO Screening Trial.

In additional analyses from the Nurses' Health Study, Linos et al, 2008, found a positive association between pre-menopausal breast cancer and red meat and this relationship was stronger among estrogen receptor positive participants. In the UK Women's Cohort Study (Taylor, 2007), positive associations between total meat and pre-menopausal and post-menopausal breast cancer were observed. Non-processed meat also was positively associated with pre-menopausal breast cancer. However, post-menopausal but not pre-menopausal breast cancer was associated with the intake of red meat and processed meat. Thus, results are conflicting and future research should further investigate the relationship between the intake of animal protein products and breast cancer specifically related to menopausal and receptor status.

Evidence summary paragraphs

Cho et al, 2006 (positive quality) evaluated the intake of red meat and breast cancer risk according to tumor hormone receptor status among 90,659 pre-menopausal women (aged 26 to 46 years) in the Nurses' Health Study II (US). Breast cancer was self-reported by biennial questionnaires mailed between 1993 and 2003 and confirmed by review of pathologic reports. A semi-quantitative food-frequency questionnaire (FFQ) with more than 130 food items was sent to women in 1991, 1995 and 1999 to

assess usual dietary intake during the past year. Total red meat and individual red meat items were included in analyses. During 12 years of follow-up, 1,021 cases of invasive breast carcinoma were identified. The highest intake of red meat was weakly and non-significantly (NS) associated with elevated risk of overall breast cancer. Greater red meat intake was strongly related to elevated risk of breast cancers that were estrogen and progesterone receptor positive (ER+/PR+; N=512), but not to those that were estrogen and progesterone receptor negative (ER−/PR−; N=167). Compared with those eating three or fewer servings per week of red meat, the multi-variate relative risks for ER+/PR+ breast cancer with increasing servings of red meat intake were 1.14 (95% CI: 0.90, 1.45) for more than three to five or fewer servings per week, 1.42 (95% CI: 1.06, 1.90) for more than five per week to one or fewer servings per day, 1.20 (95% CI: 0.89, 1.63) for more than 1 to 1.5 or fewer servings per day and 1.97 (95% CI: 1.35, 2.88) for more than 1.5 servings per day (P=0.001). The corresponding relative risks (RR) for ER−/PR− breast cancer were 1.34 (95% CI: 0.89, 2.00), 1.21 (95% CI: 0.73, 2.00), 0.69 (95% CI: 0.39, 1.23) and 0.89 (95% CI: 0.43, 1.84) (P=0.28). No strong associations were found between individual red meat items and overall breast cancer risk; however, almost all of the individual red meat items had statistically significant positive trends of increasing ER+/PR+ breast cancer risk (beef or lamb as main dish, P=0.03; pork as main dish, P=0.005; hamburger, P=0.01; hot dogs, P=0.005; other processed meats, P<0.001). Individual red meat items were not positively related to ER−/PR− cancers. The authors concluded that higher red meat intake may be a risk factor for ER+/PR+ breast cancer among pre-menopausal women.

Ferrucci et al, 2009 (positive quality) used prospective cohort data from 52,158 women (55 to 74 years) participating in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (US) to investigate meat intake and potentially carcinogenic meat-related exposures in relation to post-menopausal invasive breast cancer. Incident cancer cases were identified through self-report from annual study update questionnaire, physician reports or through reports from the next of kin, and were histologically confirmed based on pathology reports and medical records. Meat intake was assessed at baseline using the Diet History Questionnaire, a self-administered, validated FFQ, which consisted of 124 items. Red meat, white meat and processed meat were included in analyses. During a mean follow-up of 5.5 years, 1,205 invasive breast cancer cases were identified. Comparing the fifth to the first quintile, red meat was positively associated with breast cancer (HR=1.23; 95% CI: 1.00, 1.51; P=0.22). Statistically significant or borderline-positive associations between red meat and breast cancer were observed starting in the second quintile, and there was no evidence for a dose-response effect (P=0.22), consistent with a potential threshold effect. When ER+ /PR+ tumors were compared to non-cases, the effect of red meat seemed to be stronger (Q5 vs. Q1 H = 1.59; 95% CI: 1.03, 2.48; P=0.09). There were NS associations with processed meat, white meat or individual meat items. Pan-fried meat, grilled meat and well/very well done meat were not associated with breast cancer risk. The authors concluded that their results support an association between red meat and post-menopausal breast cancer.

Fung et al, 2005 (positive quality) examined the relationship between dietary patterns and breast cancer in 71,058 post-menopausal women from the Nurses' Health Study (US). Post-menopausal breast cancer was determined by self-report in biennial

questionnaire. A total of 99% of cases were confirmed by reviewing medical records. Dietary intake was assessed using the 1984 FFQ that consisted of 116 items. Two major dietary patterns were identified (prudent and Western). The prudent pattern was characterized by higher intake of fruits, vegetables, whole grains, low-fat dairy products, fish and poultry, while the Western pattern was characterized by higher intake of red and processed meats, refined grains, sweets and desserts and high-fat dairy products. Separate analyses considered the relationship between individual food items (including processed meats, red meats and poultry) and estrogen receptor-negative (ER-) breast cancer. Between 1984 and 2000, 3,026 incident cases of post-menopausal breast cancer were ascertained. Neither of the dietary patterns was associated with overall risk of post-menopausal breast cancer. However, a positive association between the Western pattern score was observed among smokers at baseline [RR = 1.44, comparing top to bottom quintiles; 95% CI: 1.02, 2.03; P=0.03). An inverse association was observed between the prudent pattern and ER- cancer (RR=0.62; 95% CI: 0.45, 0.88; P=0.006). No significant relationships between processed meats, red meats or poultry and ER- breast cancer were observed. (Relationships between processed meats, red meats or poultry and ER+ or overall breast cancer risk were not reported.) The authors concluded that they did not observe an overall association between the prudent or Western pattern and overall breast cancer risk.

Kabat et al, 2009 (positive quality) examined the association between meat, meat-cooking methods, and meat-mutagen intake and post-menopausal breast cancer in the National Institutes of Health-American Association for Retired Persons (NIH-AARP) Diet and Health Study cohort (N=120,755). Breast cancer cases were identified by linking cohort members to state cancer registries and to the US National Death Index between 1995 and 2005. Dietary intake was assessed at baseline using a self-administered FFQ with 124 items. Within six months following the initial questionnaire, participants were sent a second FFQ that included a meat-cooking module. The meat-cooking module queried consumption of hamburgers, steak, bacon and chicken, usual cooking method and level of doneness on the outside and inside. During eight years of follow-up, 3,818 cases of invasive breast cancer were identified. Intake of total meat, red meat, meat cooked at high temperatures and meat mutagens showed no association with breast cancer risk. No significant associations were seen by hormone receptor status (ER+, ER-, PR+, PR-) for intake of total meat, red meat, meat cooked at high temperatures or five indicators of mutagenic activity. Breast cancer risk was not associated with high-temperature cooking methods or level of doneness. The authors concluded that the results of this prospective study do not support the hypothesis that a high intake of meat, red meat, processed meat, meat cooked at high temperatures or meat mutagens is associated with increased risk of post-menopausal breast cancer.

Linos et al, 2008 (positive quality) assessed the relationship between red meat intake during adolescence and pre-menopausal breast cancer risk among 39,268 participants from the Nurses' Health Study II (US). Breast cancer incidence was ascertained on biennial follow-up questionnaires and confirmed by medical records and pathology reports. In 1991 and 1995, participants completed a semi-quantitative FFQ of usual dietary intake during the past year. The mean of the 1991 and 1995 FFQ was used to estimate current adult red meat intake. Individual red meat items included beef or lamb as a main dish; pork as a main dish; beef, pork, or lamb as a sandwich or mixed dish;

hamburger; bacon; hot dogs; and other processed meats. Adolescent diet was assessed retrospectively with a 124-item FFQ on diet during high school. This questionnaire was specifically designed to include foods that were commonly consumed from 1960 to 1980. The adult and high school FFQs included the same red meat items. From 1998 to 2005, 455 cases of invasive pre-menopausal breast cancer were diagnosed. Compared with women in the lowest quintile of red meat intake during high school, the multi-variate-adjusted RR for the highest quintile of intake was 1.34 (95% CI: 0.94, 1.89; P=0.05). When individual red meats were considered, there was a significant association for frequent hot dog consumption in high school and breast cancer risk (RR=1.36; 95% CI: 0.95, 1.95; P=0.03). No significant associations were observed for bacon; beef, pork or lamb sandwich or stew; meatloaf; beef or lamb as main dish; hamburger; or pork as a main dish. A borderline significant association was observed for processed meat (P=0.07). A significant linear association was observed with every additional 100g of red meat consumed per day (RR=1.20; 95% CI: 1.00, 1.43; P=0.05). This association was more pronounced in ER- and PR-positive cancer (RR=1.36; 95% CI: 1.08, 1.70; P=0.008) and was not significant in ER- and PR-negative tumors (RR=0.99; 95% CI: 0.61, 1.61; P=0.97). The authors concluded that higher red meat intake in adolescence may increase the risk of pre-menopausal breast cancer.

Taylor et al, 2007 (positive quality) assessed the effect of meat consumption and meat type on the risk of pre- and post-menopausal breast cancer in the UK Women's Cohort Study (N=33,725). To determine cancer status, details of women fulfilling the eligibility criteria were submitted to the UK Office of National Statistics and subsequently flagged on the NHS central register. Dietary intake was assessed with a 217-item FFQ. Meats considered included red meat, poultry, offal and processed meat. During a median follow-up of eight years, a total of 1,750 incident malignant cancer cases were recorded, including 283 pre-menopausal and 395 post-menopausal breast cancers. High consumption of total meat compared with none was associated with pre-menopausal breast cancer (HR=1.20; 95% CI: 0.86, 1.68) and high non-processed meat intake compared with none (HR=1.20; 95% CI: 0.86, 1.68). The estimated RR of pre-menopausal breast cancer for an increase in total meat consumption of 50g per day was 1.12 (95% CI: 1.02, 1.23; P=0.02). RR of non-processed meat per 50g per day was 1.13 (95% CI: 1.01, 1.26; P=0.03). The association of pre-menopausal breast cancer with processed meat and red meat was not statistically significant. Total meat intake was positively associated with post-menopausal breast cancer, HR=1.63 (95% CI: 1.10, 2.30) for high consumption vs. the reference category, and when treated as a continuous variable, resulted in a significant linear trend and relative risk per 50g per day of 1.10 (95% CI: 1.01, 1.20; P=0.02). Relationships between both processed meat and red meat and post-menopausal breast cancer were also significant. Risks for the three meat types were similar when considering HRs of the categorical analysis; however, fitting meat in the model as a continuous predictor resulted in a much stronger relationship with processed meat, giving an RR per 50g per day of 1.64 (95% CI: 1.09 to 2.27, P=0.003). The authors concluded that women, both pre- and post-menopausal, who consumed the most meat had the highest risk of breast cancer.

Overview table

Author, Year, Study Design, Class, Rating	Study Name/Location	Total Meat Association (Pos, Neg, None)	Red Meat (Pos, Neg, None)	Processed Meat (Pos, Neg, None)	Poultry (Pos, Neg, None)
Cho et al 2006 Study Design: Prospective cohort study Class: B Positive quality	Nurses' Health Study. Location: US.	Ø Overall. (+) ER+/PR+. Ø ER-/PR-.	Beef or lamb as main dish; pork as main dish; hamburger: (+) ER+/PR+ only.	Hot dogs: (+) ER+/PR+ only. Other processed meats: (+) ER+/PR+ only.	Not examined.
Ferrucci LM, Cross AJ et al, 2009 Study Design: Prospective Cohort Study Class: B Positive quality	Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Location: US.	Doneness: Ø.	(+) with stronger association for ER+/PR+.	Ø.	White meat: Ø.
Fung et al 2005 Study Design: Prospective Cohort Study Class: B Positive quality	Nurses' Health Study. Location: US (results presented here only represent ER-cancer).	Not examined.	Ø ER-.	Ø ER-.	Ø ER-.

Kabat et al 2009 Study Design: prospective cohort study Class: B Positive quality	NIH-AARP Diet and Health Study. Location: US (study only included post-menopausal women).	Ø Post-menopausal BC (including analyses with ER/PR status). Doneness: Ø Post-menopausal BC.	Ø Post-menopausal BC (including analyses with ER/PR status).	Not examined.	Not examined.
Linos et al 2008 Study Design: prospective cohort study Class: B Positive quality	Nurses' Health Study II. Location: US (study only included pre-menopausal women).	Not examined.	(+) Pre-menopausal BC with stronger association for ER+/PR+ (Ø for ER-/PR-) (Ø for individual food items).	Hot dogs: (+) Pre-menopausal BC. (Ø for other individual food items).	Not examined.
Taylor et al 2007 Study Design: Prospective Cohort Study Class: B Positive quality	UK Women's Cohort Study. Location: United Kingdom (study included pre- and post-menopausal women).	(+) Pre-menopausal and post-menopausal BC. Non-processed meat: (+) Pre-menopausal BC.	Ø Pre-menopausal BC. (+) Post-menopausal BC.	Ø Pre-menopausal BC. (+) Post-menopausal BC.	Not examined.

Search plan and results

Inclusion criteria

- January 2000 to September 2009
- Prospective cohort studies on colorectal, breast and prostate cancers
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates

- *Ages:* Children two to 18 years; Adults 19 years and older
- *Populations:* Healthy, those with elevated chronic disease risk.

Exclusion criteria

- With the exception of the body weight outcome, cross-sectional studies were excluded from the review
- Systematic reviews and meta-analyses on colorectal, breast and prostate cancers. Only original research studies with prospective cohort design were included in the review
- Studies specifically related to seafood or milk product intake (considered as separate questions)
- Studies that reported on animal protein intake as a component of a dietary pattern and not as an individual variable
- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: (Animal protein* OR meat[mh] OR "Egg Proteins, Dietary"[mh] OR "Fish Proteins"[mh]) AND ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "overweight"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mh:NoExp] OR “heart diseases”[mh] OR "Coronary Disease"[Mesh] OR “blood pressure”[mh] OR “chronic disease”[mh] OR obesity[mh] OR "Body Weights and Measures"[mh] OR "Colorectal Neoplasms"[mesh])
  (Animal protein* OR meat[mh] OR "Egg Proteins, Dietary"[mh] OR "Fish Proteins"[mh] OR seafood[majr] OR crustacea[majr]) AND (systematic[sb] OR Meta-Analysis[ptyp] OR "Cohort Studies"[Mesh]) AND ("Prostatic Neoplasms"[Mesh] OR "Breast Neoplasms"[Mesh])
  eggs [mh] AND ("Diabetes Mellitus, Type 2"[majr] OR "metabolic syndrome X"[majr] OR "overweight"[majr] OR "hypertension"[majr] OR "dyslipidemias"[majr] OR "cardiovascular diseases"[majr:NoExp] OR “heart diseases”[majr] OR "Coronary Disease"[Mesh] OR “blood pressure”[majr] OR “chronic disease”[majr] OR obesity[majr] OR "Body Weights and Measures"[majr])
  (Note: "Cohort Studies"[Mesh]) includes prospective studies)

Date searched: 09/01/2009; update 09/18/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 771
- Total articles identified to review from electronic databases: 166
- Articles identified via handsearch or other means: 2

- Number of Primary Articles Identified: 47
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 47
- Number of Articles Reviewed but Excluded: 121

Included articles (References)

What is the relationship between the intake of animal protein products and cardiovascular disease?

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adults: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr.* 2005 Dec; 82(6): 1, 169-1, 177; quiz 1, 363-1, 364. PMID: 16332648.
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What is the relationship between the intake of animal protein products and type 2 diabetes?

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cancer in the NIH-AARP diet and health study. *Int J Cancer.* 2009 May 15; 124(10): 2, 430-2, 435. PMID: 19165862.
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6. Taylor EF, Burley VJ, Greenwood DC, Cade JE. Meat consumption and risk of breast cancer in the UK Women's Cohort Study. *Br J Cancer.* 2007 Apr 10; 96(7): 1, 139-1, 146. Erratum in: Br J Cancer. 2007 Jun 4; 96 (11): 1, 780. PMID: 17406351.
7. Wang L, Manson JE, Buring JE, Sesso HD. Meat intake and the risk of hypertension in middle-aged and older women. *J Hypertens.* 2008 Feb; 26(2): 215-222. PMID: 18192834.

Excluded articles

Article	Reason for Exclusion
Alexander DD, Cushing CA, Lowe KA, Sceurman B, Roberts MA. Meta-analysis of animal fat or animal protein intake and colorectal cancer. *Am J Clin Nutr.* 2009 May; 89(5): 1, 402-1, 409. Epub 2009 Mar 4. PMID: 19261724.	Study design is meta-analysis (colorectal cancer).
Appleby PN, Davey GK, Key TJ. Hypertension and blood pressure among meat eaters, fish eaters, vegetarians and vegans in EPIC-Oxford. *Public Health Nutr.* 2002 Oct; 5(5): 645-654. PMID: 12372158.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Augustsson K, Michaud DS, Rimm EB, Leitzmann MF, Stampfer MJ, Willett WC, Giovannucci E. A prospective study of intake of fish and marine fatty acids and prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2003 Jan; 12(1): 64-67. PMID: 12540506.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Azadbakht L, Esmaillzadeh A. Red meat intake is associated with metabolic syndrome and the plasma C-reactive protein concentration in women. *J Nutr.* 2009 Feb; 139(2): 335-339. Epub 2008 Dec 11. PMID: 19074209.	Does not answer question: Examined relationship between red meat intake and metabolic syndrome.
Balder HF, Vogel J, Jansen MC, Weijenberg MP, van den Brandt PA, Westenbrink S, van der Meer R, Goldbohm RA. Heme and chlorophyll intake and risk of colorectal cancer in the Netherlands cohort study. *Cancer Epidemiol Biomarkers Prev.* 2006 Apr; 15(4): 717-725. PMID: 16614114.	Does not answer question: Examined relationship between heme and chlorophyll intake and colorectal cancer.
Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: A systematic literature review and meta-analysis. *Cancer Causes Control.* 2007 Nov; 18(9): 967-988. Epub 2007 Jul 19. Review. PMID: 17638104; PMCID: PMC2592095.	Does not include colorectal, breast, or prostate cancer in analyses.

Barraj L, Tran N, Mink P. A comparison of egg consumption with other modifiable coronary heart disease lifestyle risk factors: a relative risk apportionment study. *Risk Anal*. 2009 Mar; 29(3): 401-415. Epub 2008 Nov 4. PMID: 19000074.	Does not answer question: Used risk apportionment approach to estimate contribution of egg intake to coronary heart disease (CHD) risk at the population level.
Benassi-Evans B, Clifton PM, Noakes M, Keogh JB, Fenech M. High protein-high red meat versus high carbohydrate weight loss diets do not differ in effect on genome stability and cell death in lymphocytes of overweight men. *Mutagenesis.* 2009 May; 24(3): 271-277. Epub 2009 Mar 5. PMID: 19264840.	Does not include animal protein product intake in analyses.
Brink M, Weijenberg MP, de Goeij AF, Roemen GM, Lentjes MH, de Bruïne AP, Goldbohm RA, van den Brandt PA. Meat consumption and K-ras mutations in sporadic colon and rectal cancer in The Netherlands Cohort Study. *Br J Cancer.* 2005 Apr 11; 92(7): 1, 310-1, 320. PMID: 15812479.	Study design is case-cohort.
Cade JE, Burley VJ, Greenwood DC; UK Women's Cohort Study Steering Group. The UK Women's Cohort Study: Comparison of vegetarians, fish-eaters and meat-eaters. *Public Health Nutr.* 2004 Oct; 7(7): 871-878. PMID: 15482612.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Chan AT, Tranah GJ, Giovannucci EL, Willett WC, Hunter DJ, Fuchs CS. Prospective study of N-acetyltransferase-2 genotypes, meat intake, smoking and risk of colorectal cancer. *Int J Cancer.* 2005 Jul 1; 115(4): 648-652. PMID: 15700302.	Study design is case-control study (colorectal cancer).
Chavarro JE, Stampfer MJ, Hall MN, Sesso HD, Ma J. A 22-y prospective study of fish intake in relation to prostate cancer incidence and mortality. *Am J Clin Nutr.* 2008 Nov; 88(5): 1, 297-1, 303. PMID: 18996866.	Does not answer question: Examined relationship between fish intake and prostate cancer.
Chrysohoou C, Panagiotakos DB, Pitsavos C, Skoumas J, Krinos X, Chloptsios Y, Nikolaou V, Stefanadis C. Long-term fish consumption is associated with protection against arrhythmia in healthy persons in a Mediterranean region: The ATTICA study. *Am J Clin Nutr.* 2007 May; 85(5): 1, 385-1, 391. PMID: 17490977.	Does not answer question: Examined relationship between fish intake and arrhythmia.
Cotterchio M, Boucher BA, Manno M, Gallinger S, Okey AB, Harper PA. Red meat intake, doneness, polymorphisms in genes that encode carcinogen-metabolizing enzymes, and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2008 Nov; 17(11): 3, 098-3, 107. PMID: 18990750.	Study design is case-control (colorectal cancer).
Crowe FL, Key TJ, Appleby PN, Travis RC, Overvad K, Jakobsen MU, Johnsen NF, Tjønneland A, Linseisen J, Rohrmann S, Boeing H, Pischon T, Trichopoulou A, Lagiou P, Trichopoulos D, Sacerdote C, Palli D, Tumino R, Krogh V, Bueno-de-Mesquita HB, Kiemeney LA, Chirlaque MD, Ardanaz E, Sánchez MJ, Larrañaga N, González CA, Quirós JR, Manjer J, Wirfält E, Stattin P, Hallmans G, Khaw KT, Bingham S, Ferrari P, Slimani N, Jenab M, Riboli E. Dietary fat intake and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr.* 2008 May; 87(5): 1, 405-1, 413. PMID: 18469265.	Does not answer question: Examined relationship between animal fat intake and prostate cancer.

Dallongeville J, Yarnell J, Ducimetière P, Arveiler D, Ferrières J, Montaye M, Luc G, Evans A, Bingham A, Hass B, Ruidavets JB, Amouyel P. Fish consumption is associated with lower heart rates.*Circulation.* 2003 Aug 19; 108(7): 820-825. Epub 2003 Aug 11. PMID: 12912821.	Does not answer question: Examined relationship between fish intake and heart rates.
Davey GK, Spencer EA, Appleby PN, Allen NE, Knox KH, Key TJ. EPIC-Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33 883 meat-eaters and 31 546 non meat-eaters in the UK. *Public Health Nutr.* 2003 May; 6(3): 259-269. PMID: 12740075.	Does not include health outcomes in analyses.
de Mello VD, Zelmanovitz T, Perassolo MS, Azevedo MJ, Gross JL. Withdrawal of red meat from the usual diet reduces albuminuria and improves serum fatty acid profile in type 2 diabetes patients with macroalbuminuria. *Am J Clin Nutr*. 2006 May; 83(5): 1, 032-1, 038. PMID: 16685043.	Participants diagnosed with type 2 diabetes (T2D).
Dixon LB, Balder HF, Virtanen MJ, Rashidkhani B, Männistö S, Krogh V, van Den Brandt PA, Hartman AM, Pietinen P, Tan F, Virtamo J, Wolk A, Goldbohm RA. Dietary patterns associated with colon and rectal cancer: results from the Dietary Patterns and Cancer (DIETSCAN) Project. *Am J Clin Nutr.* 2004 Oct; 80(4): 1, 003-1, 011. PMID: 15447912.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Djoussé L, Gaziano JM. Egg consumption and risk of heart failure in the Physicians' Health Study. *Circulation.* 2008 Jan 29; 117(4): 512-516. Epub 2008 Jan 14. PMID: 18195171; PMCID: PMC2706003.	Does not answer question: Examined relationship between egg consumption and heart failure.
Egeberg R, Olsen A, Autrup H, Christensen J, Stripp C, Tetens I, Overvad K, Tjønneland A. Meat consumption, N-acetyl transferase 1 and 2 polymorphism and risk of breast cancer in Danish postmenopausal women. *Eur J Cancer Prev.* 2008 Feb; 17(1): 39-47. PMID: 18090909.	Study design is nested case-control study (breast cancer).
Eichholzer M, Bisig B. Daily consumption of (red) meat or meat products in Switzerland: Results of the 1992/93 Swiss Health Survey. *Eur J Clin Nutr.* 2000 Feb; 54(2): 136-142. PMID: 10694784.	Does not include health outcomes in analyses.
Elliott P, Stamler J, Dyer AR, Appel L, Dennis B, Kesteloot H, Ueshima H, Okayama A, Chan Q, Garside DB, Zhou B. Association between protein intake and blood pressure: The INTERMAP Study. *Arch Intern Med.* 2006 Jan 9; 166(1): 79-87. PMID: 16401814.	Study design is cross-sectional epidemiological study.
Engeset D, Andersen V, Hjartåker A, Lund E. Consumption of fish and risk of colon cancer in the Norwegian Women and Cancer (NOWAC) study. *Br J Nutr.* 2007 Sep; 98(3): 576-582. Epub 2007 Apr 10. Erratum in: *Br J Nutr.* 2008 Mar; 99(3): 696. PMID: 17419892.	Does not answer question: Examined relationship between fish intake and colon cancer.
Erkkilä AT, Lichtenstein AH, Mozaffarian D, Herrington DM. Fish intake is associated with a reduced progression of coronary artery atherosclerosis in postmenopausal women with coronary artery disease. *Am J Clin Nutr.* 2004 Sep; 80(3): 626-632. PMID: 15321802.	Participants diagnosed with CHD.

Erkkilä AT, Schwab US, de Mello VD, Lappalainen T, Mussalo H, Lehto S, Kemi V, Lamberg-Allardt C, Uusitupa MI. Effects of fatty and lean fish intake on blood pressure in subjects with coronary heart disease using multiple medications. *Eur J Nutr.* 2008 Sep; 47(6): 319-328. Epub 2008 Jul 29. PMID: 18665413.	Participants diagnosed with CHD.
Faramawi MF, Johnson E, Fry MW, Sall M, Zhou Y. Consumption of different types of meat and the risk of renal cancer: Meta-analysis of case-control studies. *Cancer Causes Control.* 2007 Mar; 18(2): 125-133. Epub 2007 Jan 22. Erratum in: *Cancer Causes Control.* 2007 Jun; 18 (5): 581. Yi, Zhou [corrected to Zhou, Yi]. PMID: 17242980.	Does not include colorectal, breast or prostate cancer in analyses.
Ferrucci LM, Sinha R, Graubard BI, Mayne ST, Ma X, Schatzkin A, Schoenfeld PS, Cash BD, Flood A, Cross AJ. Dietary meat intake in relation to colorectal adenoma in asymptomatic women. *Am J Gastroenterol.* 2009 May; 104(5): 1, 231-1, 140. Epub 2009 Apr 14. PMID: 19367270.	Study design is case-control study (colorectal cancer).
Geelen A, Schouten JM, Kamphuis C, Stam BE, Burema J, Renkema JM, Bakker EJ, van't Veer P, Kampman E. Fish consumption, n-3 fatty acids, and colorectal cancer: a meta-analysis of prospective cohort studies. *Am J Epidemiol*. 2007 Nov 15; 166(10): 1, 116-1, 125. Epub 2007 Sep 6. PMID: 17823383.	Study design is meta-analysis (colorectal cancer).
Gillum RF, Mussolino ME, Madans JH. Fish consumption and hypertension incidence in African Americans and whites: The NHANES I Epidemiologic Follow-up Study. *J Natl Med Assoc.* 2001 Apr; 93(4): 124-128. PMID: 12653399; PMCID: PMC2593988.	Does not answer question: Examined relationship between fish intake and hypertension (HTN).
Goldin BR, Brauner E, Adlercreutz H, Ausman LM, Lichtenstein AH. Hormonal response to diets high in soy or animal protein without and with isoflavones in moderately hypercholesterolemic subjects. *Nutr Cancer.* 2005; 51(1): 1-6. PMID: 15749623.	Does not answer question: Examined hormonal response to diets high in soy or animal protein.
Gonzalez CA, Riboli E. Diet and cancer prevention: Where we are, where we are going. Nutr Cancer. 2006; 56(2): 225-31. Review. PMID: 17474869.	Study design is narrative review.
Grillenberger M, Neumann CG, Murphy SP, Bwibo NO, Weiss RE, Jiang L, Hautvast JG, West CE. Intake of micronutrients high in animal-source foods is associated with better growth in rural Kenyan school children. *Br J Nutr*. 2006 Feb; 95(2): 379-390. PMID: 16469157.	Study population not from a developed country as defined by the Human Development Index (2009).
Gross JL, Zelmanovitz T, Moulin CC, De Mello V, Perassolo M, Leitão C, Hoefel A, Paggi A, Azevedo MJ. Effect of a chicken-based diet on renal function and lipid profile in patients with type 2 diabetes: a randomized crossover trial. *Diabetes Care.* 2002 Apr; 25(4): 645-651. PMID: 11919119.	Participants diagnosed with T2D.

Günther AL, Remer T, Kroke A, Buyken AE. Early protein intake and later obesity risk: which protein sources at which time points throughout infancy and childhood are important for body mass index and body fat percentage at 7 y of age? *Am J Clin Nutr.* 2007 Dec; 86(6): 1, 765-1, 772. PMID: 18065597.	Does not answer question: Examined protein intake during infancy and childhood and body weight outcomes at age seven years.
He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, Greenland P. Accumulated evidence on fish consumption and coronary heart disease mortality: A meta-analysis of cohort studies. *Circulation.* 2004 Jun 8; 109(22): 2, 705-2, 711. PMID: 15184295.	Does not answer question: examined relationship between fish intake and CHD.
High red-meat intake, obesity linked to cancer.*Health News.* 2002 Feb; 8(2): 9. PMID: 11862847.	News article.
Hodgson JM, Burke V, Beilin LJ, Puddey IB. Partial substitution of carbohydrate intake with protein intake from lean red meat lowers blood pressure in hypertensive persons. *Am J Clin Nutr.* 2006 Apr; 83(4): 780-787. PMID: 16600928.	Participants diagnosed with HTN.
Hu FB, Manson JE, Willett WC. Types of dietary fat and risk of coronary heart disease: a critical review.*J Am Coll Nutr.* 2001 Feb; 20(1): 5-19. Review. PMID: 11293467.	Study design is narrative review.
Huncharek M, Kupelnick B, Wheeler L. Dietary cured meat and the risk of adult glioma: A meta-analysis of nine observational studies. *J Environ Pathol Toxicol* Oncol. 2003; 22(2): 129-137. PMID: 14533876.	Does not include colorectal, breast, or prostate cancer in analyses.
Huncharek M, Kupelnick B. A meta-analysis of maternal cured meat consumption during pregnancy and the risk of childhood brain tumors. *Neuroepidemiology.* 2004 Jan-Apr; 23(1-2): 78-84. PMID: 14739572.	Does not include colorectal, breast, or prostate cancer in analyses.
Hunninghake DB, Maki KC, Kwiterovich PO Jr, Davidson MH, Dicklin MR, Kafonek SD. Incorporation of lean red meat into a National Cholesterol Education Program Step I diet: A long-term, randomized clinical trial in free-living persons with hypercholesterolemia. *J Am Coll Nutr.* 2000 Jun; 19(3): 351-360. PMID: 10872897.	Participants diagnosed with hypercholesterolemia.
Iso H, Sato S, Kitamura A, Naito Y, Shimamoto T, Komachi Y. Fat and protein intakes and risk of intraparenchymal hemorrhage among middle-aged Japanese. *Am J Epidemiol.* 2003 Jan 1; 157(1): 32-39. Erratum in: *Am J Epidemiol.* 2004 Feb 1; 159(3): 318. PMID: 12505888.	Does not answer question: examined relationship between protein intake and intraparenchymal hemorrhage.
Järvinen R, Knekt P, Rissanen H, Reunanen A. Intake of fish and long-chain n-3 fatty acids and the risk of coronary heart mortality in men and women. *Br J Nutr.* 2006 Apr; 95(4): 824-829. PMID: 16571163.	Does not answer question: examined relationship between fish intake and CHD.
Jenkins DJ, Wong JM, Kendall CW, Esfahani A, Ng VW, Leong TC, Faulkner DA, Vidgen E, Greaves KA, Paul G, Singer W. The effect of a plant-based low-carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. *Arch Intern Med.* 2009 Jun 8; 169(11): 1, 046-1, 054. PMID: 19506174.	Participants diagnosed hyperlipidemia.

Joshi AD, Corral R, Siegmund KD, Haile RW, Le Marchand L, Martínez ME, Ahnen DJ, Sandler RS, Lance P, Stern MC. Red meat and poultry intake, polymorphisms in the nucleotide excision repair and mismatch repair pathways and colorectal cancer risk. 2009 Mar; 30(3): 472-479. Epub 2008 Nov 24. PMID: 19029193; PMCID: PMC2722151.	Study design is case-control family-based study (colorectal cancer).
Kabat GC, Miller AB, Jain M, Rohan TE. A cohort study of dietary iron and heme iron intake and risk of colorectal cancer in women. *Br J Cancer.* 2007 Jul 2; 97 (1): 118-122. Epub 2007 Jun 5. Erratum in: *Br J Cancer.* 2007 Dec 3; 97(11): 1, 600. PMID: 77551493; PMCID: PMC2359661.	Does not answer question: examined relationship between iron and heme iron intake and colorectal cancer.
König A, Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, Lawrence RS, Savitz DA, Teutsch SM. A quantitative analysis of fish consumption and coronary heart disease mortality. *Am J Prev Med.* 2005 Nov; 29(4): 335-346. PMID: 16242600.	Does not answer question: examined relationship between fish intake and CHD.
Kono S. Secular trend of colon cancer incidence and mortality in relation to fat and meat intake in Japan. *Eur J Cancer Prev*. 2004 Apr; 13(2): 127-132. PMID: 15100579.	Study design is non-comparative, correlational study.
Kontogianni MD, Panagiotakos DB, Pitsavos C, Chrysohoou C, Stefanadis C. Relationship between meat intake and the development of acute coronary syndromes: the CARDIO2000 case-control study. *Eur J Clin Nutr.* 2008 Feb; 62(2): 171-177. Epub 2007 Mar 14. PMID: 17356558.	Does not include health outcome of interest in analyses.
Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation*. 2002 Nov 19; 106(21): 2, 747-2, 757. Erratum in: *Circulation.* 2003 Jan 28; 107 (3): 512. PMID: 12438303.	Expert opinion.
Larsson SC, Orsini N, Wolk A. Processed meat consumption and stomach cancer risk: A meta-analysis. *J Natl Cancer Inst.* 2006 Aug 2; 98(15): 1, 078-1, 087. PMID: 16882945.	Does not include colorectal, breast or prostate cancer in analyses.
Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: A meta-analysis of prospective studies. *Int J Cancer.* 2006 Dec 1; 119(11): 2, 657-2, 664. PMID: 16991129.	Study design is meta-analysis (colorectal cancer).
Lee JE, Spiegelman D, Hunter DJ, Albanes D, Bernstein L, van den Brandt PA, Buring JE, Cho E, English DR, Freudenheim JL, Giles GG, Graham S, Horn-Ross PL, Håkansson N, Leitzmann MF, Männistö S, McCullough ML, Miller AB, Parker AS, Rohan TE, Schatzkin A, Schouten LJ, Sweeney C, Willett WC, Wolk A, Zhang SM, Smith-Warner SA. Fat, protein, and meat consumption and renal cell cancer risk: A pooled analysis of 13 prospective studies. *J Natl Cancer Inst*. 2008 Dec 3; 100(23): 1, 695-1, 706. Epub 2008 Nov 25. PMID: 19033572; PMCID: PMC2727138.	Does not include colorectal, breast or prostate cancer in analyses.
Levitan EB, Wolk A, Mittleman MA. Fish consumption, marine omega-3 fatty acids, and incidence of heart failure: A population-based prospective study of middle-aged and elderly men. *Eur Heart J.* 2009 Jun; 30(12): 1, 495-1, 500. Epub 2009 Apr 21. PMID: 19383731; PMCID: PMC2695952.	Does not answer question: Examined relationship between fish intake and heart failure.

Lichtenstein AH, Jalbert SM, Adlercreutz H, Goldin BR, Rasmussen H, Schaefer EJ, Ausman LM. Lipoprotein response to diets high in soy or animal protein with and without isoflavones in moderately hypercholesterolemic subjects. *Arterioscler Thromb Vasc Biol.* 2002 Nov 1; 22(11): 1, 852-1, 858. PMID: 12426215.	Participants diagnosed with hypercholesterolemia.
Linseisen J, Kesse E, Slimani N; EPIC Working Group on Dietary Pattern, Subgroup Meat. Meat consumption in Europe: Results from the EPIC study.*IARC Sci Publ*. 2002; 156: 211-212. PMID: 12484168.	Does not include health outcomes in analyses.
Liu L, Ikeda K, Yamori Y; WHO-CARDIAC Study Group. Inverse relationship between urinary markers of animal protein intake and blood pressure in Chinese: results from the WHO Cardiovascular Diseases and Alimentary Comparison (CARDIAC) Study. *Int J Epidemiol*. 2002 Feb; 31(1): 227-233. PMID: 11914325.	Does not answer question: Examined the relationship between urinary excretion of 3-methylhistidine (as marker of animal protein intake) and blood pressure (BP).
Lucey AJ, Paschos GK, Cashman KD, Martínéz JA, Thorsdottir I, Kiely M. Influence of moderate energy restriction and seafood consumption on bone turnover in overweight young adults. *Am J Clin Nutr.* 2008 Apr; 87(4): 1, 045-1, 052. PMID: 18400730.	Does not include health outcome of interest in analyses.
Lüchtenborg M, Weijenberg MP, de Goeij AF, Wark PA, Brink M, Roemen GM, Lentjes MH, de Bruïne AP, Goldbohm RA, van 't Veer P, van den Brandt PA. Meat and fish consumption, APC gene mutations and hMLH1 expression in colon and rectal cancer: A prospective cohort study (The Netherlands). *Cancer Causes Control.* 2005 Nov; 16(9): 1, 041-1, 054. PMID: 16184469.	Results reported based on the same dataset as Brink, 2005.
Mamo JC, James AP, Soares MJ, Griffiths DG, Purcell K, Schwenke JL. A low-protein diet exacerbates postprandial chylomicron concentration in moderately dyslipidaemic subjects in comparison to a lean red meat protein-enriched diet. *Eur J Clin Nutr.* 2005 Oct; 59(10): 1, 142-1, 148. PMID: 16015257.	Does not answer question: Examined relationship between protein intake and postprandial response.
Männistö S, Dixon LB, Balder HF, Virtanen MJ, Krogh V, Khani BR, Berrino F, van den Brandt PA, Hartman AM, Pietinen P, Tan F, Wolk A, Goldbohm RA. Dietary patterns and breast cancer risk: Results from three cohort studies in the DIETSCAN project. *Cancer Causes Control.* 2005 Aug; 16(6): 725-733. PMID: 16049811.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Marques-Vidal P, Ravasco P, Ermelinda Camilo M. Foodstuffs and colorectal cancer risk: A review. *Clin Nutr.* 2006 Feb; 25(1): 14-36. Epub 2005 Nov 14. Review. PMID: 16290272.	Study design is systematic review (colorectal cancer).
Matheson EM, Mainous AG 3rd, Hill EG, Carnemolla MA. Shellfish consumption and risk of coronary heart disease. *J Am Diet Assoc.* 2009 Aug; 109(8): 1, 422-1, 426. PMID: 19631050.	Does not answer question: Examined relationship between shellfish intake and CHD.

Matthan NR, Jalbert SM, Ausman LM, Kuvin JT, Karas RH, Lichtenstein AH. Effect of soy protein from differently processed products on cardiovascular disease risk factors and vascular endothelial function in hypercholesterolemic subjects. *Am J Clin Nutr.* 2007 Apr; 85(4): 960-966. Erratum in: *Am J Clin Nutr.* 2007 Aug; 86(2): 525. PMID: 17413093.	Participants were hypercholesterolemic.
McCarty MF. The origins of western obesity: A role for animal protein? *Med Hypotheses.* 2000 Mar; 54(3): 488-494. PMID: 10783494.	Study design is narrative review.
McNaughton SA, Mishra GD, Stephen AM, Wadsworth ME. Dietary patterns throughout adult life are associated with body mass index, waist circumference, blood pressure, and red cell folate. *J Nutr.* 2007 Jan; 137(1): 99-105. PMID: 17182808.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Melanson K, Gootman J, Myrdal A, Kline G, Rippe JM. Weight loss and total lipid profile changes in overweight women consuming beef or chicken as the primary protein source. *Nutrition.* 2003 May; 19(5): 409-414. PMID: 12714091.	Dropout rate is higher than inclusion criteria.
Missmer SA, Smith-Warner SA, Spiegelman D, Yaun SS, Adami HO, Beeson WL, van den Brandt PA, Fraser GE, Freudenheim JL, Goldbohm RA, Graham S, Kushi LH, Miller AB, Potter JD, Rohan TE, Speizer FE, Toniolo P, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Hunter DJ. Meat and dairy food consumption and breast cancer: A pooled analysis of cohort studies. *Int J Epidemiol.* 2002 Feb; 31(1): 78-85. PMID: 11914299.	Study design is meta-analysis (breast cancer).
Möllsten AV, Dahlquist GG, Stattin EL, Rudberg S. Higher intakes of fish protein are related to a lower risk of microalbuminuria in young Swedish type 1 diabetic patients. *Diabetes Care.* 2001 May; 24(5): 805-810. PMID: 11347734.	Participants diagnosed with T2D.
Mortensen LS, Hartvigsen ML, Brader LJ, Astrup A, Schrezenmeir J, Holst JJ, Thomsen C, Hermansen K. Differential effects of protein quality on postprandial lipemia in response to a fat-rich meal in type 2 diabetes: comparison of whey, casein, gluten, and cod protein. *Am J Clin Nutr.* 2009 Jul; 90(1): 41-48. Epub 2009 May 20. PMID: 19458012.	Participants diagnosed with T2D.
Mozaffarian D, Psaty BM, Rimm EB, Lemaitre RN, Burke GL, Lyles MF, Lefkowitz D, Siscovick DS. Fish intake and risk of incident atrial fibrillation. *Circulation.* 2004 Jul 27; 110(4): 368-373. Epub 2004 Jul 19. PMID: 15262826; PMCID: PMC1201400.	Does not answer question: Examined relationship between fish intake and atrial fibrillation.
Nagata C, Shimizu H, Kametani M, Takeyama N, Ohnuma T, Matsushita S. Diet and colorectal adenoma in Japanese males and females. *Dis Colon Rectum.* 2001 Jan; 44(1): 105-111. PMID: 11805576.	Study design is case-control study (colorectal cancer).
Nenseter MS, Østerud B, Larsen T, Strøm E, Bergei C, Hewitt S, Holven KB, Hagve TA, Mjøs SA, Solvang M, Pettersen J, Opstvedt J, Ose L. Effect of Norwegian fish powder on risk factors for coronary heart disease among hypercholesterolemic individuals. *Nutr Metab Cardiovasc Dis.* 2000 Dec; 10(6): 323-330. PMID: 11302007.	Did not answer question: Examined relationship between fish powder and CHD.

Nettleton JA, Steffen LM, Loehr LR, Rosamond WD, Folsom AR. Incident heart failure is associated with lower whole-grain intake and greater high-fat dairy and egg intake in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Diet Assoc*. 2008 Nov; 108(11): 1, 881-1, 887. PMID: 18954578; PMCID: PMC2650810.	Does not answer question: Examined relationship between egg intake and heart failure.
Nkondjock A, Receveur O. Fish-seafood consumption, obesity, and risk of type 2 diabetes: an ecological study. *Diabetes Metab.* 2003 Dec; 29(6): 635-642. PMID: 14707894.	Does not answer question: Examined relationship between fish intake and T2D.
Norat T, Lukanova A, Ferrari P, Riboli E. Meat consumption and colorectal cancer risk: Dose-response meta-analysis of epidemiological studies. *Int J Cancer.* 2002 Mar 10; 98(2): 241-256. PMID: 11857415.	Study design is meta-analysis (colorectal cancer).
Norat T, Riboli E. Meat consumption and colorectal cancer: A review of epidemiologic evidence. *Nutr Rev.* 2001 Feb; 59(2): 37-47. Review. PMID: 11310774.	Study design is meta-analysis (colorectal cancer).
Norat T, Riboli E. Meat consumption and colorectal cancer: A review of epidemiologic evidence. *Nutr Rev.* 2001 Feb; 59(2): 37-47. Review. PMID: 11310774.	Study design is narrative review (colorectal cancer).
Nowson CA, Wattanapenpaiboon N, Pachett A. Low-sodium Dietary Approaches to Stop Hypertension-type diet including lean red meat lowers blood pressure in postmenopausal women. *Nutr Res.* 2009 Jan; 29(1): 8-18. PMID: 19185772.	Does not include animal protein products in analyses.
Olmedilla-Alonso B, Granado-Lorencio F, Herrero-Barbudo C, Blanco-Navarro I, Blázquez-García S, Pérez-Sacristán B. Consumption of restructured meat products with added walnuts has a cholesterol-lowering effect in subjects at high cardiovascular risk: a randomised, crossover, placebo-controlled study. *J Am Coll Nutr.* 2008 Apr; 27(2): 342-348. PMID: 18689569.	Does not answer question: Examined effect of restructured meat product on cholesterol.
Panagiotakos DB, Pitsavos C, Zampelas A, Chrysohoou C, Griffin BA, Stefanadis C, Toutouzas P. Fish consumption and the risk of developing acute coronary syndromes: The CARDIO2000 study. *Int J Cardiol.* 2005 Jul 20; 102(3): 403-409. PMID: 16004884.	Does not answer question: Examined relationship between fish intake and health outcomes.
Panagiotakos DB, Zeimbekis A, Boutziouka V, Economou M, Kourlaba G, Toutouzas P, Polychronopoulos E. Long-term fish intake is associated with better lipid profile, arterial blood pressure, and blood glucose levels in elderly people from Mediterranean islands (MEDIS epidemiological study). *Med Sci Monit.* 2007 Jul; 13(7): CR307-CR312. PMID: 17599024.	Does not answer question: Examined relationship between fish intake and health outcomes.
Pham TM, Fujino Y, Kubo T, Ide R, Tokui N, Mizoue T, Ogimoto I, Matsuda S, Yoshimura T. Fish intake and the risk of fatal prostate cancer: Findings from a cohort study in Japan. *Public Health Nutr.* 2009 May; 12(5): 609-613. Epub 2008 Jul 29. PMID: 18664313.	Does not answer question: Examined relationship between fish intake and prostate cancer.

Pieniak Z, Verbeke W, Perez-Cueto F, Brunsø K, De Henauw S. Fish consumption and its motives in households with versus without self-reported medical history of CVD: A consumer survey from five European countries. *BMC Public Health.* 2008 Sep 10; 8: 306. PMID: 18783593; PMCID: PMC2556335.	Does not include health outcomes in analyses.
Processed meat consumption linked to type 2 diabetes. *Nephrol News Issues.* 2002 Apr; 16(5): 68-69. PMID: 11962157.	News article.
Ramel A, Parra D, Martinéz JA, Kiely M, Thorsdottir I. Effects of seafood consumption and weight loss on fasting leptin and ghrelin concentrations in overweight and obese European young adults. *Eur J Nutr.* 2009 Mar; 48(2): 107-114. Epub 2009 Jan 13. PMID: 19142567.	Does not answer question: Examined relationship between seafood and leptin and ghrelin concentrations.
Rosell M, Appleby P, Spencer E, Key T. Weight gain over 5 years in 21, 966 meat-eating, fish-eating, vegetarian, and vegan men and women in EPIC-Oxford. *Int J Obes (Lond).* 2006 Sep; 30(9): 1, 389-1, 396. Epub 2006 Mar 14. PMID: 16534521.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Sandhu MS, White IR, McPherson K. Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: A meta-analytical approach. *Cancer Epidemiol Biomarkers Prev.* 2001 May; 10(5): 439-446. PMID: 11352852.	Study design is systematic review/meta-analysis (colorectal cancer).
Santarelli RL, Pierre F, Corpet DE. Processed meat and colorectal cancer: A review of epidemiologic and experimental evidence. *Nutr Cancer.* 2008; 60(2): 131-144. Review. PMID: 18444144; PMCID: PMC2661797.	Study design is narrative review.
Satia JA, Tseng M, Galanko JA, Martin C, Sandler RS. Dietary patterns and colon cancer risk in Whites and African Americans in the North Carolina Colon Cancer Study. *Nutr Cancer.* 2009; 61(2): 179-193. PMID: 19235034.	Study design is case-control study (colon cancer).
Schulz M, Hoffmann K, Weikert C, Nöthlings U, Schulze MB, Boeing H. Identification of a dietary pattern characterized by high-fat food choices associated with increased risk of breast cancer: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Br J Nutr.* 2008 Nov; 100(5): 942-946. PMID: 18377685.	Does not answer question: Examines relationship between high fat foods and breast cancer.
Seierstad SL, Seljeflot I, Johansen O, Hansen R, Haugen M, Rosenlund G, Frøyland L, Arnesen H. Dietary intake of differently fed salmon: The influence on markers of human atherosclerosis. *Eur J Clin Invest.* 2005 Jan; 35(1): 52-59. PMID: 15638820.	Participants diagnosed with T2D.
Shiell AW, Campbell-Brown M, Haselden S, Robinson S, Godfrey KM, Barker DJ. High-meat, low-carbohydrate diet in pregnancy: Relation to adult blood pressure in the offspring. *Hypertension*. 2001 Dec 1; 38(6): 1, 282-1, 288. PMID: 11751704.	Does not answer question: Examines relationship between dietary intake during pregnancy and health of adult offspring.
Sieri S, Krogh V, Muti P, Micheli A, Pala V, Crosignani P, Berrino F. Fat and protein intake and subsequent breast cancer risk in postmenopausal women. *Nutr Cancer.* 2002; 42(1): 10-17. PMID: 12235640.	Study design is case-control study (breast cancer).

Skjelbred CF, Saebø M, Hjartåker A, Grotmol T, Hansteen IL, Tveit KM, Hoff G, Kure EH. Meat, vegetables and genetic polymorphisms and the risk of colorectal carcinomas and adenomas. *BMC Cancer*. 2007 Dec 19; 7: 228. PMID: 18093316; PMCID: PMC2228310.	Study design is case-control study (colorectal cancer).
Smith DR, Wood R, Tseng S, Smith SB. Increased beef consumption increases apolipoprotein A-I but not serum cholesterol of mildly hypercholesterolemic men with different levels of habitual beef intake. *Exp Biol Med (Maywood).* 2002 Apr; 227(4): 266-275. PMID: 11910049.	Participants diagnosed with mild hypercholesterolemia.
SoRelle R. Fish and long-chain omega-3 fatty acids could be lifesavers for diabetic women. *Circulation.* 2003 Apr 22; 107(15): e9, 033-9, 035. PMID: 12707254.	Participants were diagnosed with diabetes.
Sørensen M, Autrup H, Olsen A, Tjønneland A, Overvad K, Raaschou-Nielsen O. Prospective study of NAT1 and NAT2 polymorphisms, tobacco smoking and meat consumption and risk of colorectal cancer. *Cancer Lett.* 2008 Aug 8; 266(2): 186-193. Epub 2008 Mar 26. PMID: 18372103.	Study design is case-control study (colorectal cancer).
Spencer EA, Appleby PN, Davey GK, Key TJ. Diet and body mass index in 38000 EPIC-Oxford meat-eaters, fish-eaters, vegetarians and vegans. *Int J Obes Relat Metab Disord.* 2003 Jun; 27(6): 728-734. PMID: 12833118.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Stewart JW, Kaplan ML, Beitz DC. Pork with a high content of polyunsaturated fatty acids lowers LDL cholesterol in women. *Am J Clin Nutr.* 2001 Aug; 74(2): 179-187. PMID: 11470718.	Intervention consisted of modified pork high in PUFAs.
Tanskanen A, Hibbeln JR, Tuomilehto J, Uutela A, Haukkala A, Viinamäki H, Lehtonen J, Vartiainen E. Fish consumption and depressive symptoms in the general population in Finland. *Psychiatr Serv.* 2001 Apr; 52(4): 529-531. PMID: 11274502.	Does not include health outcome of interest in analyses.
Tapola NS, Lyyra ML, Karvonen HM, Uusitupa MI, Sarkkinen ES. The effect of meat products enriched with plant sterols and minerals on serum lipids and blood pressure. *Int J Food Sci Nutr.* 2004 Aug; 55(5): 389-397. PMID: 15545047.	Intervention consisted of meat products enriched with plant sterols; participants diagnosed with hypercholesterolemia.
Tappel A. Heme of consumed red meat can act as a catalyst of oxidative damage and could initiate colon, breast and prostate cancers, heart disease and other diseases. *Med Hypotheses*. 2007; 68(3): 562-564. Epub 2006 Oct 11. PMID: 17045417.	Study design is narrative review.
Teixeira Rde C, Molina Mdel C, Zandonade E, Mill JG. Cardiovascular risk in vegetarians and omnivores: A comparative study. *Arq Bras Cardiol.* 2007 Oct; 89(4): 237-244. English, Portuguese. PMID: 17992380.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Terry P, Rohan TE, Wolk A, Maehle-Schmidt M, Magnusson C. Fish consumption and breast cancer risk. *Nutr Cancer.* 2002; 44(1): 1-6. PMID: 12672635.	Study design is case-control study (breast cancer).

Thorsdottir I, Birgisdottir B, Kiely M, Martinez J, Bandarra N. Fish consumption among young overweight European adults and compliance to varying seafood content in four weight loss intervention diets. *Public Health Nutr.* 2009 May; 12(5): 592-598. Epub 2008 Jun 19. PMID: 18561865.	Does not answer question: Examined compliance to eating varying types of seafood in weight loss intervention diets.
Thorsdottir I, Tomasson H, Gunnarsdottir I, Gisladottir E, Kiely M, Parra MD, Bandarra NM, Schaafsma G, Martinéz JA. Randomized trial of weight-loss-diets for young adults varying in fish and fish oil content. *Int J Obes* (Lond). 2007 Oct; 31(10): 1, 560-1, 566. Epub 2007 May 15. PMID: 17502874.	Does not answer question: Examined fish intake and weight loss.
Tiemersma EW, Kampman E, Bueno de Mesquita HB, Bunschoten A, van Schothorst EM, Kok FJ, Kromhout D. Meat consumption, cigarette smoking, and genetic susceptibility in the etiology of colorectal cancer: results from a Dutch prospective study. *Cancer Causes Control.* 2002 May; 13(4): 383-393. PMID: 12074508.	Study design is case-control study (colorectal cancer).
Timonen M, Horrobin D, Jokelainen J, Laitinen J, Herva A, Räsänen P. Fish consumption and depression: The Northern Finland 1966 birth cohort study. *J Affect Disord.* 2004 Nov 1; 82(3): 447-452. PMID: 15555697.	Does not include health outcome of interest in analyses.
Tzoulaki I, Brown IJ, Chan Q, Van Horn L, Ueshima H, Zhao L, Stamler J, Elliott P; International Collaborative Research Group on Macro-/Micronutrients and Blood Pressure. Relation of iron and red meat intake to blood pressure: cross sectional epidemiological study. *BMJ.* 2008 Jul 15; 337: a258. doi: 10.1136/bmj.a258. PMID: 18632704; PMCID: PMC2658466.	Study design is cross-sectional epidemiological study.
Umesawa M, Sato S, Imano H, Kitamura A, Shimamoto T, Yamagishi K, Tanigawa T, Iso H. Relations between protein intake and blood pressure in Japanese men and women: the Circulatory Risk in Communities Study (CIRCS). *Am J Clin Nutr.* 2009 Aug; 90(2): 377-384. Epub 2009 Jun 10. PMID: 19515740.	Study design is cross-sectional.
Varraso R, Jiang R, Barr RG, Willett WC, Camargo CA Jr. Prospective study of cured meats consumption and risk of chronic obstructive pulmonary disease in men. *Am J Epidemiol*. 2007 Dec 15; 166(12): 1, 438-1, 445. Epub 2007 Sep 4. PMID: 17785711; PMCID: PMC2573990.	Does not include health outcome of interest in analyses.
Virtanen JK, Mozaffarian D, Chiuve SE, Rimm EB. Fish consumption and risk of major chronic disease in men. *Am J Clin Nutr.* 2008 Dec; 88(6): 1, 618-1, 625. PubMed PMID: 19064523; PMCID: PMC2613199.	Does not answer question: Examined relationship between fish intake and chronic disease.
Wakai K, Tamakoshi K, Date C, Fukui M, Suzuki S, Lin Y, Niwa Y, Nishio K, Yatsuya H, Kondo T, Tokudome S, Yamamoto A, Toyoshima H, Tamakoshi A; JACC Study Group. Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. *Cancer Sci.* 2005 Sep; 96(9): 590-599. PMID: 16128744.	Does not answer question: Examined relationship between breast cancer and fat intake, not animal protein.

Weggemans RM, Zock PL, Katan MB. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: A meta-analysis. *Am J Clin Nutr.* 2001 May; 73(5): 885-891. PMID: 11333841.	Does not examine relationship between intake of animal protein product and health outcome.
Weghuber D, Widhalm K. Effect of 3-month treatment of children and adolescents with familial and polygenic hypercholesterolaemia with a soya-substituted diet. *Br J Nutr.* 2008 Feb; 99(2): 281-286. Epub 2007 Aug 13. PMID: 17697400.	Participants diagnosed with hypercholesterolemia.
Welch AA, Bingham SA, Ive J, Friesen MD, Wareham NJ, Riboli E, Khaw KT. Dietary fish intake and plasma phospholipid n-3 polyunsaturated fatty acid concentrations in men and women in the European Prospective Investigation into Cancer-Norfolk United Kingdom cohort. *Am J Clin Nutr.* 2006 Dec; 84(6): 1, 330-1, 339. PMID: 17158413.	Does not include health outcomes in analyses; fish is the independent variable.
Wu K, Hu FB, Willett WC, Giovannucci E. Dietary patterns and risk of prostate cancer in U.S. men. *Cancer Epidemiol Biomarkers Prev.* 2006 Jan; 15(1): 167-171. PMID: 16434606.	Does not include animal protein product intake, specifically, in analyses. Examined dietary patterns.
Yoon H, Benamouzig R, Little J, François-Collange M, Tomé D. Systematic review of epidemiological studies on meat, dairy products and egg consumption and risk of colorectal adenomas. *Eur J Cancer Prev*. 2000 Jun; 9(3): 151-164. PMID: 10954254.	Study design is systematic review (colorectal cancer).
Yuan JM, Ross RK, Gao YT, Yu MC. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *Am J Epidemiol.* 2001 Nov 1; 154(9): 809-816. PMID: 11682363.	Does not answer question: Examined relationship between fish intake and myocardial infarction.

CHAPTER 9. COOKED DRY BEANS AND PEAS – BODY WEIGHT

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF COOKED DRY BEANS AND PEAS AND BODY WEIGHT?

Conclusion statement

Limited evidence exists to establish a clear relationship between intake of cooked dry beans and peas and body weight.

Grade

Limited

Evidence summary overview

The few intervention studies on the relationship between intake of cooked dry beans and peas (not including soy) and body weight find mixed results. This conclusion is based on the review of one meta-analysis (Anderson and Major, 2002), one systematic review (Williams, 2008), four trials (Crujeiras, 2007; Pittaway, 2006; Pittaway, 2007; Pittaway, 2008) and one cross-sectional study (Papanikolaou, 2008) for beans and peas. Additionally, the Committee reviewed one systematic review (Cope, 2008) and one cohort study (Maskarinec, 2008) specifically pertaining to soy foods, all published since 2000.

In a meta-analysis of 11 studies, Anderson and Major (2002) found that the intake of non-soy legumes was associated with decreased body weight. In a systematic review examining the role of whole grains and legumes in preventing and managing overweight and obesity, Williams et al (2008) concluded that weight loss is achievable with energy-controlled diets high in legumes but felt there was insufficient evidence to draw conclusions about the protective effect of legumes on weight.

Results from feeding trials with beans and peas are mixed, but diet treatments with beans and peas are generally no more successful in weight loss than the control or comparison treatment. In two randomized crossover trials comparing chickpea-to wheat-supplemented diets, no significant (NS) differences between dietary interventions was observed (Pittaway, 2006; Pittaway, 2007). In a study that included chickpea-supplemented ad libitum, a NS decrease in body weight was observed during the chickpea phase compared to the control phase (Pittaway, 2008). In a randomized controlled trial (RCT) comparing hypocaloric diets high in non-soybean legumes to a diet without legumes, both groups lost weight with greater weight loss achieved by those consuming legumes. A comparison of bean eaters from National Health Examination and Nutrition Surveys (NHANES) 1999 to 2002 suggest that bean consumers had lower body weights and waist circumferences in comparison to non-consumers (Papanikolaou, 2008).

In a systematic review of soy foods and weight loss, Cope et al (2008) concluded that there was limited evidence to support the hypothesis that soy foods increase weight loss when fed at isocaloric levels or that soy foods affect caloric intake when included as part of a diet. In a cohort study, women consuming more soy during adulthood had a lower body mass index (BMI), but the relation was primarily observed for Caucasian and postmenopausal participants (Maskarinec, 2008).

Evidence summary paragraphs

Beans and Peas (Not Including Soy)

Systematic Review / Meta-Analysis

Anderson and Major, 2002 (neutral quality), a meta-analysis of 11 international studies, quantitatively analyzed changes in serum lipoprotein levels and body weight resulting from intake of non-soya pulses. Intake of non-soya pulses was associated with decreases in fasting serum cholesterol (-7.2%; 95% CI: -5.8 to -8.6%), low-density lipoprotein (LDL) cholesterol (-6.2%; 95% CI: -2.8 to -9.5%), triacylglycerols (-16.6%; 95% CI: -11.8 to -21.5%) and body weight (-0.9%; 95% CI: 2.2 to -4.1%), as well as an increase in high-density lipoprotein (HDL) cholesterol (2.6%; 95% CI: 6.3 to -1.0%). The authors concluded that the available evidence indicates that regular consumption of pulses may have important protective effects on risk for CVD.

Williams et al, 2008 (positive quality), a systematic review of 53 international studies, assessed the evidence about the role of grains and legumes in the prevention and management of overweight and obesity. Databases searched included PubMed, Medline, Scopus, CINAHL and ScienceDirect, for the period 1980 to 2005. The search terms used were cereal, grain, wholegrain, legume, pulse, bread, pasta, rice, wheat, barley, oat, rye, soy, bean and pea, in conjunction with obesity, overweight, satiety, BMI and waist. The authors concluded that strong evidence supports that a diet high in whole grains is associated with lower BMI, smaller waist circumference and reduced risk of being overweight, and that a diet high in whole grains and legumes can help reduce weight gain. In addition, significant weight loss is achievable with energy-controlled diets that are high in cereals and legumes. Weak evidence supports that high intakes of refined grains may cause small increases in waist circumference in women, and there is insufficient evidence to draw conclusions about the protective effect of legumes on weight. There is no evidence that low-carbohydrate (CHO) diets restricting cereal intakes offer long-term advantages for sustained weight loss. The authors conclude that a diet high in whole grain cereals and legumes will support good overall health and is likely to help maintain a healthy body weight.

Trials

Crujeiras et al, 2007 (neutral quality), an RCT conducted in Spain, evaluated whether a hypocaloric diet high in non-soybean legumes would decrease oxidative stress in obese subjects in addition to the recognized effects associated with weight loss, especially in relation to lipid peroxidation. Thirty obese subjects (17 men and 13 women) with mean age of 36±8 years and mean BMI of 32.0±5.3kg/m^2 were included in the study. The subjects were randomly assigned to one of two energy-restricted (-30% energy with respect to the subject's energy expenditure) dietary treatments for eight weeks: 1) LD, or legume diet, with four days a week non-soybean legumes (lentils, chickpeas, peas and fava beans) servings (N=15); 2) CD, or control diet group, without legume consumption (N=15). The macronutrient content was designed to supply 20% energy from protein, 50% from CHO and 30% from fat, for both diets. Compliance was assessed with three-day weighted food records. Mean caloric intake was 2,479±1,832kcal per day at baseline, and 1,462±354kcal per day at the end point (P=0.001). There was a significant decrease in body weight in both groups following the energy-restricted diets, with higher weight loss in the LD group as compared to the CD (-7.7±3% vs. -5.3±2.7%; P=0.023). The decrease in body weight correlated with

the dietary fiber content (R=0.46; P=0.014).

Pittaway et al, 2006 (positive quality), a randomized crossover trial conducted in Australia, compared the effects of a chickpea-supplemented diet and those of a wheat-supplemented diet on serum lipids and lipoproteins. 52 participants enrolled in the trial, and 47 adults completed the study (mean age = 53.0±9.8 years; mean BMI = 27.6±4.1kg/m^2). The chickpea diet involved daily consumption of 140g of canned, drained chickpeas, chickpea bread and chickpea shortbread biscuits provided by the study personnel. The wheat diet involved consumption of wholemeal (wheat) bread, high-fiber (wheat) breakfast cereals and shortbread biscuits that participants purchased from their usual grocery store. Both interventions were designed to be weight maintenance diets and were at least five weeks in duration. Participants were asked to maintain their usual body weight and patterns of physical activity throughout the study period. There were NS differences in body weight and BMI between the start and the end of each dietary period or at the end of the two intervention diets (all P>0.2).

Pittaway et al, 2007 (positive quality), a randomized crossover trial conducted in Australia, compared the effects on serum lipids, glucose tolerance, satiety and bowel function of a diet supplemented with chickpeas to a wheat based diet of similar fiber content, and also the impact of a lower fiber diet on bowel function and satiety. Subjects consumed the two dietary interventions for five weeks each, with a washout period of six to eight weeks between interventions; the additional low-fiber diet study was followed for three weeks only. The chickpea diet was based on consuming 140g of canned, drained chickpeas daily, plus bread and shortbread biscuits made with 30% chickpea flour. The wheat diet was based on consuming whole wheat bread and high-fiber breakfast cereals daily, while the lower-fiber diet included white bread and lower fiber breakfast cereals. Thirty one subjects (mean age 50.6±10.5 years) were enrolled in the trial, 27 (17 females, 10 males) completed both diet interventions and 18 (11 females, seven males) completed the lower-fiber diet study. Body weight was similar following the chickpea and wheat intervention diets (NS differences).

Pittaway et al, 2008 (positive quality), an ordered crossover trial conducted in Australia, observed the effects of chickpea supplementation on ad libitum nutrient intake, body weight, serum lipids, lipoproteins and other metabolic changes. Subjects consumed normal intake for four weeks, ad libitum diet with at least 104g of chickpeas per day for 12 weeks and normal intake for four weeks. Fifty subjects (mean age 52.2±6.1 years) were enrolled and 45 (13 premenopausal women, 19 postmenopausal women and 13 men) completed the trial. A small, NS decrease in mean body weight was observed during the chickpea compared with the usual phase (0.45kg; 95% CI: -0.87, 0.03kg; P=0.07).

Cross-Sectional Study

Papanikolaou et al, 2008 (positive quality), a cross-sectional study in the US, evaluated the association of consuming beans on nutrient intakes and physiological parameters using data from the NHANES 1999 to 2002. A secondary analysis was completed with a reliable 24-hour dietary recall where three groups of bean consumers were identified: 1) Baked bean (BB); 2) Variety bean (VB); and 3) Variety bean or baked bean (VBBB). No significant differences in body weight, BMI or waist

circumference were observed between BB consumers and non-consumers. The VB consumers had lower body weights (77.1±1.2 vs. 80.4±0.3kg, P=0.004), smaller waist circumferences (93.9±1.1 vs. 96.0±0.3cm, P=0.04) and a 29% lower increased waist size risk (OR=0.71; 95% CI: 0.55, 0.91; P=0.009) in comparison to non-consumers. The VBBB consumers had a lower body weight (77.5±1.1 vs. 80.5± 0.3kg, P=0.008) and a smaller waist size (94.2±1.0 vs. 96.1± 0.3cm, P=0.043) relative to non-consumers. Also, adult consumers of VBBB had a 23% reduced risk of increased waist size (OR=0.77; 95% CI: 0.62, 0.95; P=0.018) and a 22% reduced risk of being obese (OR=0.78; 95% CI: 0.64, 0.97; P=0.026) compared to non-consumers. The authors concluded that bean consumers had better overall nutrient intake levels and better body weights and waist circumferences in comparison to non-consumers.

Soy Foods

Systematic Review

Cope et al, 2008 (neutral quality), a systematic review including 91 international references, identified and evaluated evidence regarding four propositions related to soyfoods and weight loss. PubMed and Web of Science were searched using the keywords soy, weight loss, fat loss, cholesterol, cardiovascular, glucose, LDL, HDL, bone, osteoporosis, isoflavone.

Certain soyfoods will improve weight and fat loss when fed at isocaloric levels: This proposition is supported by animal studies, but there is no compelling support in human studies

Certain soyfoods will improve weight and fat loss when included as part of a diet by affecting caloric intake: This proposition has limited supportive evidence in animal and human studies

Certain soyfoods will prevent or improve risk factors related to glucoregulatory function and cardiovascular health during weight loss: This proposition is supported by limited evidence and additional evidence is needed before conclusions can be made

Certain soyfoods will minimize the loss of bone mass during weight loss: This proposition is not supported by evidence.

Cohort Study

Maskarinec et al, 2008 (neutral quality), a cohort study assessed the relation between lifetime soy consumption and BMI among 1,418 women in Hawaii. Data was from two previous studies: The Breast Estrogen and Nutrition Study (BEAN) (N=225) and the Nested Case-Control Study (NCC) of mammographic densities (N=1,193). Dietary intake was assessed by a 26-page self-administered Diet and Health Questionnaire (DHQ) and a Life-time Soy Questionnaire (LTSQ) at study entry. A second LTSQ was completed at five years. Annual frequency of usual serving sizes for four categories of soy foods were classified into four categories for adults: None, less than one serving a week, more than one servings a week and more than two servings a week. Also, a four-level variable that combined intake during early life and adulthood was created. Results showed a significant trend for the association of adult soy intake with BMI at study entry (P=0.02). Women reporting more than two soy servings per week had a 0.7kg/m^2 lower BMI than women consuming no soy foods. This relation was stronger for the 937 postmenopausal women (1.2kg/m^2; P=0.01), while no trend was seen for

the 481 premenopausal women (P=0.76). When analyzed separately by ethnicity, the trend was only significant for Caucasians (P=0.01) with a 2.1kg/m^2 lower BMI in the highest than in the lowest intake group. Early life soy intake was not related to BMI at study entry or at age 21. The overall model with combined adult and child soy intake was significant (P<0.0001). The contrast between low vs. high adult soy intake was significant (P=0.002) with a difference of 0.9kg/m^2 between the low and high adult soy intake categories. This difference was of similar magnitude in pre- and post-menopausal women (P=0.08 and 0.01). After stratification by ethnicity, the effect was only significant for Caucasians (P=0.001) with a 2.35kg/m^2 lower BMI for the high adult soy intake category as compared to the low intake category. The contrast between low and high adulthood soy intake was significant (P=0.02); women in the low soy intake groups had a yearly weight gain of 0.05kg per year greater than those in the high soy intake groups. Again, the contrast was only significant for Caucasian women (P=0.01). In this study, women consuming more soy during adulthood had a lower BMI, but the relation was primarily observed for Caucasian and postmenopausal participants.

Overview table

Author, Year, Study Design, Class, Rating	Participants	Study Methodology	Outcomes
Anderson JW et al 2002 Study Design: Meta-analysis Class: M Neutral quality	N=11 international studies in meta-analysis.	Quantitatively analyzed changes in serum lipoprotein levels and body weight resulting from intake of non-soya pulses.	Intake of non-soya pulses was associated with ↓ in fasting serum cholesterol (-7.2%; 95% CI: -5.8 to -8.6%), LDL-C (-6.2%; 95% CI: -2.8 to -9.5%), triacylglycerols (-16.6%; 95% CI: -11.8 to -21.5%) and body weight (-0.9%; 95% CI: 2.2 to -4.1%), as well as an ↑ in HDL-C (2.6%; 95% CI: 6.3 to -1.0%).

Cope MB et al 2008 Study Design: Systematic Review Class: M Neutral quality	N=91 international references in systematic review.	Identified and evaluated evidence regarding four propositions related to soyfoods and weight loss. Databases searched: PubMed and Web of Science. Keywords: Soy, weight loss, fat loss, cholesterol, cardiovascular, glucose, LDL, HDL, bone, osteoporosis, isoflavone.	Certain soyfoods will improve weight or fat loss when fed at isocaloric levels: This proposition is supported by animal studies, but there is no compelling support in human studies. Certain soyfoods will improve weight and fat loss when included as part of a diet by affecting caloric intake: This proposition has limited supportive evidence in animal and human studies. Certain soyfoods will prevent or improve risk factors related to glucoregulatory function and cardiovascular health during weight loss; this proposition is supported by limited evidence and additional evidence is needed before conclusions can be made. Certain soyfoods will minimize the loss of bone mass during weight loss: This proposition is not supported by evidence.
Crujeiras AB, Parra D et al, 2007 Study Design: Randomized Controlled Trial Class: A Neutral quality	N=30 obese subjects (17 men and 13 women). Mean age: 36±8 years. Mean BMI: 32.0±5.3kg/m^2. Location: Spain.	Intervention: Two energy-restricted (-30% energy with respect to the subject's energy expenditure) dietary treatments for eight weeks: 1) LD diet with four days per week non-soybean legume (lentils, chickpeas, peas and fava beans) servings (N=15); 2) CD, or control diet, without legume consumption (N=15). Macronutrient content: 20% PRO, 50% CHO and 30% fat for both diets. Compliance assessed with three-day weighted food records.	Mean caloric intake (per day) was 2,479±1,832kcal at baseline and 1,462±354kcal at the end point (P=0.001). Significant ↓ in body weight in both groups following the energy-restricted diets, with ↑ weight loss in the LD group, as compared to the CD (-7.7±3% vs. -5.3±2.7%; P=0.023). ↓ in body weight correlated with dietary fiber content (R=0.46; P=0.014).

Maskarinec G, Aylward AG et al, 2008 Study Design: Prospective Cohort Study Class: B Neutral quality	N=1,418 women from two previous studies: Breast Estrogen and Nutrition Study (BEAN) (N=225) Nested Case-Control (NCC) study of mammographic densities (N=1,193). Location: United States.	Dietary intake was assessed by a 26-page self-administered Diet and Health Questionnaire (DHQ) and a Life-time Soy Questionnaire (LTSQ) at study entry. A second LTSQ was completed at five years. Annual frequency of usual serving sizes for four categories of soy foods were classified into four categories for adults: None <one serving a week >one serving a week >two servings a week. Also, a four-level variable that combined intake during early life and adulthood was created.	Results showed a significant trend for the association of adult soy intake with BMI at study entry (P=0.02). Women reporting >two soy servings a week had a 0.7kg/m^2 ↓ BMI than women consuming no soy foods. This relation was stronger for the 937 postmenopausal women (1.2kg/m^2; P=0.01), while no trend was seen for the 481 premenopausal women (P=0.76). When analyzed separately by ethnicity, the trend was only significant for Caucasians (P=0.01) with a 2.1kg/m^2 lower BMI in the highest than in the lowest intake group. Early life soy intake was not related to BMI at study entry or at age 21. The overall model with combined adult and child soy intake was significant (P<0.0001). The contrast between low vs. high adult soy intake was significant (P=0.002) with a difference of 0.9kg/m^2 between the ↓ and ↑ adult soy intake categories. This difference was of similar magnitude in pre- and postmenopausal women (P=0.08 and 0.01). After stratification by ethnicity, the effect was only significant for Caucasians (P=0.001) with a 2.35kg/m^2 ↓ BMI for the ↑ adult soy intake category, as compared to the ↓ intake category. The contrast between ↓ and ↑ adulthood soy intake was significant (P=0.02); women in the ↓ soy intake groups had a yearly weight gain of 0.05kg per year >those in the ↑ soy intake groups. Again, the contrast was only significant for Caucasian women (P=0.01).

Papanikolaou Y and Fulgoni VL, 2008 Study Design: Cross-Sectional Study Class: D Positive quality	N=8,229. Data from the NHANES 1999 to 2000 and NHANES 2001 to 2002. Location: United States.	Bean consumption was defined by 24-hour dietary recall. Three groups of bean consumers were identified: 1) Baked bean (BB) 2) Variety bean (VB) 3) Variety bean and baked bean (VBBB). Risk factors of interest: BP, LDL-X, fasting blood glucose, waist size, HDL-C and BMI.	NS differences in body weight, BMI or waist circumference (WC) were observed between BB consumers and non-consumers. VB consumers had ↓ body weights (77.1±1.2 vs. 80.4 ±0.3kg, P=0.004), smaller WC (93.9±1.1 vs. 96.0±0.3cm, P=0.04) and a 29% ↓ increased waist size risk (OR=0.71; 95% CI: 0.55,0.91; P=0.009) in comparison to non-consumers. VBBB consumers had a lower body weight (77.5±1.1 vs. 80.5± 0.3kg, P=0.008) and a smaller waist size (94.2±1.0 vs. 96.1± 0.3cm, P=0.043) relative to non-consumers. Also, adult consumers of VBBB had a 23% ↓ risk of increased waist size (OR=0.77; 95% CI: 0.62, 0.95; P=0.018) and a 22% ↓ risk of being obese (OR=0.78; 95% CI: 0.64,0.97; P=0.026) compared to non-consumers.
Pittaway et al 2006 Study Design: Randomized, crossover intervention trial Class: A Neutral quality	N=52 participants enrolled in the trial. N=47 adults completed the study. Mean age: 53.0 ± 9.8 years. Mean BMI: 27.6±4.1kg/m^2. Location: Australia.	Two periods of weight maintenance dietary intervention, each at least five weeks in duration: 1) Chickpea-supplemented diet 2) Wheat-supplemented diet. The chickpea diet involved daily consumption of 140g of canned, drained chickpeas, chickpea bread and chickpea shortbread biscuits provided by study personnel. Wheat diet involved consumption of whole meal (wheat) bread, high-fiber (wheat) breakfast cereals and shortbread biscuits that participants purchased from their usual grocery store. Participants asked to maintain their usual body weight and patterns of physical activity during the study.	There were NS differences in body weight and BMI between the start and the end of each dietary period or at the end of the two intervention diets (all P>0.2).

Pittaway JK et al 2007 Study Design: Randomized Crossover Trial Class: A Positive quality	N=31 subjects (mean age 50.6±10.5 years) enrolled in trial. N=27 (17 females, 10 males) completed both diet interventions N=18 (11 female, seven male) completed the lower fiber diet study. Location: Australia.	Randomized crossover trial comparing the effects on serum lipids, glucose tolerance, satiety and bowel function of a diet supplemented with chickpeas to a wheat-based diet of similar fiber content, and also the impact of a lower-fiber diet on bowel function and satiety. Subjects consumed the two dietary interventions for five weeks each, with a washout period of six to eight weeks between interventions; the additional low-fiber diet study was followed for three weeks only. The chickpea diet was based on consuming 140g of canned, drained chickpeas daily, plus bread and shortbread biscuits made with 30% chickpea flour. The wheat diet was based on consuming whole wheat bread and high-fiber breakfast cereals daily, while the lower-fiber diet included white bread and lower-fiber breakfast cereals.	Body weight was similar following the chickpea and wheat intervention diets (NS differences).
Pittaway JK et al 2008 Study Design: Ordered Crossover Trial Class: C Positive quality	N=50 subjects (mean age 52.2±6.1 years) were enrolled. N=45 (13 premenopausal women, 19 postmenopausal women and 13 men) completed the trial. Location: Australia.	Non-randomized crossover trial observing the effects of chickpea supplementation on ad libitum nutrient intake, body weight, serum lipids, lipoproteins and other metabolic changes. Subjects consumed normal intake for four weeks, ad libitum diet with at least 104g of chickpeas per day for 12 weeks and normal intake for four weeks.	Small, NS ↓ in mean body weight was observed during the chickpea compared with the usual phase (0.45kg; 95% CI: -0.87, 0.03kg; P=0.07).

Williams PG et al 2008 Study Design: Systematic Review Class: M Positive quality	N=53 international studies.	Systematic review assessing the evidence about the role of grains and legumes in the prevention and management of overweight and obesity. Databases searched: PubMed, Medline, Scopus, CINAHL and ScienceDirect, for the period 1980 to 2005. Search terms used: Cereal, grain, whole grain, legume, pulse, bread, pasta, rice, wheat, barley, oat, rye, soy, bean and pea, in conjunction with obesity, overweight, satiety, BMI and waist.	Strong evidence supports that a diet high in whole grains is associated with ↓ BMI, smaller waist circumference (WC) and ↓ risk of being overweight, and that a diet high in whole grains and legumes can help reduce weight gain. In addition, significant weight loss is achievable with energy-controlled diets that are ↑ in cereals and legumes. Weak evidence supports that ↑ intakes of refined grains may cause small ↑ in WC in women and there is insufficient evidence to draw conclusions about the protective effect of legumes on weight. No evidence that low-CHO diets restricting cereal intakes offer long-term advantages for sustained weight loss. Authors conclude that a diet ↑ in whole grain cereals and legumes will support good overall health and is likely to help maintain a healthy body weight.

Search plan and results

Inclusion criteria

- January 2000 to August 2009
- Cooked dry beans and peas provided in a whole food form and analyses addressed whole food (e.g., rather than protein)
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children two to 18 years; Adults: 19 years and older
- *Populations:* Healthy and those with elevated chronic disease risk.

Exclusion criteria

- Studies that considered cooked dry beans and peas as part of a larger dietary pattern
- Cooked dry beans and peas in forms not commonly consumed
- Studies examining postprandial, short-term response
- Medical treatment/therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human

Development Index (http://hdr.undp.org/en/statistics)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.)

Search terms and electronic databases used

- Pubmed: (Fabaceae[majr] OR dried beans* OR peas OR legumes) AND ("Diabetes Mellitus, Type 2"[majr] OR "metabolic syndrome X"[majr] OR "overweight"[majr] OR "hypertension"[majr] OR "dyslipidemias"[majr] OR "cardiovascular diseases"[majr] OR “heart diseases”[majr] OR “chronic disease”[majr] OR obesity[majr] OR "Body Weights and Measures"[majr] OR “body weight”[majr] OR “body composition”[majr] OR “Gastrointestinal Transit”[majr] OR “energy intake”[majr] OR “blood pressure”[majr] OR Laxation OR laxatives[mh]) AND "english and humans"[Filter]

Date searched: 08/19/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 772
- Total articles identified to review from electronic databases: 60
- Articles identified via handsearch or other means: 2
- Number of Primary Articles Identified: 14
- Number of Review Articles Identified: 13
- Total Number of Articles Identified: 17
- Number of Articles Reviewed but Excluded: 45

Included articles (References)

What is the relationship between the intake of cooked dry beans and peas and body weight?

Beans and Peas (Not Including Soy)

Systematic Reviews/Meta-analyses:

1. Anderson JW, Major AW. Pulses and lipaemia, short- and long-term effect: Potential in the prevention of cardiovascular disease. *Br J Nutr.* 2002 Dec; 88 Suppl 3: S263-S271. PMID: 12498626.
2. Williams PG, Grafenauer SJ, O'Shea JE. Cereal grains, legumes and weight management: A comprehensive review of the scientific evidence. *Nutr Rev.* 2008 Apr; 66 (4): 171-182. *Review*. PMID: 18366531.

Primary Citations:

1. CrujeirasAB, Parra D, Abete I, Martínez JA. A hypocaloric diet enriched in legumes specifically mitigates lipid peroxidation in obese subjects. *Free Radic Res*. 2007 Apr; 41 (4): 498-506. PMID: 17454132.
2. Pittaway JK, Ahuja KD, Cehun M, Chronopoulos A, Robertson IK, Nestel PJ, Ball MJ. Dietary supplementation with chickpeas for at least five weeks results in small but significant reductions in serum total and low-density lipoprotein cholesterols in adult women and men. *Ann Nutr Metab*. 2006; 50 (6): 512-518. Epub 2006 Dec 21. PMID: 17191025. (Hand search)
3. Pittaway JK, Robertson IK, Ball MJ. Chickpeas may influence fatty acid and

fiber intake in an ad libitum diet, leading to small improvements in serum lipid profile and glycemic control. *J Am Diet Assoc.* 2008 Jun; 108 (6): 1, 009-1, 013. PMID: 18502235.
4. Pittaway JK, Ahuja KD, Robertson IK, Ball MJ. Effects of a controlled diet supplemented with chickpeas on serum lipids, glucose tolerance, satiety and bowel function. *J Am Coll Nutr*. 2007 Aug; 26 (4): 334-340. PMID: 17906185.
5. Papanikolaou Y, Fulgoni VL 3rd. Bean consumption is associated with greater nutrient intake, reduced systolic blood pressure, lower body weight and a smaller waist circumference in adults: Results from the National Health and Nutrition Examination Survey 1999-2002. *J Am Coll Nutr*. 2008 Oct; 27 (5): 569-576. PMID: 18845707.

Soy Foods

Systematic Reviews/Meta-analyses:

1. Cope MB, Erdman JW Jr, Allison DB. The potential role of soy foods in weight and adiposity reduction: An evidence-based review. *Obes Rev*. 2008 May; 9 (3): 219-235. Review. PMID: 18419671.

Primary Citations:

2. Maskarinec G, Aylward AG, Erber E, Takata Y, Kolonel LN. Soy intake is related to a lower body mass index in adult women. *Eur J Nutr*. 2008 Apr; 47 (3): 138-144. Epub 2008 Apr 22. PMID: 18427855; PMCID: PMC2674433.

What is the relationship between the intake of cooked dry beans and peas and cardiovascular outcomes?

Beans and Peas (Not Including Soy)

Systematic Reviews/Meta-analyses:

1. Anderson JW, Major AW. Pulses and lipaemia, short- and long-term effect: Potential in the prevention of cardiovascular disease. *Br J Nutr*. 2002 Dec; 88 Suppl 3: S, 263-S, 271. PMID: 12498626.

Primary Citations:

1. CrujeirasAB, Parra D, Abete I, Martínez JA. A hypocaloric diet enriched in legumes specifically mitigates lipid peroxidation in obese subjects. *Free Radic Res*. 2007 Apr; 41 (4): 498-506. PMID: 17454132.
2. Bazzano LA, He J, Ogden LG, Loria C, Vupputuri S, Myers L, Whelton PK. Legume consumption and risk of coronary heart disease in US men and women: NHANES I Epidemiologic Follow-up Study. *Arch Intern Med*. 2001 Nov 26; 161 (21): 2, 573-2, 578. PMID: 11718588.
3. Finley JW, Burrell JB, Reeves PG. Pinto bean consumption changes SCFA profiles in fecal fermentations, bacterial populations of the lower bowel and lipid profiles in blood of humans. *J Nutr.* 2007 Nov; 137 (11): 2, 391-2, 398. PMID: 17951475.
4. Kabagambe EK, Baylin A, Ruiz-Narvarez E, Siles X, Campos H. Decreased consumption of dried mature beans is positively associated with urbanization and nonfatal acute myocardial infarction. *J Nutr*. 2005 Jul; 135 (7): 1, 770-1, 775. PMID: 15987863.
5. Papanikolaou Y, Fulgoni VL 3rd. Bean consumption is associated with greater

nutrient intake, reduced systolic blood pressure, lower body weight and a smaller waist circumference in adults: Results from the National Health and Nutrition Examination Survey 1999-2002. *J Am Coll Nutr*. 2008 Oct; 27 (5): 569-576. PMID: 18845707.

6. Pittaway JK, Ahuja KD, Cehun M, Chronopoulos A, Robertson IK, Nestel PJ, Ball MJ. Dietary supplementation with chickpeas for at least five weeks results in small but significant reductions in serum total and low-density lipoprotein cholesterols in adult women and men. *Ann Nutr Metab.* 2006; 50 (6): 512-518. Epub 2006 Dec 21. PMID: 17191025. (Hand search)
7. Pittaway JK, Robertson IK, Ball MJ. Chickpeas may influence fatty acid and fiber intake in an ad libitum diet, leading to small improvements in serum lipid profile and glycemic control. *J Am Diet Assoc.* 2008 Jun; 108 (6): 1, 009-1, 013. PMID: 18502235.
8. Pittaway JK, Ahuja KD, Robertson IK, Ball MJ. Effects of a controlled diet supplemented with chickpeas on serum lipids, glucose tolerance, satiety and bowel function. *J Am Coll Nutr*. 2007 Aug; 26 (4): 334-340. PMID: 17906185.
9. Steffen LM, Kroenke CH, Yu X, Pereira MA, Slattery ML, Van Horn L, Gross MD, Jacobs DR Jr. Associations of plant food, dairy product, and meat intakes with 15-year incidence of elevated blood pressure in young black and white adults: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr*. 2005 Dec; 82 (6): 1, 169-1, 177; quiz 1, 363-1, 364. PMID: 16332648.

Soy Foods

Primary Citations:

1. Kokubo Y, Iso H, Ishihara J, Okada K, Inoue M, Tsugane S; JPHC Study Group. Association of dietary intake of soy, beans and isoflavones with risk of cerebral and myocardial infarctions in Japanese populations: The Japan Public Health Center-based (JPHC) study cohort I. *Circulation.* 2007 Nov 27; 116 (22): 2, 553-2, 562. Epub 2007 Nov 19. PMID: 18025534.
2. Nagata C. Ecological study of the association between soy product intake and mortality from cancer and heart disease in Japan. *Int J Epidemiol*. 2000 Oct; 29 (5): 832-836. PMID: 11034965. (Hand search)
3. Welty FK, Lee KS, Lew NS, Zhou JR. Effect of soy nuts on blood pressure and lipid levels in hypertensive, pre-hypertensive and normotensive postmenopausal women. *Arch Intern Med*. 2007 May 28; 167 (10): 1, 060-1, 067. PMID: 17533209. (Hand search)

What is the relationship between the intake of cooked dry beans and peas and type 2 diabetes?

Primary Citations:

1. Villegas R, Gao YT, Yang G, Li HL, Elasy TA, Zheng W, Shu XO. Legume and soy food intake and the incidence of type 2 diabetes in the Shanghai Women's Health Study. *Am J Clin Nutr*. 2008 Jan; 87 (1): 162-167. PMID: 18175751; PMCID: PMC2361384.

Excluded articles

Article	Reason for Exclusion
Alper CM, Mattes RD. Effects of chronic peanut consumption on energy balance and hedonics. *Int J Obes Relat Metab Disord.* 2002 Aug; 26 (8): 1, 129-1, 137. PMID: 12119580.	Does not answer question; does not examine relationship between beans and peas and health.
Anderson JW, Fuller J, Patterson K, Blair R, Tabor A. Soy compared to casein meal replacement shakes with energy-restricted diets for obese women: Randomized controlled trial. *Metabolism.* 2007 Feb; 56 (2): 280-288. PMID: 17224344.	Does not meet inclusion criteria for food form.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Hu FB, Willett WC. Soy consumption, markers of inflammation, and endothelial function: A cross-over study in postmenopausal women with the metabolic syndrome. *Diabetes Care.* 2007 Apr; 30 (4): 967-973. PMID: 17392557.	Participants diagnosed with metabolic syndrome.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Padyab M, Hu FB, Willett WC. Soy inclusion in the diet improves features of the metabolic syndrome: A randomized crossover study in postmenopausal women. *Am J Clin Nutr.* 2007 Mar; 85 (3): 735-741. PMID: 17344494.	Participants diagnosed with metabolic syndrome.
Beiseigel JM, Hunt JR, Glahn RP, Welch RM, Menkir A, Maziya-Dixon BB. Iron bioavailability from maize and beans: A comparison of human measurements with Caco-2 cell and algorithm predictions. *Am J Clin Nutr*. 2007 Aug; 86 (2): 388-396. PMID: 17684210.	Does not answer question; does not examine relationship between beans and peas and health.
Bes-Rastrollo M, Wedick NM, Martinez-Gonzalez MA, Li TY, Sampson L, Hu FB. Prospective study of nut consumption, long-term weight change and obesity risk in women. *Am J Clin Nutr.* 2009 Jun; 89 (6): 1, 913-1, 919. Epub 2009 Apr 29. PMID: 19403639; PMCID: PMC2683001.	Does not answer question; does not examine relationship between beans and peas and health.
Bourdon I, Olson B, Backus R, Richter BD, Davis PA, Schneeman BO. Beans, as a source of dietary fiber, increase cholecystokinin and apolipoprotein b48 response to test meals in men. *J Nutr*. 2001 May; 131 (5): 1, 485-1, 490. PMID: 11340104.	Examines postprandial response.
Duranti M. Grain legume proteins and nutraceutical properties. *Fitoterapia.* 2006 Feb; 77 (2): 67-82. Epub 2006 Jan 6. Review. PMID: 16406359.	Study design is narrative review.
Ejigui J, Savoie L, Marin J, Desrosiers T. Improvement of the nutritional quality of a traditional complementary porridge made of fermented yellow maize (Zea mays): Effect of maize-legume combinations and traditional processing methods. *Food Nutr Bull.* 2007 Mar; 28 (1): 23-34. PMID: 17718009.	Does not answer question; does not examine relationship between beans and peas and health.
Griel AE, Eissenstat B, Juturu V, Hsieh G, Kris-Etherton PM. Improved diet quality with peanut consumption. *J Am Coll Nutr*. 2004 Dec; 23 (6): 660-668. PMID: 15637214.	Does not answer question; does not examine relationship between beans and peas and health.

Hovey AL, Jones GP, Devereux HM, Walker KZ. Whole cereal and legume seeds increase faecal short chain fatty acids compared to ground seeds. *Asia Pac J Clin Nutr.* 2003; 12 (4): 477-482. PMID: 14672874.	Sample size less than inclusion criteria.
Jenkins DJ, Hu FB, Tapsell LC, Josse AR, Kendall CW. Possible benefit of nuts in type 2 diabetes. *J Nutr.* 2008 Sep; 138 (9): 1, 752S-1, 756S. PMID: 18716181.	Study design is narrative review.
Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. Nut and peanut butter consumption and risk of type 2 diabetes in women. *JAMA*. 2002 Nov 27; 288 (20): 2, 554-2, 560. PMID: 12444862.	Does not answer question; does not examine relationship between beans and peas and health.
Johnson SK, Chua V, Hall RS, Baxter AL. Lupin kernel fibre foods improve bowel function and beneficially modify some putative faecal risk factors for colon cancer in men. *Br J Nutr*. 2006 Feb; 95 (2): 372-378. PMID: 16469156.	Does not meet inclusion criteria for food form.
Johnson SK, Thomas SJ, Hall RS. Palatability and glucose, insulin and satiety responses of chickpea flour and extruded chickpea flour bread eaten as part of a breakfast. *Eur J Clin Nutr*. 2005 Feb; 59 (2): 169-176. PMID: 15483639.	Does not meet inclusion criteria for food form.
Kris-Etherton PM, Hu FB, Ros E, Sabaté J. The role of tree nuts and peanuts in the prevention of coronary heart disease: Multiple potential mechanisms. *J Nutr.* 2008 Sep; 138 (9): 1, 746S-1, 751S. Review. PMID: 18716180.	Study design is narrative review.
Larkin TA, Astheimer LB, Price WE. Dietary combination of soy with a probiotic or prebiotic food significantly reduces total and LDL cholesterol in mildly hypercholesterolaemic subjects. *Eur J Clin Nutr*. 2009 Feb; 63 (2): 238-245. Epub 2007 Oct 17. PMID: 17940545.	Participants were hypercholesterolemic.
Lee YP, Puddey IB, Hodgson JM. Protein, fibre and blood pressure: Potential benefit of legumes. *Clin Exp Pharmacol Physiol.* 2008 Apr; 35 (4): 473-476. Review. PMID: 18307744.	Study design is narrative review.
Li TY, Brennan AM, Wedick NM, Mantzoros C, Rifai N, Hu FB. Regular consumption of nuts is associated with a lower risk of cardiovascular disease in women with type 2 diabetes. *J Nutr*. 2009 Jul; 139 (7): 1, 333-1, 338. Epub 2009 May 6. PMID: 19420347; PMCID: PMC2696988.	Participants diagnosed with type 2 diabetes.
Lichtenstein AH, Matthan NR. The effect of soybean-based foods on plasma lipid and lipoprotein concentrations. *Am J Clin Nutr.* 2007 Oct; 86 (4): 1, 253; author reply 1, 253-1, 254. PMID: 17921413.	Publication is letter to the editor.
Lokko P, Lartey A, Armar-Klemesu M, Mattes RD. Regular peanut consumption improves plasma lipid levels in healthy Ghanaians. *Int J Food Sci Nutr*. 2007 May; 58 (3): 190-200. PMID: 17514537.	Does not answer question; does not examine relationship between beans and peas and health.

Masini E, Bani D, Marzocca C, Mateescu MA, Mannaioni PF, Federico R, Mondovì B. Pea seedling histaminase as a novel therapeutic approach to anaphylactic and inflammatory disorders. A plant histaminase in allergic asthma and ischemic shock. *ScientificWorldJournal*. 2007 Jun 12; 7: 888-902. Review. PMID: 17619775.	Does not include selected outcome in analyses.
Mattes RD, Kris-Etherton PM, Foster GD. Impact of peanuts and tree nuts on body weight and healthy weight loss in adults. *J Nutr*. 2008 Sep; 138 (9): 1, 741S-1, 745S. PMID: 18716179.	Study design is narrative review.
Nasca MM, Zhou JR, Welty FK. Effect of soy nuts on adhesion molecules and markers of inflammation in hypertensive and normotensive postmenopausal women. *Am J Cardiol.* 2008 Jul 1; 102 (1): 84-86. Epub 2008 Apr 16. PMID: 18572041.	Does not include selected outcome in analyses.
Noel SE, Newby PK, Ordovas JM, Tucker KL. A traditional rice and beans pattern is associated with metabolic syndrome in Puerto Rican older adults. *J Nutr.* 2009 Jul; 139 (7): 1, 360-1, 367. Epub 2009 May 20. PMID: 19458029; PMCID: PMC2696989.	Examines the relationship between dietary patterns, not specifically beans and peas, and health outcomes.
Nöthlings U, Schulze MB, Weikert C, Boeing H, van der Schouw YT, Bamia C, Benetou V, Lagiou P, Krogh V, Beulens JW, Peeters PH, Halkjaer J, Tjønneland A, Tumino R, Panico S, Masala G, Clavel-Chapelon F, de Lauzon B, Boutron-Ruault MC, Vercambre MN, Kaaks R, Linseisen J, Overvad K, Arriola L, Ardanaz E, Gonzalez CA, Tormo MJ, Bingham S, Khaw KT, Key TJ, Vineis P, Riboli E, Ferrari P, Boffetta P, Bueno-de-Mesquita HB, van der A DL, Berglund G, Wirfält E, Hallmans G, Johansson I, Lund E, Trichopoulo A. Intake of vegetables, legumes fruit, and risk for all-cause, cardiovascular and cancer mortality in a European diabetic population. *J Nutr*. 2008 Apr; 138 (4): 775-781. PMID: 18356334.	Participants diagnosed with diabetes .
Okamoto K, Horisawa R. Soy products and risk of an aneurysmal rupture subarachnoid hemorrhage in Japan. *Eur J Cardiovasc Prev Rehabil.* 2006 Apr; 13 (2): 284-287. PMID: 16575286.	Does not include selected outcome in analyses.
Oosthuizen W, Scholtz CS, Vorster HH, Jerling JC, Vermaak WJ. Extruded dry beans and serum lipoprotein and plasma haemostatic factors in hyperlipidaemic men. *Eur J Clin Nutr.* 2000 May; 54 (5): 373-379. PMID: 10822283.	Participants diagnosed with hyperlipidemia.
Qin LQ, Xu JY, Wang PY, Hoshi K. Soyfood intake in the prevention of breast cancer risk in women: A meta-analysis of observational epidemiological studies. *J Nutr Sci Vitaminol* (Tokyo). 2006 Dec; 52 (6): 428-436. PMID: 17330506.	Does not include selected outcome in analyses.
Ridges L, Sunderland R, Moerman K, Meyer B, Astheimer L, Howe P. Cholesterol lowering benefits of soy and linseed enriched foods. *Asia Pac J Clin Nutr*. 2001; 10 (3): 204-211. PMID: 11708310.	Participants were hypercholesterolemic.

Rivas M, Garay RP, Escanero JF, Cia P Jr, Cia P, Alda JO. Soy milk lowers blood pressure in men and women with mild to moderate essential hypertension. *J Nutr.* 2002 Jul; 132 (7): 1, 900-1, 902. PMID: 12097666.	Participants diagnosed with hypertension.
Salas-Salvadó J, Bulló M, Pérez-Heras A, Ros E. Dietary fibre, nuts and cardiovascular diseases. *Br J Nutr.* 2006 Nov; 96 Suppl 2: S46-S51. Review. Erratum in: *Br J Nutr*. 2008 Feb; 99 (2): 447-448. PMID: 17125533.	Study design is narrative review.
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Xu BJ, Yuan SH, Chang SK. Comparative studies on the antioxidant activities of nine common food legumes against copper-induced human low-density lipoprotein oxidation in vitro. *J Food Sci.* 2007 Sep; 72 (7): S522-S527. PMID: 17995667.	Does not answer question; does not examine relationship between beans and peas and health .
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Yeh CC, You SL, Chen CJ, Sung FC. Peanut consumption and reduced risk of colorectal cancer in women: A prospective study in Taiwan. *World J Gastroenterol*. 2006 Jan 14; 12 (2): 222-227. PMID: 16482621.	Does not include selected outcome in analyses.
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CHAPTER 10. COOKED DRY BEANS AND PEAS – CARDIOVASCULAR OUTCOMES

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF COOKED DRY BEANS AND PEAS AND CARDIOVASCULAR OUTCOMES?

Conclusion statement

There is limited evidence that intake of cooked dry beans and peas lowers serum lipids.

Grade

Limited

Evidence summary overview

Limited evidence exists that dry beans and peas have unique abilities to lower serum lipids; most of the lipid lowering seen in studies is related to the soluble fiber content of these products. The conclusion reached for this question is based on the review of one meta-analysis (Anderson and Major, 2002), five trials (Crujeiras, 2007; Finley, 2007; Pittaway, 2006; Pittaway, 2007; Pittaway, 2008), two prospective cohort studies (Bazzano, 2001; Steffen, 2005), one case-control study (Kabagambe, 2005), and one cross-sectional study (Papanikolaou, 2008). The Committee also considered one randomized crossover trial (Welty, 2007), one prospective cohort study (Kokubo, 2007), and one longitudinal study (Nagata, 2000) regarding soy foods, all published since 2000.

Anderson and Major (2002) quantitatively analyzed changes in serum lipoprotein levels resulting from intake of non-soya pulses. The authors concluded that regular consumption of pulses may have important protective effects on risk for CVD, including decreases in serum cholesterol, low-density lipoprotein cholesterol (LDL-C) and triacylglycerols (TAG) and increases in high-density lipoprotein cholesterol (HDL-C).

In the intervention studies, dry beans and peas lowered serum lipids as expected based on soluble fiber content. In a series of studies including the daily consumption of more than 100g of chickpeas per day for five to 12 weeks, Pittaway et al (2006, 2007, 2008) observed improvements in serum total cholesterol (TC) and LDL-C compared to a control diet without legumes. Similar improvements in TC were observed following an eight-week weight loss intervention that included non-soybean legumes four days each week, and the decrease in TC was directly correlated with increased fiber intake (Crujeiras, 2007).

Bazzano et al (2001) found a strong and independent inverse association between dietary intake of legumes and risk of CHD in the Nutrition Examination Survey Epidemiologic Follow-up Study (NHEFS), which is a prospective cohort study of the First National Health and Nutrition Examination Survey (NHANES I) from 1971 to 1975. Legume consumption four or more times per week compared with less than once a week was associated with a 22% lower risk of coronary heart disease (CHD) and an 11% lower risk of cardiovascular disease (CVD). In the Coronary Artery Risk Development in Young Adults (CARDIA) Study (Steffen, 2005), tertiles of legume

intake were less than 0.1, 0.1 to 0.2 and more than 0.2 times per day, supporting extremely low usual intake of legumes. The authors noted that limited consumption of legumes and insufficient statistical power precluded definitive conclusions from being drawn about the relationship between intake of legumes and elevated blood pressure (BP). However, it is unclear whether null findings were due to the lack of association or limited range in consumption. In a case-control study in Costa Rica, Kabagambe et al (2005) observed an inverse association between myocardial infarction (MI) and the intake of one serving of beans per day (one third cup of cooked beans) in adjusted analyses. However, no additional benefit was observed with more than one serving per day.

In more than 12 years of follow-up of the Japan Public Health Center-Based Study Cohort I (Kokubo, 2007), investigators saw a decrease in the risk of MI, cerebral infarction and CVD mortality among women consuming soy at least five times per week compared to those consuming soy zero to two times per week. However, no associations were observed for men. In a longitudinal study in Japan, Nagata et al (2000) also observed an inverse correlation between soy product intake and heart disease mortality in women, but not men.

In a randomized crossover trial in which hypertensive, pre-hypertensive and normotensive post-menopausal women consumed the Therapeutic Lifestyle Changes (TLC) diet alone or with 1/2 cup unsalted soy nuts (25g soy protein) replacing 25g of non-soy protein, benefits to BP and LDL-C were greater for the hypertensive women than the normotensive participants (Welty, 2007).

Evidence summary paragraphs

Beans and Peas (Not Including Soy)

Meta-Analysis

Anderson and Major, 2002 (neutral quality), a meta-analysis of 11 international studies, quantitatively analyzed changes in serum lipoprotein levels resulting from intake of non-soya pulses. Intake of non-soya pulses was associated with decreases in fasting serum cholesterol (-7.2%; 95% CI: -5.8 to -8.6%), LDL-C (-6.2%; 95% CI: -2.8 to -9.5%), TAG (-16.6%; 95% CI: -11.8 to -21.5%) and body weight (-0.9%; 95% CI: 2.2 to -4.1%), as well as an increase in HDL-C (2.6%; 95% CI: 6.3 to -1.0%). The authors concluded that the available evidence indicates that regular consumption of pulses may have important protective effects on risk for CVD.

Primary Citations

Trials

Crujeiras et al, 2007 (neutral quality), a randomized controlled trial (RCT) conducted in Spain, evaluated whether a hypocaloric diet high in non-soybean legumes would decrease oxidative stress in obese subjects in addition to the recognized effects associated with weight loss, especially in relation to lipid peroxidation. Thirty obese subjects (17 men and 13 women) with mean age of 36±8 years and mean body mass index (BMI) of 32.0±5.3kg/m^2 were included in the study. The subjects were randomly assigned to one of two energy-restricted (-30% energy with respect to the subject's energy expenditure) dietary treatments for eight weeks: 1) LD or legume diet with four days a week non-soybean legumes (lentils, chickpeas, peas and fava beans) servings

(N=15); 2) CD or control diet group without legume consumption (N=15). The macronutrient content was designed to supply 20% energy from proteins (PRO), 50% from carbohydrates (CHO) and 30% from fat, for both diets. Compliance was assessed with three-day weighted food records. Mean caloric intake was 2,479±1,832kcal per day at baseline, and 1,462±354kcal per day at the end point (P=0.001). The diets did not have statistical differences in cholesterol content (P=0.641); fiber content in the LD diet was statistically higher than in the CD diet (25±6 vs.18±5g per day; P=0.005). Total plasma cholesterol concentrations decreased in both diets, being significantly different between both diet groups (-14.4±10.6 vs. -3.9±10.7%; P<0.001). The decrease in total cholesterol was directly correlated with body weight loss (R=0.50; P=0.006) and with increased fiber intake (R=0.44; P=0.022).

Finley et al, 2007 (positive quality), an RCT conducted in the US, assessed whether pinto bean consumption affects in vitro fecal bacterial fermentation and production of short chain fatty acids, colonic bacterial populations and serum lipids in 40 healthy adults and 40 adults with pre-metabolic syndrome matched for sex and age. After a four-week equilibration period, subjects were randomly assigned to consume a bean entree containing 1/2 cup pinto beans or an isocaloric chicken soup entree daily for 12 weeks. Of the 80 subjects that were randomized, 73 completed the trial (39 males, 34 females, aged 18 to 55 years). Beans lowered serum TC (P<0.014) by approximately 8% in the healthy adults and by 4% in the adults with pre-metabolic syndrome, and lowered serum HDL-C (P<0.05) and LDL-C (P<0.05) in both groups without affecting serum TG, VLDL cholesterol or glucose.

Pittaway et al, 2006 (positive quality), a randomized crossover trial conducted in Australia, compared the effects of a chickpea-supplemented diet and those of a wheat-supplemented diet on serum lipids and lipoproteins. Fifty-two participants enrolled in the trial, and 47 adults completed the study (mean age = 53.0±9.8 years; mean BMI=27.6±4.1kg/m^2). The chickpea diet involved daily consumption of 140g of canned, drained chickpeas, chickpea bread and chickpea shortbread biscuits provided by the study personnel. The wheat diet involved consumption of whole meal (wheat) bread, high-fiber (wheat) breakfast cereals and shortbread biscuits that participants purchased from their usual grocery store. Both interventions were at least five weeks in duration. There were no significant differences in body weight and BMI between the start and the end of each dietary period or at the end of the two intervention diets (all P>0.2). Serum lipids and lipoproteins were not significantly (NS) different at the start of the intervention diets. Protein (0.9% of energy, P=0.01) and monounsaturated fat (MUFA) (3.3% of total fat, P<0.001) intakes were slightly but significantly lower and the CHO intake significantly higher (1.7% of energy, P<0.001) on the chickpea diet as compared with the wheat diet. Serum TC was 3.9% lower (0.22mmol per L; 95% CI: 0.1, 0.35; P=0.001) and LDL-C was 4.6% lower (0.18mmol per L; 95% CI: 0.07, 0.29; P=0.002) at the completion of the chickpea diet as compared with the wheat diet. Multivariate analyses suggested that the differences in serum lipids were mainly due to small differences in polyunsaturated fatty acid (PUFA) and dietary fiber contents between the two intervention diets. Serum HDL-C and TAG levels were NS different between the two intervention diets. The authors concluded that inclusion of chickpeas in an intervention diet resulted in lower serum total and LDL-C levels as compared with a wheat-supplemented diet.

Pittaway et al, 2007 (positive-quality), a randomized crossover trial conducted in

Australia, compared the effects on serum lipids, glucose tolerance, satiety and bowel function of a diet supplemented with chickpeas to a wheat-based diet of similar fiber content, and also the impact of a lower fiber diet on bowel function and satiety. Subjects consumed the two dietary interventions for five weeks each, with a washout period of six to eight weeks between interventions; the additional low fiber diet study was followed for three weeks only. The chickpea diet was based on consuming 140g of canned, drained chickpeas daily, plus bread and shortbread biscuits made with 30% chickpea flour. The wheat diet was based on consuming whole wheat bread and high fiber breakfast cereals daily, while the lower fiber diet included white bread and lower fiber breakfast cereals. Thirty-one subjects (mean age 50.6±10.5 years) were enrolled in the trial, 27 (17 female, 10 male) completed both diet interventions and 18 (11 female, seven male) completed the lower fiber diet study. Compared to the wheat diet, the chickpea diet resulted in reductions in serum TC of 0.25mmol per L (P<0.01) and LDL-C of 0.20mmol per L (P=0.02), while there were NS differences in glucose tolerance. Some participants reported a perceived improvement in general bowel health and greater satiety during the chickpea diet.

Pittaway et al, 2008 (positive quality), an ordered crossover trial conducted in Australia, observed the effects of chickpea supplementation on ad libitum nutrient intake, body weight, serum lipids, lipoproteins and other metabolic changes. Subjects consumed normal intake for four weeks, ad libitum diet with at least 104g of chickpeas per day for 12 weeks, and normal intake for four weeks. 50 subjects (mean age 52.2±6.1 years) were enrolled and 45 (13 pre-menopausal women, 19 post-menopausal women and 13 men) completed the trial. During the chickpea phase, mean dietary fiber intake was 6.77g per day higher and mean PUFA consumption was 2.66% higher (P<0.001), causing the polyunsaturated to saturated fatty acids (SFA) ratio to change from 0.39 to 0.47 (P=0.045). Serum TC decreased by 7.7mg per dL (0.20mmol per L) and LDL-C decreased by 7.3mg per dL (0.19mmol per L) after the chickpea phase (both P<0.01). In addition, fasting insulin decreased by 0.75µIU per ml (0.19mmol per L) and the homeostasis assessment model of insulin resistance was decreased by 0.21 (both P=0.01). Dietary fiber had the greatest single effect, reducing serum TC by 15.8mg per dL (0.41mmol per L, P=0.01).

Prospective Cohort Studies

Bazzano et al, 2001 (positive quality), a prospective cohort study in the US, examined the relationship between legume consumption and risk of CHD. Participants were 9,632 subjects from the Nutrition Examination Survey Epidemiologic Follow-up Study (NHEFS), which is a prospective cohort study of NHANES I from 1971 to 1975 and aged 25 to 74 years. Dietary assessment was analyzed using a three-month food-frequency questionnaire (FFQ) with 13 major categories including legume intake. Incidence of CHD and CVD was obtained from medical records and death certificates. Over an average of 19 years of follow-up, 1,802 incident cases of CHD and 3,680 incident cases of CVD were documented. Legume consumption was significantly and inversely associated with risk of CHD (P=0.002 for trend) and CVD (P=0.02 for trend) after adjustment for established CVD risk factors. Legume consumption four times or more per week compared with less than once a week was associated with a 22% lower risk of CHD (RR=0.78; 95% CI: 0.68, 0.90) and an 11% lower risk of CVD (RR=0.89; 95% CI: 0.80, 0.98). The authors concluded that their study reported a strong and independent inverse association between dietary intake of

legumes and risk of CHD in a representative sample of the noninstitutionalized adult US population.

Steffen et al, 2005 (positive quality), a prospective cohort study conducted in the US, evaluated associations of dietary intake with the 15-year incidence of elevated blood pressure (EBP) in participants from the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Dietary intake (interviewer-administered diet history) was measured at baseline and year seven, while clinic exams were scheduled at baseline and years two, five, seven, 10 and 15. Out of 5,115 participants (aged 18 to 30 years at baseline) in the original cohort, 4,304 participants were included in the analysis (883 black men, 1,249 black women, 989 white men and 1,183 white women). Over 15 years, 23.2% of study participants experienced incident EBP (defined as incidence SBP higher than 130mmHg, DBP higher than 85mmHg, or the use of antihypertensive medications); 591 (13.7%) had HTN and 406 (9.4%) had high-normal blood pressure. Of those who developed EBP, 64% were black men and women. After adjustment for confounding variables, plant food intake (whole grains, refined grains, fruits, vegetables, nuts and legumes) was inversely related to EBP. Concerning specific plant subgroups, whole grain, fruit and nuts were inversely associated with EBP ($P \leq 0.05$), whereas no association was observed with refined grains, vegetables or legumes. Tertiles of legume intake were less than 0.1, 0.1 to 0.2 and more than 0.2 times per day. Hazard ratios for legume intake from tertiles one through three were 1.00, 0.93 (95% CI: 0.80, 1.09), and 0.88 (95% CI: 0.75, 1.03; P=0.11). Authors noted that limited consumption of legumes and insufficient statistical power precluded definitive conclusions from being drawn. It is unclear whether null findings were due to the lack of association or limited range in consumption.

Case-Control Study

Kabagambe et al, 2005 (positive quality), a case-control study conducted in Costa Rica, determined whether consumption of dried mature beans, the main legume in Latin America, is associated with MI. A total of 2,119 survivors of a first acute MI (73% male, 27% female, mean age 59±11 years) and 2,119 healthy age- , sex- and area of residence-matched controls (mean age 58±11 years) were included in the analysis. Dietary intake was assessed through FFQs. Compared with non-consumers, intake of one serving of beans per day (1/3 cup of cooked beans) was inversely associated with MI in adjusted analyses (OR=0.62; 95% CI: 0.45, 0.88). However, no additional benefit was observed with more than one serving per day (OR=0.73; 95% CI: 0.52, 1.03).

Cross-Sectional Study

Papanikolaou et al, 2008 (positive quality), a cross-sectional study in the US, evaluated the association of consuming beans on nutrient intakes and physiological parameters using data from the NHANES 1999 to 2002. A secondary analysis was completed with a reliable 24-hour dietary recall where three groups of bean consumers were identified: 1) Baked bean (BB); 2) Variety bean (VB); and 3) Variety bean or baked bean (VBBB). Adult BB consumers had lower SBP (120.4±1.4 vs. 123.3±0.4mmHg, P=0.019) in comparison to non-consumers. There were NS differences in odds ratios (OR) for most risk factors (elevated blood pressure risk, lower HDL-C, elevated LDL-C, elevated TAG and elevated fasting blood glucose) based on BB consumption. There were also NS differences in odds ratios for most risk

factors (elevated DBP, lower HDL-C, elevated LDL-C, elevated TAG, and elevated fasting blood glucose) based on VBBB consumption. However, in 20 to 40 year olds, there was a 47% reduced risk of elevated SBP (OR=0.53; 95% CI: 0.29, 0.96; P=0.037) in VBBB consumers relative to non-consumers. Considering all adults, VBBB consumers had lower SBP relative to non-consumers (121.7±1.1 vs. 123.4 ±0.4mmHg, P=0.092). In conclusion, bean consumers had better overall nutrient intake levels and lower SBP in comparison to non-consumers.

Soy Foods

Trials

Welty et al, 2007 (neutral quality), a randomized crossover trial conducted in the US, determined the effect of soy nuts on systolic and diastolic blood pressure and lipid levels in hypertensive (SBP higher than 140mmHg), pre-hypertensive (SBP 120 to 139mmHg) and normotensive (SBP lower than 120mmHg) post-menopausal women. After a four-week run-in period, women were randomized to eight weeks of a Therapeutic Lifestyle Changes (TLC) diet alone and eight weeks of a TLC diet of similar energy, fat and protein content in which 1/2 cup unsalted soy nuts (25g soy protein, 101mg aglycone isoflavones) replaced 25g of non-soy protein, with a four-week washout between diets. Sixty women were included in the trial (48 normotensive, mean age 53.5±5.3 years and 12 hypertensive, mean age 58.3±6.5 years). Compared with the TLC diet alone, the TLC diet with soy nuts lowered SBP by 9.9% (P=0.003) and DBP by 6.8% (P=0.001) in hypertensive women, 5.5% (P=0.003) and 2.7% (P=0.18) in pre-hypertensive women, and 4.5% (P=0.003) and 3.0% (P=0.06) in normotensive women. In addition, soy nut supplementation lowered LDL-C by 11% and apolipoprotein B levels by 8% (P=0.04 for both) in hypertensive women but had no effect in normotensive women. No changes in TC, HDL-C, or TG were observed in any group.

Prospective Cohort Studies

Kokubo et al, 2007 (neutral quality), a prospective cohort study conducted in Japan, identified if the risk of cerebral infarction (CI) and MI was reduced through exposure to a large quantity of isoflavones, using data from the Japan Public Health Center-Based Study Cohort I. Intake of isoflavones, soy and beans was assessed through FFQs twice during the mean follow-up period of 12.5 years. Of the original cohort of 27,063 men and 27,435 women aged 40 to 59 years at baseline, 40,462 subjects were included in the analysis. During the mean follow-up period of 12.5 years, 587 cases of CI, 308 cases of MI and 232 cases of mortality for CI and MI combined were identified. For women, the multivariate hazard ratios for those consuming soy five or more times per week compared to those consuming soy zero to two times per week was 0.64 (95% CI: 0.43, 0.95; P=0.037) for CI, 0.55 (95% CI: 0.26, 1.09, P=0.098) for MI and 0.71 (95% CI: 0.49, 1.01, P=0.065) for CI and MI combined. No significant association between intake of miso soup or beans with CI or MI was observed among women. For men, there was NS association between dietary intake of soy, miso soup or beans with CI or MI. The multivariable HR for those who consumed soy foods five or more days per week compared with zero to two days per week was 0.31 (95% CI: 0.13, 0.74; P=0.006) for ischemic CVD mortality in women, but no association was found in men. No significant associations between intake of miso soup and beans and ischemic CVD mortality were present in either men or women.

Longitudinal Study

Nagata et al, 2000 (neutral quality), a longitudinal study conducted in Japan, examined ecological correlations between soy product intake and mortality rates from several types of cancer and heart disease. Morbidity data were taken from the Special Report on Vital Statistics and Population Census of Japan in 1995 and nutrient intake data were taken from the National Nutritional Survey reports between 1980 and 1985. 6,000 randomly selected households were included in the analysis. An inverse correlation between soy product intake (as total amount) and heart disease mortality was statistically significant in women after controlling for covariates (R=-0.32, P=0.04). No significant association was observed for men.

Overview table

Author, Year, Study Design, Class, Rating	Participants	Study Methodology	Outcomes
Anderson JW et al 2002 Study Design: Meta-analysis Class: M Neutral quality	Meta-analysis of 11 international studies.	Quantitatively analyzed Δs in serum lipoprotein levels resulting from intake of non-soya pulses.	Intake of non-soya pulses was associated with ↓ in fasting serum cholesterol (-7.2%; 95% CI: -5.8 to -8.6%), LDL-C (-6.2%; 95% CI: -2.8 to -9.5%), TAG (-16.6%; 95% CI: -11.8 to -21.5%) and body weight (-0.9%; 95% CI: 2.2 to -4.1%), as well as ↑ in HDL-C (2.6%; 95% CI: 6.3 to -1.0%).
Bazzano LA, He J et al, 2001 Study Design: Prospective Cohort Study Class: B Positive quality	N=9,632. Age: 25 to 74 years. Nutrition Examination Survey Epidemiologic Follow-up Study (NHEFS), which is a prospective cohort study of NHANES I, from 1971 to 1975. Location: United States.	Legume intake assessed using three-month FFQ. Incidence of CHD and CVD obtained from medical records and death certificates.	Over an average of 19 years of follow-up, 1,802 incident cases of CHD and 3,680 incident cases of CVD were documented. Legume consumption significantly and inversely associated with risk of CHD (P=0.002 for trend) and CVD (P=0.02 for trend) after adjustment for established CVD risk factors. Legume consumption ≥four times per week compared with <once a week was associated with a 22% ↓ risk of CHD (RR=0.78; 95% CI: 0.68, 0.90) and an 11% ↓ risk of CVD (RR=0.89; 95% CI: 0.80, 0.98).

Crujeiras AB, Parra D et al, 2007 Study Design: Randomized Controlled Trial Class: A Neutral quality	N=30 obese subjects (17 men, 13 women). Mean age: 36±8 years. Mean BMI: 32.0±5.3kg/m^2. Location: Spain.	Intervention: Two energy-restricted (-30% energy with respect to subject's energy expenditure) dietary treatments for eight weeks: 1) LD diet with four days a week non-soybean legume (lentils, chickpeas, peas and faba beans) servings (N=15) 2) CD or control diet without legume consumption (N=15). Macronutrients content: 20% PRO, 50% CHO and 30% fat for both diets. Compliance assessed with three-day weighted food records.	Mean caloric intake 2,479±1,832kcal per day at baseline and 1,462±354kcal per day at end point (P=0.001). Diets did not have statistical differences in cholesterol content (P=0.641); fiber content in LD diet statistically ↑ than in CD diet (25±6 vs.18±5g per day; P=0.005). Total plasma cholesterol concentrations ↓ in both diets, being significantly different between both diet groups (-14.4±10.6 vs. -3.9±10.7%; P<0.001). ↓ in TC directly correlated with body weight ↓ (R=0.50; P=0.006) and with ↑ fiber intake (R=0.44; P=0.022).
Finley JW et al 2007 Study Design: Randomized Controlled Trial Class: A Positive quality	N=40 healthy adults and 40 adults with pre-metabolic syndrome matched for sex and age. Of the 80 subjects that were randomized, 73 completed the trial (39 males, 34 females) Age: 18 to 55 years. Location: United States.	Assessed whether pinto bean consumption affects in vitro fecal bacterial fermentation and production of short chain fatty acids, colonic bacterial populations and serum lipids. After a four-week equilibration period, subjects were randomly assigned to consume a bean entree containing 1/2 cup pinto beans or an isocaloric chicken soup entree daily for 12 weeks.	Beans ↓ serum TC (P<0.014) by ~8% in healthy adults and by 4% in adults with pre-metabolic syndrome, and ↓ serum HDL-C (P<0.05) and LDL-C (P<0.05) in both groups without affecting serum TG, VLDL-C or glucose.
Kabagambe EK et al 2005 Study Design: Case-Control Study Class: C Positive quality	N=2,119 survivors of a first acute MI (73% male, 27% female, mean age 59±11 years) and 2,119 healthy age-, sex- and area of residence-matched controls (mean age 58±11 years). Location: Costa Rica.	Determined whether consumption of dried mature beans, the main legume in Latin America, is associated with MI. Dietary intake assessed through FFQs.	Compared with non-consumers, intake of one serving of beans per day (1/3 cup of cooked beans) was inversely associated with MI in adjusted analyses (OR=0.62; 95% CI: 0.45, 0.88). However, no additional benefit observed with >one serving per day (OR=0.73, 95% CI: 0.52, 1.03).

Kokubo et al 2007 Study Design: Prospective Cohort Study Class: B Neutral quality	Participants from the Japan Public Health Center-Based Study Cohort I. Of the original cohort of 27,063 men and 27,435 women aged 40 to 59 years at baseline, 40,462 subjects were included in analysis. Location: Japan.	Identified if risk of cerebral infarction (CI) and MI was ↓ through exposure to a large quantity of isoflavones. Intake of isoflavones, soy and beans assessed through FFQs twice during mean follow-up period of 12.5 years.	During mean follow-up period of 12.5 years, 587 cases of CI, 308 cases of MI and 232 cases of mortality for CI and MI combined were identified. For women, multivariate HRs for those consuming soy ≥five times per week compared to those consuming soy zero to two times per week was 0.64 (95% CI: 0.43, 0.95; P=0.037) for CI, 0.55 (95% CI: 0.26, 1.09, P=0.098) for MI and 0.71 (95% CI: 0.49, 1.01, P=0.065) for CI and MI combined. NS association between intake of miso soup or beans with CI or MI observed among women. For men, NS association between dietary intake of soy, miso soup or beans with CI or MI. Multivariable HR for those who consumed soy foods ≥five days per week compared with zero to two days per week was 0.31 (95% CI: 0.13, 0.74; P=0.006) for ischemic CVD mortality in women, but no association found in men. NS associations between intake of miso soup and beans and ischemic CVD mortality present in either men or women.
Nagata 2000 Study Design: Longitudinal study Class: C Neutral quality	N=6,000 randomly selected households. Location: Japan.	Examined ecological correlations between soy product intake and mortality rates from several types of cancer and heart disease. Morbidity data taken from the Special Report on Vital Statistics and Population Census of Japan in 1995 and nutrient intake data taken from the National Nutritional Survey reports between 1980 and 1985.	An inverse correlation between soy product intake (as total amount) and heart disease mortality was statistically significant in women after controlling for covariates (R=-0.32, P=0.04). NS association observed for men.

Papanikolaou Y and Fulgoni VL, 2008 Study Design: Cross-Sectional Study Class: D Positive quality	N=8,229. Data from the NHANES 1999 to 2000 and NHANES 2001 to 2002. Location: United States.	Bean consumption defined by 24-hour dietary recall. Three groups of bean consumers identified: 1) Baked bean (BB) 2) Variety bean (VB) 3) Variety bean and baked bean (VBBB). Risk factors of interest: BP, LDL-C, FBG, waist size, HDL-C and BMI.	Adult BB consumers had lower SBP (120.4±1.4 vs. 123.3±0.4mmHg, P=0.019) in comparison to non-consumers. NS differences in OR for most risk factors (↑ BP risk, ↓ HDL-C, ↑ LDL-C, ↑ TAG and ↑ FBG) based on BB consumption. NS differences in OR for most risk factors (↑ DBP, ↓ HDL-C, ↑ LDL-C, ↑ TAG and ↑ FBG) based on VBBB consumption. However, in 20- to 40-year-olds, a 47% ↓ risk of ↑ SBP (OR=0.53; 95% CI: 0.29,0.96; P=0.037) in VBBB consumers relative to non-consumers. Considering all adults, VBBB consumers had ↓ SBP relative to non-consumers (121.7±1.1 vs. 123.4±0.4mmHg, P=0.092).

Pittaway et al 2006 Study Design: Randomized, crossover intervention trial Class: A Neutral quality	N=52 participants enrolled. N=47 adults completed study. Mean age: 53.0±9.8 years. Mean BMI: 27.6±4.1kg/m^2. Location: Australia.	Two periods of dietary intervention, each at least five weeks in duration: 1) a chickpea-supplemented diet and 2) a wheat-supplemented diet. Chickpea diet involved daily consumption of 140g of canned, drained chickpeas, chickpea bread, and chickpea shortbread biscuits provided by study personnel. Wheat diet involved consumption of whole meal (wheat) bread, high-fiber (wheat) breakfast cereals and shortbread biscuits that participants purchased from their usual grocery store. Measurements: Serum TC, LDL-C, HDL-C and TAG.	NS differences in body weight and BMI between the start and end of each dietary period or at end of the two intervention diets (all P>0.2). Serum lipids and lipoproteins NS different at the start of intervention diets. PRO (0.9% of energy, P=0.01) and MUFA (3.3% of total fat, P<0.001) intakes were slightly but significantly ↓ and CHO intake significantly ↑ (1.7% of energy, P<0.001) on the chickpea diet as compared with wheat diet. Serum TC was 3.9% ↓ (0.22mmol per L; 95% CI: 0.1, 0.35; P=0.001) and LDL-C was 4.6% ↓(0.18mmol per L; 95% CI: 0.07, 0.29; P=0.002) at the completion of the chickpea diet as compared with wheat diet. Multivariate analyses suggested that differences in serum lipids were mainly due to small differences in PUFA and dietary fiber contents between the two intervention diets. Serum HDL-C and TAG levels NS different between the two intervention diets.

Pittaway JK et al 2007 Study Design: Randomized Crossover Trial Class: A Positive quality	N=31 subjects (mean age 50.6±10.5 years) enrolled in the trial. N=27 (17 female, 10 male) completed both diet interventions and 18 (11 female, 7 male) completed the lower fiber diet study. Location: Australia.	Compared effects on serum lipids, glucose tolerance, satiety and bowel function of a diet supplemented with chickpeas to a wheat-based diet of similar fiber content and also impact of a lower fiber diet on bowel function and satiety. Subjects consumed two dietary interventions for five weeks each, with a washout period of six to eight weeks between interventions; the additional low fiber diet study followed for three weeks only. Chickpea diet based on consuming 140g of canned, drained chickpeas daily, plus bread and shortbread biscuits made with 30% chickpea flour. Wheat diet based on consuming whole wheat bread and ↑ fiber breakfast cereals daily, while lower fiber diet included white bread and lower fiber breakfast cereals.	Compared to wheat diet, chickpea diet resulted in ↓ in serum TC of 0.25mmol per L (P<0.01) and LDL-C of 0.20mmol per L (P=0.02), while NS differences in glucose tolerance. Some participants reported a perceived improvement in general bowel health and greater satiety during chickpea diet.
Pittaway JK et al 2008 Study Design: Ordered Crossover Trial Class: C Positive quality	N=50 subjects (mean age 52.2±6.1 years) enrolled and 45 (13 pre-menopausal women, 19 post-menopausal women and 13 men) completed the trial. Location: Australia.	Observed effects of chickpea supplementation on ad libitum nutrient intake, body weight, serum lipids, lipoproteins and other metabolic Δ. Subjects consumed normal intake for four weeks, ad libitum diet with at least 104g of chickpeas per day for 12 weeks, and normal intake for four weeks.	During the chickpea phase, mean dietary fiber intake was 6.77g per day ↑ and mean PUFA consumption was 2.66% ↑ (P<0.001), causing the PUFA to SFA ratio to Δ from 0.39 to 0.47 (P=0.045). Serum TC ↓ by 7.7mg per dL (0.20mmol per L) and LDL-C ↓ by 7.3mg per dL (0.19mmol per L) after the chickpea phase (both P<0.01). In addition, fasting insulin ↓ by 0.75μIU per ml (0.19mmol per L) and homeostasis assessment model of insulin resistance was ↓ by 0.21 (both P=0.01). Dietary fiber had the greatest single effect, ↓ serum TC by 15.8mg per dL (0.41mmol per L, P=0.01).

Steffen LM, Kroenke CH et al, 2005 Study Design: Prospective cohort study Class: B Positive quality	Participants from the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Out of 5,115 participants (aged 18 to 30 years at baseline) in the original cohort, 4,304 participants were included in analysis (883 black men, 1,249 black women, 989 white men and 1,183 white women). Location: United States.	Evaluated associations of dietary intake with 15-year incidence of elevated blood pressure (EBP). Dietary intake measured at baseline and year seven, while clinic exams were scheduled at baseline and years two, five, seven, 10 and 15. Dietary intake assessed with interviewer-administered diet history.	Over 15 years, 23.2% of study participants experienced incident EBP (defined as incidence SBP >130mmHg, DBP >85mmHg, or the use of antihypertensive medications); 591 (13.7%) had HTN and 406 (9.4%) had high-normal BP. Of those who developed EBP, 64% were black men and women. After adjustment for confounding variables, plant food intake (whole grains, refined grains, fruits, vegetables, nuts and legumes) inversely related to EBP. Concerning specific plant subgroups, whole grain, fruit and nuts inversely associated with EBP (P≤0.05), whereas no association observed with refined grains, vegetables or legumes. Tertiles of legume intake were <0.1, 0.1 to 0.2 and >0.2 times per day. HR for legume intake from tertiles one through three were 1.00, 0.93 (95% CI: 0.80, 1.09) and 0.88 (95% CI: 0.75, 1.03; P=0.11). Authors noted that limited consumption of legumes and insufficient statistical power precluded definitive conclusions from being drawn. Unclear whether null findings were due to lack of association or limited range in consumption.

Welty FK et al 2007 Study Design: Randomized Crossover Trial Class: A Neutral quality	Hypertensive (SBP>140mmHg), pre-hypertensive (SBP 120 to 139mmHg) and normotensive (SBP<120mmHg) post-menopausal women. N=60 women included in the trial: 48 normotensive, mean age 53.5±5.3 years 12 hypertensive, mean age 58.3±6.5 years. Location: United States.	Determined effect of soy nuts on SBP and DBP and lipid levels. After a four-week run-in period, women randomized to eight weeks of a TLC diet alone and eight weeks of a TLC diet of similar energy, fat and PRO content in which 1/2 cup unsalted soy nuts (25g soy PRO, 101mg aglycone isoflavones) replaced 25g of non-soyPRO, with a four-week washout between diets.	Compared with TLC diet alone, TLC diet with soy nuts ↓ SBP by 9.9% (P=0.003) and DBP by 6.8% (P=0.001) in hypertensive women, 5.5% (P=0.003) and 2.7% (P=0.18) in pre-hypertensive women, and 4.5% (P=0.003) and 3.0% (P=0.06) in normotensive women. In addition, soy nut supplementation ↓ LDL-C by 11% and apolipoprotein B levels by 8% (P=0.04 for both) in hypertensive women, but no effect in normotensive women. No Δ in TC, HDL-C, or TG observed in any group.

Search plan and results

Inclusion criteria

- January 2000 to August 2009
- Cooked dry beans and peas provided in a whole food form and analyses addressed whole food (e.g., rather than protein)
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children two to 18 years; Adults: 19 years and older
- *Populations:* Healthy and those with elevated chronic disease risk.

Exclusion criteria

- Studies that considered cooked dry beans and peas as part of a larger dietary pattern
- Cooked dry beans and peas in forms not commonly consumed
- Studies examining postprandial, short-term response
- Medical treatment/therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.)

Search terms and electronic databases used

- Pubmed: (Fabaceae[majr] OR dried beans* OR peas OR legumes) AND ("Diabetes Mellitus, Type 2"[majr] OR "metabolic syndrome X"[majr] OR "overweight"[majr] OR "hypertension"[majr] OR "dyslipidemias"[majr] OR "cardiovascular diseases"[majr] OR “heart diseases”[majr] OR “chronic disease”[majr] OR obesity[majr] OR "Body Weights and Measures"[majr] OR “body weight”[majr] OR “body composition”[majr] OR “Gastrointestinal Transit”[majr] OR “energy intake”[majr] OR “blood pressure”[majr] OR Laxation OR laxatives[mh]) AND "english and humans"[Filter]

Date searched: 08/19/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 772
- Total articles identified to review from electronic databases: 60
- Articles identified via handsearch or other means: 2
- Number of Primary Articles Identified: 14
- Number of Review Articles Identified: 13
- Total Number of Articles Identified: 17
- Number of Articles Reviewed but Excluded: 45

Included articles (References)

What is the relationship between the intake of cooked dry beans and peas and body weight?

Beans and Peas (Not Including Soy)

Systematic Reviews/Meta-analyses:

1. Anderson JW, Major AW. Pulses and lipaemia, short- and long-term effect: Potential in the prevention of cardiovascular disease. *Br J Nutr.* 2002 Dec; 88 Suppl 3: S263-S271. PMID: 12498626.
2. Williams PG, Grafenauer SJ, O'Shea JE. Cereal grains, legumes and weight management: A comprehensive review of the scientific evidence. *Nutr Rev.* 2008 Apr; 66 (4): 171-182. *Review*. PMID: 18366531.

Primary Citations:

1. CrujeirasAB, Parra D, Abete I, Martínez JA. A hypocaloric diet enriched in legumes specifically mitigates lipid peroxidation in obese subjects. *Free Radic Res*. 2007 Apr; 41 (4): 498-506. PMID: 17454132.
2. Pittaway JK, Ahuja KD, Cehun M, Chronopoulos A, Robertson IK, Nestel PJ, Ball MJ. Dietary supplementation with chickpeas for at least five weeks results in small but significant reductions in serum total and low-density lipoprotein cholesterols in adult women and men. *Ann Nutr Metab*. 2006; 50 (6): 512-518. Epub 2006 Dec 21. PMID: 17191025. (Hand search)
3. Pittaway JK, Robertson IK, Ball MJ. Chickpeas may influence fatty acid and fiber intake in an ad libitum diet, leading to small improvements in serum lipid profile and glycemic control. *J Am Diet Assoc.* 2008 Jun; 108 (6): 1, 009-1, 013. PMID: 18502235.
4. Pittaway JK, Ahuja KD, Robertson IK, Ball MJ. Effects of a controlled diet supplemented with chickpeas on serum lipids, glucose tolerance, satiety and bowel function. *J Am Coll Nutr*. 2007 Aug; 26 (4): 334-340. PMID: 17906185.

5. Papanikolaou Y, Fulgoni VL 3rd. Bean consumption is associated with greater nutrient intake, reduced systolic blood pressure, lower body weight and a smaller waist circumference in adults: Results from the National Health and Nutrition Examination Survey 1999-2002. *J Am Coll Nutr*. 2008 Oct; 27 (5): 569-576. PMID: 18845707.

Soy Foods

Systematic Reviews/Meta-analyses:

1. Cope MB, Erdman JW Jr, Allison DB. The potential role of soy foods in weight and adiposity reduction: An evidence-based review. *Obes Rev*. 2008 May; 9 (3): 219-235. Review. PMID: 18419671.

Primary Citations:

1. Maskarinec G, Aylward AG, Erber E, Takata Y, Kolonel LN. Soy intake is related to a lower body mass index in adult women. *Eur J Nutr*. 2008 Apr; 47 (3): 138-144. Epub 2008 Apr 22. PMID: 18427855; PMCID: PMC2674433.

What is the relationship between the intake of cooked dry beans and peas and cardiovascular outcomes?

Beans and Peas (Not Including Soy)

Systematic Reviews/Meta-analyses:

1. Anderson JW, Major AW. Pulses and lipaemia, short- and long-term effect: Potential in the prevention of cardiovascular disease. *Br J Nutr*. 2002 Dec; 88 Suppl 3: S, 263-S, 271. PMID: 12498626.

Primary Citations:

1. CrujeirasAB, Parra D, Abete I, Martínez JA. A hypocaloric diet enriched in legumes specifically mitigates lipid peroxidation in obese subjects. *Free Radic Res*. 2007 Apr; 41 (4): 498-506. PMID: 17454132.
2. Bazzano LA, He J, Ogden LG, Loria C, Vupputuri S, Myers L, Whelton PK. Legume consumption and risk of coronary heart disease in US men and women: NHANES I Epidemiologic Follow-up Study. *Arch Intern Med*. 2001 Nov 26; 161 (21): 2, 573-2, 578. PMID: 11718588.
3. Finley JW, Burrell JB, Reeves PG. Pinto bean consumption changes SCFA profiles in fecal fermentations, bacterial populations of the lower bowel and lipid profiles in blood of humans. *J Nutr.* 2007 Nov; 137 (11): 2, 391-2, 398. PMID: 17951475.
4. Kabagambe EK, Baylin A, Ruiz-Narvarez E, Siles X, Campos H. Decreased consumption of dried mature beans is positively associated with urbanization and nonfatal acute myocardial infarction. *J Nutr*. 2005 Jul; 135 (7): 1, 770-1, 775. PMID: 15987863.
5. Papanikolaou Y, Fulgoni VL 3rd. Bean consumption is associated with greater nutrient intake, reduced systolic blood pressure, lower body weight and a smaller waist circumference in adults: Results from the National Health and Nutrition Examination Survey 1999-2002. *J Am Coll Nutr*. 2008 Oct; 27 (5): 569-576. PMID: 18845707.
6. Pittaway JK, Ahuja KD, Cehun M, Chronopoulos A, Robertson IK, Nestel PJ, Ball MJ. Dietary supplementation with chickpeas for at least five weeks results

in small but significant reductions in serum total and low-density lipoprotein cholesterols in adult women and men. *Ann Nutr Metab.* 2006; 50 (6): 512-518. Epub 2006 Dec 21. PMID: 17191025. (Hand search)

7. Pittaway JK, Robertson IK, Ball MJ. Chickpeas may influence fatty acid and fiber intake in an ad libitum diet, leading to small improvements in serum lipid profile and glycemic control. *J Am Diet Assoc.* 2008 Jun; 108 (6): 1, 009-1, 013. PMID: 18502235.
8. Pittaway JK, Ahuja KD, Robertson IK, Ball MJ. Effects of a controlled diet supplemented with chickpeas on serum lipids, glucose tolerance, satiety and bowel function. *J Am Coll Nutr*. 2007 Aug; 26 (4): 334-340. PMID: 17906185.
9. Steffen LM, Kroenke CH, Yu X, Pereira MA, Slattery ML, Van Horn L, Gross MD, Jacobs DR Jr. Associations of plant food, dairy product, and meat intakes with 15-year incidence of elevated blood pressure in young black and white adults: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr*. 2005 Dec; 82 (6): 1, 169-1, 177; quiz 1, 363-1, 364. PMID: 16332648.

Soy Foods

Primary Citations:

1. Kokubo Y, Iso H, Ishihara J, Okada K, Inoue M, Tsugane S; JPHC Study Group. Association of dietary intake of soy, beans and isoflavones with risk of cerebral and myocardial infarctions in Japanese populations: The Japan Public Health Center-based (JPHC) study cohort I. *Circulation.* 2007 Nov 27; 116 (22): 2, 553-2, 562. Epub 2007 Nov 19. PMID: 18025534.
2. Nagata C. Ecological study of the association between soy product intake and mortality from cancer and heart disease in Japan. *Int J Epidemiol*. 2000 Oct; 29 (5): 832-836. PMID: 11034965. (Hand search)
3. Welty FK, Lee KS, Lew NS, Zhou JR. Effect of soy nuts on blood pressure and lipid levels in hypertensive, pre-hypertensive and normotensive postmenopausal women. *Arch Intern Med*. 2007 May 28; 167 (10): 1, 060-1, 067. PMID: 17533209. (Hand search)

What is the relationship between the intake of cooked dry beans and peas and type 2 diabetes?

Primary Citations:

1. Villegas R, Gao YT, Yang G, Li HL, Elasy TA, Zheng W, Shu XO. Legume and soy food intake and the incidence of type 2 diabetes in the Shanghai Women's Health Study. *Am J Clin Nutr*. 2008 Jan; 87 (1): 162-167. PMID: 18175751; PMCID: PMC2361384.

Excluded articles

Article	Reason for Exclusion
Alper CM, Mattes RD. Effects of chronic peanut consumption on energy balance and hedonics. *Int J Obes Relat Metab Disord.* 2002 Aug; 26 (8): 1, 129-1, 137. PMID: 12119580.	Does not answer question; does not examine relationship between beans and peas and health.

Anderson JW, Fuller J, Patterson K, Blair R, Tabor A. Soy compared to casein meal replacement shakes with energy-restricted diets for obese women: Randomized controlled trial. *Metabolism.* 2007 Feb; 56 (2): 280-288. PMID: 17224344.	Does not meet inclusion criteria for food form.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Hu FB, Willett WC. Soy consumption, markers of inflammation, and endothelial function: A cross-over study in postmenopausal women with the metabolic syndrome. *Diabetes Care.* 2007 Apr; 30 (4): 967-973. PMID: 17392557.	Participants diagnosed with metabolic syndrome.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Padyab M, Hu FB, Willett WC. Soy inclusion in the diet improves features of the metabolic syndrome: A randomized crossover study in postmenopausal women. *Am J Clin Nutr.* 2007 Mar; 85 (3): 735-741. PMID: 17344494.	Participants diagnosed with metabolic syndrome.
Beiseigel JM, Hunt JR, Glahn RP, Welch RM, Menkir A, Maziya-Dixon BB. Iron bioavailability from maize and beans: A comparison of human measurements with Caco-2 cell and algorithm predictions. *Am J Clin Nutr*. 2007 Aug; 86 (2): 388-396. PMID: 17684210.	Does not answer question; does not examine relationship between beans and peas and health.
Bes-Rastrollo M, Wedick NM, Martinez-Gonzalez MA, Li TY, Sampson L, Hu FB. Prospective study of nut consumption, long-term weight change and obesity risk in women. *Am J Clin Nutr.* 2009 Jun; 89 (6): 1, 913-1, 919. Epub 2009 Apr 29. PMID: 19403639; PMCID: PMC2683001.	Does not answer question; does not examine relationship between beans and peas and health.
Bourdon I, Olson B, Backus R, Richter BD, Davis PA, Schneeman BO. Beans, as a source of dietary fiber, increase cholecystokinin and apolipoprotein b48 response to test meals in men. *J Nutr*. 2001 May; 131 (5): 1, 485-1, 490. PMID: 11340104.	Examines postprandial response.
Duranti M. Grain legume proteins and nutraceutical properties. *Fitoterapia.* 2006 Feb; 77 (2): 67-82. Epub 2006 Jan 6. Review. PMID: 16406359.	Study design is narrative review.
Ejigui J, Savoie L, Marin J, Desrosiers T. Improvement of the nutritional quality of a traditional complementary porridge made of fermented yellow maize (Zea mays): Effect of maize-legume combinations and traditional processing methods. *Food Nutr Bull.* 2007 Mar; 28 (1): 23-34. PMID: 17718009.	Does not answer question; does not examine relationship between beans and peas and health.
Griel AE, Eissenstat B, Juturu V, Hsieh G, Kris-Etherton PM. Improved diet quality with peanut consumption. *J Am Coll Nutr*. 2004 Dec; 23 (6): 660-668. PMID: 15637214.	Does not answer question; does not examine relationship between beans and peas and health.
Hovey AL, Jones GP, Devereux HM, Walker KZ. Whole cereal and legume seeds increase faecal short chain fatty acids compared to ground seeds. *Asia Pac J Clin Nutr.* 2003; 12 (4): 477-482. PMID: 14672874.	Sample size less than inclusion criteria.

Jenkins DJ, Hu FB, Tapsell LC, Josse AR, Kendall CW. Possible benefit of nuts in type 2 diabetes. *J Nutr.* 2008 Sep; 138 (9): 1, 752S-1, 756S. PMID: 18716181.	Study design is narrative review.
Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. Nut and peanut butter consumption and risk of type 2 diabetes in women. *JAMA*. 2002 Nov 27; 288 (20): 2, 554-2, 560. PMID: 12444862.	Does not answer question; does not examine relationship between beans and peas and health.
Johnson SK, Chua V, Hall RS, Baxter AL. Lupin kernel fibre foods improve bowel function and beneficially modify some putative faecal risk factors for colon cancer in men. *Br J Nutr*. 2006 Feb; 95 (2): 372-378. PMID: 16469156.	Does not meet inclusion criteria for food form.
Johnson SK, Thomas SJ, Hall RS. Palatability and glucose, insulin and satiety responses of chickpea flour and extruded chickpea flour bread eaten as part of a breakfast. *Eur J Clin Nutr*. 2005 Feb; 59 (2): 169-176. PMID: 15483639.	Does not meet inclusion criteria for food form.
Kris-Etherton PM, Hu FB, Ros E, Sabaté J. The role of tree nuts and peanuts in the prevention of coronary heart disease: Multiple potential mechanisms. *J Nutr.* 2008 Sep; 138 (9): 1, 746S-1, 751S. Review. PMID: 18716180.	Study design is narrative review.
Larkin TA, Astheimer LB, Price WE. Dietary combination of soy with a probiotic or prebiotic food significantly reduces total and LDL cholesterol in mildly hypercholesterolaemic subjects. *Eur J Clin Nutr*. 2009 Feb; 63 (2): 238-245. Epub 2007 Oct 17. PMID: 17940545.	Participants were hypercholesterolemic.
Lee YP, Puddey IB, Hodgson JM. Protein, fibre and blood pressure: Potential benefit of legumes. *Clin Exp Pharmacol Physiol.* 2008 Apr; 35 (4): 473-476. Review. PMID: 18307744.	Study design is narrative review.
Li TY, Brennan AM, Wedick NM, Mantzoros C, Rifai N, Hu FB. Regular consumption of nuts is associated with a lower risk of cardiovascular disease in women with type 2 diabetes. *J Nutr*. 2009 Jul; 139 (7): 1, 333-1, 338. Epub 2009 May 6. PMID: 19420347; PMCID: PMC2696988.	Participants diagnosed with type 2 diabetes.
Lichtenstein AH, Matthan NR. The effect of soybean-based foods on plasma lipid and lipoprotein concentrations. *Am J Clin Nutr.* 2007 Oct; 86 (4): 1, 253; author reply 1, 253-1, 254. PMID: 17921413.	Publication is letter to the editor.
Lokko P, Lartey A, Armar-Klemesu M, Mattes RD. Regular peanut consumption improves plasma lipid levels in healthy Ghanaians. *Int J Food Sci Nutr*. 2007 May; 58 (3): 190-200. PMID: 17514537.	Does not answer question; does not examine relationship between beans and peas and health.
Masini E, Bani D, Marzocca C, Mateescu MA, Mannaioni PF, Federico R, Mondovì B. Pea seedling histaminase as a novel therapeutic approach to anaphylactic and inflammatory disorders. A plant histaminase in allergic asthma and ischemic shock. *ScientificWorldJournal*. 2007 Jun 12; 7: 888-902. Review. PMID: 17619775.	Does not include selected outcome in analyses.

Mattes RD, Kris-Etherton PM, Foster GD. Impact of peanuts and tree nuts on body weight and healthy weight loss in adults. *J Nutr*. 2008 Sep; 138 (9): 1, 741S-1, 745S. PMID: 18716179.	Study design is narrative review.
Nasca MM, Zhou JR, Welty FK. Effect of soy nuts on adhesion molecules and markers of inflammation in hypertensive and normotensive postmenopausal women. *Am J Cardiol.* 2008 Jul 1; 102 (1): 84-86. Epub 2008 Apr 16. PMID: 18572041.	Does not include selected outcome in analyses.
Noel SE, Newby PK, Ordovas JM, Tucker KL. A traditional rice and beans pattern is associated with metabolic syndrome in Puerto Rican older adults. *J Nutr.* 2009 Jul; 139 (7): 1, 360-1, 367. Epub 2009 May 20. PMID: 19458029; PMCID: PMC2696989.	Examines the relationship between dietary patterns, not specifically beans and peas, and health outcomes.
Nöthlings U, Schulze MB, Weikert C, Boeing H, van der Schouw YT, Bamia C, Benetou V, Lagiou P, Krogh V, Beulens JW, Peeters PH, Halkjaer J, Tjønneland A, Tumino R, Panico S, Masala G, Clavel-Chapelon F, de Lauzon B, Boutron-Ruault MC, Vercambre MN, Kaaks R, Linseisen J, Overvad K, Arriola L, Ardanaz E, Gonzalez CA, Tormo MJ, Bingham S, Khaw KT, Key TJ, Vineis P, Riboli E, Ferrari P, Boffetta P, Bueno-de-Mesquita HB, van der A DL, Berglund G, Wirfält E, Hallmans G, Johansson I, Lund E, Trichopoulo A. Intake of vegetables, legumes fruit, and risk for all-cause, cardiovascular and cancer mortality in a European diabetic population. *J Nutr*. 2008 Apr; 138 (4): 775-781. PMID: 18356334.	Participants diagnosed with diabetes.
Okamoto K, Horisawa R. Soy products and risk of an aneurysmal rupture subarachnoid hemorrhage in Japan. *Eur J Cardiovasc Prev Rehabil.* 2006 Apr; 13 (2): 284-287. PMID: 16575286.	Does not include selected outcome in analyses.
Oosthuizen W, Scholtz CS, Vorster HH, Jerling JC, Vermaak WJ. Extruded dry beans and serum lipoprotein and plasma haemostatic factors in hyperlipidaemic men. *Eur J Clin Nutr.* 2000 May; 54 (5): 373-379. PMID: 10822283.	Participants diagnosed with hyperlipidemia.
Qin LQ, Xu JY, Wang PY, Hoshi K. Soyfood intake in the prevention of breast cancer risk in women: A meta-analysis of observational epidemiological studies. *J Nutr Sci Vitaminol* (Tokyo). 2006 Dec; 52 (6): 428-436. PMID: 17330506.	Does not include selected outcome in analyses.
Ridges L, Sunderland R, Moerman K, Meyer B, Astheimer L, Howe P. Cholesterol lowering benefits of soy and linseed enriched foods. *Asia Pac J Clin Nutr*. 2001; 10 (3): 204-211. PMID: 11708310.	Participants were hypercholesterolemic.
Rivas M, Garay RP, Escanero JF, Cia P Jr, Cia P, Alda JO. Soy milk lowers blood pressure in men and women with mild to moderate essential hypertension. *J Nutr.* 2002 Jul; 132 (7): 1, 900-1, 902. PMID: 12097666.	Participants diagnosed with hypertension.
Salas-Salvadó J, Bulló M, Pérez-Heras A, Ros E. Dietary fibre, nuts and cardiovascular diseases. *Br J Nutr.* 2006 Nov; 96 Suppl 2: S46-S51. Review. Erratum in: *Br J Nutr*. 2008 Feb; 99 (2): 447-448. PMID: 17125533.	Study design is narrative review.

Schäfer G, Schenk U, Ritzel U, Ramadori G, Leonhardt U. Comparison of the effects of dried peas with those of potatoes in mixed meals on postprandial glucose and insulin concentrations in patients with type 2 diabetes. Am *J Clin Nutr.* 2003 Jul; 78 (1): 99-103. PMID: 12816777.	Participants diagnosed with type 2 diabetes.
Sirtori CR, Eberini I, Arnoldi A. Hypocholesterolaemic effects of soya proteins: Results of recent studies are predictable from the Anderson meta-analysis data. *Br J Nutr.* 2007 May; 97 (5): 816-822. Review. PMID: 17408521.	Does not meet inclusion criteria for food form.
Taku K, Umegaki K, Sato Y, Taki Y, Endoh K, Watanabe S. Soy isoflavones lower serum total and LDL cholesterol in humans: A meta-analysis of 11 randomized controlled trials. *Am J Clin Nutr*. 2007 Apr; 85 (4): 1, 148-1, 156. Erratum in: *Am J Clin Nutr.* 2007 Sep; 86 (3): 809. PMID: 17413118.	Does not meet inclusion criteria for food form.
Thorp AA, Howe PR, Mori TA, Coates AM, Buckley JD, Hodgson J, Mansour J, Meyer BJ. Soy food consumption does not lower LDL cholesterol in either equol or nonequol producers. *Am J Clin Nutr*. 2008 Aug; 88 (2): 298-304. PMID: 18689364.	Does not meet inclusion criteria for food form.
Van Horn L, Liu K, Gerber J, Garside D, Schiffer L, Gernhofer N, Greenland P. Oats and soy in lipid-lowering diets for women with hypercholesterolemia: Is there synergy? *J Am Diet Assoc*. 2001 Nov; 101 (11): 1, 319-1, 325. PMID: 11716313.	Participants diagnosed with hypercholesterolemia.
Williamson DA, Geiselman PJ, Lovejoy J, Greenway F, Volaufova J, Martin CK, Arnett C, Ortego L. Effects of consuming mycoprotein, tofu or chicken upon subsequent eating behavior, hunger and safety. *Appetite*. 2006 Jan; 46 (1): 41-48. Epub 2005 Dec 20. PMID: 16364496.	Does not include selected outcome in analyses.
Winham DM, Hutchins AM, Johnston CS. Pinto bean consumption reduces biomarkers for heart disease risk. *J Am Coll Nutr*. 2007 Jun; 26 (3): 243-249. PMID: 17634169.	Dropout rate higher than inclusion criteria.
Wylie-Rosett J, Segal-Isaacson CJ, Segal-Isaacson A. Carbohydrates and increases in obesity: Does the type of carbohydrate make a difference? *Obes Res*. 2004 Nov; 12 Suppl 2: 124S-129S. Review. PMID: 15601960.	Study design is narrative review.
Xu BJ, Yuan SH, Chang SK. Comparative studies on the antioxidant activities of nine common food legumes against copper-induced human low-density lipoprotein oxidation in vitro. *J Food Sci.* 2007 Sep; 72 (7): S522-S527. PMID: 17995667.	Does not answer question; does not examine relationship between beans and peas and health .
Yan L, Spitznagel EL. Soy consumption and prostate cancer risk in men: A revisit of a meta-analysis. *Am J Clin Nutr.* 2009 Apr; 89 (4): 1, 155-1, 163. Epub 2009 Feb 11. PMID: 19211820.	Does not include selected outcome in analyses.

Yang G, Shu XO, Jin F, Zhang X, Li HL, Li Q, Gao YT, Zheng W. Longitudinal study of soy food intake and blood pressure among middle-aged and elderly Chinese women. *Am J Clin Nutr.* 2005 May; 81 (5): 1, 012-1, 017. PMID: 15883423.	Does not meet inclusion criteria for food form.
Yeh CC, You SL, Chen CJ, Sung FC. Peanut consumption and reduced risk of colorectal cancer in women: A prospective study in Taiwan. *World J Gastroenterol*. 2006 Jan 14; 12 (2): 222-227. PMID: 16482621.	Does not include selected outcome in analyses.
Zhang X, Shu XO, Gao YT, Yang G, Li Q, Li H, Jin F, Zheng W. Soy food consumption is associated with lower risk of coronary heart disease in Chinese women. *J Nutr.* 2003 Sep; 133 (9): 2, 874-2, 878. PMID: 12949380.	Soy protein included in analyses.

CHAPTER 11. COOKED DRY BEANS AND PEAS – TYPE 2 DIABETES

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF COOKED DRY BEANS AND PEAS AND TYPE 2 DIABETES?

Conclusion statement

Limited evidence is available to determine a relationship between the intake of cooked dry beans and peas and type 2 diabetes.

Grade

Limited

Evidence summary overview

Only one study was found that measured the relationship between dry beans and peas and type 2 diabetes (T2D). The association between the consumption of legume and soy foods and T2D was examined over an average follow-up of approximately five years in the Shanghai Women's Health Study (Villegas, 2005). Average daily intake of individual food items was combined for the following food groups: Total legumes and three mutually exclusive groups [soybeans (dried and fresh), peanuts and other legumes]. The median intake of total legumes was 30.5g per day, for soybeans was 11.0g per day, for peanuts was 0.7g per day, and for other legumes was 15.5g per day. Total legume consumption and consumption of soybeans and other legumes were each associated with a decrease in risk of T2D.

Evidence summary paragraphs

Villegas et al, 2005 (positive quality), a prospective cohort study (Shanghai Women's Health Study) conducted in China, examined the association between legume and soy food consumption and self-reported T2D. Participants were 64,191 women aged 40-70 years. Dietary intake was assessed by validated food-frequency questionnaire (FFQ). Mean follow-up was 4.6 years. Average daily intake of individual food items (grams per day) was combined to compute the following food groups: Total legumes and three mutually exclusive groups [soybeans (dried and fresh), peanuts and other legumes]; soy milk and "other soy products" were analyzed separately. The median intake of total legumes was 30.5g per day, for soybeans was 11.0g per day, for peanuts was 0.7g per day and for other legumes was 15.5g per day. Total legume consumption and consumption of soybeans and other legumes were each associated with a decrease in risk of T2D:

All legumes relative risk (RR) between extreme quintiles=0.62; 95% CI: 0.51, 0.74; P for trend<0.0001

Soybeans RR between extreme quintiles=0.53; 95% CI: 0.45, 0.62; P for trend<0.0001

Other legumes (not including peanuts) RR between extreme quintiles=0.76; 95% CI: 0.64, 0.90; P for trend<0.0001

Soy milk RR between high and no intake=0.61; 95% CI: 0.54, 0.70; P for trend<0.0001.

There was no significant (NS) association between consumption of other soy products

or total soy protein and the risk of T2D. The authors concluded that consumption of legumes was inversely associated with the risk of T2D in this population.

Overview table

Author, Year, Study Design, Class, Rating	Participants	Study Methodology	Outcomes
Villegas R, Gao YT et al, 2008 Study Design: Prospective Cohort Study Class: B Positive quality	N=64,191 women. Age at baseline: 40-70 years. Shanghai Women's Health Study.	Dietary intake assessed by validated FFQ. Average daily intake of individual food items (g per day) was combined to compute the following food groups: Total legumes Three mutually exclusive groups [soybeans (dried and fresh), peanuts and other legumes]. Soy milk and "other soy products" were analyzed separately. T2D was self-reported.	Mean follow-up was 4.6 years. The median intake of total legumes (per day) was 30.5g; for soybeans 11.0g; for peanuts 0.7g and for other legumes 15.5g. Total legume consumption and consumption of soybeans and other legumes were each associated with a ↓ in risk of T2D (RR between extreme quintiles): All legumes=0.62; 95% CI: 0.51, 0.74; P for trend<0.0001 Soybeans=0.53; 95% CI: 0.45, 0.62; P for trend<0.0001 Other legumes (not including peanuts)=0.76; 95% CI: 0.64, 0.90; P for trend<0.0001. Soy milk RR between high and no intake=0.61; 95% CI: 0.54, 0.70; P for trend<0.0001. NS association between consumption of other soy products or total soy protein and the risk of T2D.

Search plan and results

Inclusion criteria

- January 2000 to August 2009
- Cooked dry beans and peas provided in a whole food form and analyses addressed whole food (e.g., rather than protein)
- Human subjects
- English language
- International

- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children two to 18 years; Adults: 19 years and older
- *Populations:* Healthy and those with elevated chronic disease risk.

Exclusion criteria

- Studies that considered cooked dry beans and peas as part of a larger dietary pattern
- Cooked dry beans and peas in forms not commonly consumed
- Studies examining postprandial, short-term response
- Medical treatment/therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.)

Search terms and electronic databases used

- Pubmed: (Fabaceae[majr] OR dried beans* OR peas OR legumes) AND ("Diabetes Mellitus, Type 2"[majr] OR "metabolic syndrome X"[majr] OR "overweight"[majr] OR "hypertension"[majr] OR "dyslipidemias"[majr] OR "cardiovascular diseases"[majr] OR “heart diseases”[majr] OR “chronic disease”[majr] OR obesity[majr] OR "Body Weights and Measures"[majr] OR “body weight”[majr] OR “body composition”[majr] OR “Gastrointestinal Transit”[majr] OR “energy intake”[majr] OR “blood pressure”[majr] OR Laxation OR laxatives[mh]) AND "english and humans"[Filter]

Date searched: 08/19/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 772
- Total articles identified to review from electronic databases: 60
- Articles identified via handsearch or other means: 2
- Number of Primary Articles Identified: 14
- Number of Review Articles Identified: 13
- Total Number of Articles Identified: 17
- Number of Articles Reviewed but Excluded: 45

Included articles (References)

What is the relationship between the intake of cooked dry beans and peas and body weight?

Beans and Peas (Not Including Soy)

Systematic Reviews/Meta-analyses:

1. Anderson JW, Major AW. Pulses and lipaemia, short- and long-term effect:

Potential in the prevention of cardiovascular disease. *Br J Nutr.* 2002 Dec; 88 Suppl 3: S263-S271. PMID: 12498626.
2. Williams PG, Grafenauer SJ, O'Shea JE. Cereal grains, legumes and weight management: A comprehensive review of the scientific evidence. *Nutr Rev.* 2008 Apr; 66 (4): 171-182. *Review*. PMID: 18366531.

Primary Citations:

1. CrujeirasAB, Parra D, Abete I, Martínez JA. A hypocaloric diet enriched in legumes specifically mitigates lipid peroxidation in obese subjects. *Free Radic Res*. 2007 Apr; 41 (4): 498-506. PMID: 17454132.
2. Pittaway JK, Ahuja KD, Cehun M, Chronopoulos A, Robertson IK, Nestel PJ, Ball MJ. Dietary supplementation with chickpeas for at least five weeks results in small but significant reductions in serum total and low-density lipoprotein cholesterols in adult women and men. *Ann Nutr Metab*. 2006; 50 (6): 512-518. Epub 2006 Dec 21. PMID: 17191025. (Hand search)
3. Pittaway JK, Robertson IK, Ball MJ. Chickpeas may influence fatty acid and fiber intake in an ad libitum diet, leading to small improvements in serum lipid profile and glycemic control. *J Am Diet Assoc.* 2008 Jun; 108 (6): 1, 009-1, 013. PMID: 18502235.
4. Pittaway JK, Ahuja KD, Robertson IK, Ball MJ. Effects of a controlled diet supplemented with chickpeas on serum lipids, glucose tolerance, satiety and bowel function. *J Am Coll Nutr*. 2007 Aug; 26 (4): 334-340. PMID: 17906185.
5. Papanikolaou Y, Fulgoni VL 3rd. Bean consumption is associated with greater nutrient intake, reduced systolic blood pressure, lower body weight and a smaller waist circumference in adults: Results from the National Health and Nutrition Examination Survey 1999-2002. *J Am Coll Nutr*. 2008 Oct; 27 (5): 569-576. PMID: 18845707.

Soy Foods

Systematic Reviews/Meta-analyses:

1. Cope MB, Erdman JW Jr, Allison DB. The potential role of soy foods in weight and adiposity reduction: An evidence-based review. *Obes Rev*. 2008 May; 9 (3): 219-235. Review. PMID: 18419671.

Primary Citations:

1. Maskarinec G, Aylward AG, Erber E, Takata Y, Kolonel LN. Soy intake is related to a lower body mass index in adult women. *Eur J Nutr*. 2008 Apr; 47 (3): 138-144. Epub 2008 Apr 22. PMID: 18427855; PMCID: PMC2674433.

What is the relationship between the intake of cooked dry beans and peas and cardiovascular outcomes?

Beans and Peas (Not Including Soy)

Systematic Reviews/Meta-analyses:

1. Anderson JW, Major AW. Pulses and lipaemia, short- and long-term effect: Potential in the prevention of cardiovascular disease. *Br J Nutr*. 2002 Dec; 88 Suppl 3: S, 263-S, 271. PMID: 12498626.

Primary Citations:

1. CrujeirasAB, Parra D, Abete I, Martínez JA. A hypocaloric diet enriched in legumes specifically mitigates lipid peroxidation in obese subjects. *Free Radic Res*. 2007 Apr; 41 (4): 498-506. PMID: 17454132.
2. Bazzano LA, He J, Ogden LG, Loria C, Vupputuri S, Myers L, Whelton PK. Legume consumption and risk of coronary heart disease in US men and women: NHANES I Epidemiologic Follow-up Study. *Arch Intern Med*. 2001 Nov 26; 161 (21): 2, 573-2, 578. PMID: 11718588.
3. Finley JW, Burrell JB, Reeves PG. Pinto bean consumption changes SCFA profiles in fecal fermentations, bacterial populations of the lower bowel and lipid profiles in blood of humans. *J Nutr.* 2007 Nov; 137 (11): 2, 391-2, 398. PMID: 17951475.
4. Kabagambe EK, Baylin A, Ruiz-Narvarez E, Siles X, Campos H. Decreased consumption of dried mature beans is positively associated with urbanization and nonfatal acute myocardial infarction. *J Nutr*. 2005 Jul; 135 (7): 1, 770-1, 775. PMID: 15987863.
5. Papanikolaou Y, Fulgoni VL 3rd. Bean consumption is associated with greater nutrient intake, reduced systolic blood pressure, lower body weight and a smaller waist circumference in adults: Results from the National Health and Nutrition Examination Survey 1999-2002. *J Am Coll Nutr*. 2008 Oct; 27 (5): 569-576. PMID: 18845707.
6. Pittaway JK, Ahuja KD, Cehun M, Chronopoulos A, Robertson IK, Nestel PJ, Ball MJ. Dietary supplementation with chickpeas for at least five weeks results in small but significant reductions in serum total and low-density lipoprotein cholesterols in adult women and men. *Ann Nutr Metab.* 2006; 50 (6): 512-518. Epub 2006 Dec 21. PMID: 17191025. (Hand search)
7. Pittaway JK, Robertson IK, Ball MJ. Chickpeas may influence fatty acid and fiber intake in an ad libitum diet, leading to small improvements in serum lipid profile and glycemic control. *J Am Diet Assoc.* 2008 Jun; 108 (6): 1, 009-1, 013. PMID: 18502235.
8. Pittaway JK, Ahuja KD, Robertson IK, Ball MJ. Effects of a controlled diet supplemented with chickpeas on serum lipids, glucose tolerance, satiety and bowel function. *J Am Coll Nutr*. 2007 Aug; 26 (4): 334-340. PMID: 17906185.
9. Steffen LM, Kroenke CH, Yu X, Pereira MA, Slattery ML, Van Horn L, Gross MD, Jacobs DR Jr. Associations of plant food, dairy product, and meat intakes with 15-year incidence of elevated blood pressure in young black and white adults: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr*. 2005 Dec; 82 (6): 1, 169-1, 177; quiz 1, 363-1, 364. PMID: 16332648.

Soy Foods

Primary Citations:

1. Kokubo Y, Iso H, Ishihara J, Okada K, Inoue M, Tsugane S; JPHC Study Group. Association of dietary intake of soy, beans and isoflavones with risk of cerebral and myocardial infarctions in Japanese populations: The Japan Public Health Center-based (JPHC) study cohort I. *Circulation.* 2007 Nov 27; 116 (22): 2, 553-2, 562. Epub 2007 Nov 19. PMID: 18025534.
2. Nagata C. Ecological study of the association between soy product intake and mortality from cancer and heart disease in Japan. *Int J Epidemiol*. 2000 Oct; 29

(5): 832-836. PMID: 11034965. (Hand search)

3. Welty FK, Lee KS, Lew NS, Zhou JR. Effect of soy nuts on blood pressure and lipid levels in hypertensive, pre-hypertensive and normotensive postmenopausal women. *Arch Intern Med*. 2007 May 28; 167 (10): 1, 060-1, 067. PMID: 17533209. (Hand search)

What is the relationship between the intake of cooked dry beans and peas and type 2 diabetes?

Primary Citations:

1. Villegas R, Gao YT, Yang G, Li HL, Elasy TA, Zheng W, Shu XO. Legume and soy food intake and the incidence of type 2 diabetes in the Shanghai Women's Health Study. *Am J Clin Nutr*. 2008 Jan; 87 (1): 162-167. PMID: 18175751; PMCID: PMC2361384.

Excluded articles

Article	Reason for Exclusion
Alper CM, Mattes RD. Effects of chronic peanut consumption on energy balance and hedonics. *Int J Obes Relat Metab Disord.* 2002 Aug; 26 (8): 1, 129-1, 137. PMID: 12119580.	Does not answer question; does not examine relationship between beans and peas and health.
Anderson JW, Fuller J, Patterson K, Blair R, Tabor A. Soy compared to casein meal replacement shakes with energy-restricted diets for obese women: Randomized controlled trial. *Metabolism.* 2007 Feb; 56 (2): 280-288. PMID: 17224344.	Does not meet inclusion criteria for food form.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Hu FB, Willett WC. Soy consumption, markers of inflammation, and endothelial function: A cross-over study in postmenopausal women with the metabolic syndrome. *Diabetes Care.* 2007 Apr; 30 (4): 967-973. PMID: 17392557.	Participants diagnosed with metabolic syndrome.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Padyab M, Hu FB, Willett WC. Soy inclusion in the diet improves features of the metabolic syndrome: A randomized crossover study in postmenopausal women. *Am J Clin Nutr.* 2007 Mar; 85 (3): 735-741. PMID: 17344494.	Participants diagnosed with metabolic syndrome.
Beiseigel JM, Hunt JR, Glahn RP, Welch RM, Menkir A, Maziya-Dixon BB. Iron bioavailability from maize and beans: A comparison of human measurements with Caco-2 cell and algorithm predictions. *Am J Clin Nutr*. 2007 Aug; 86 (2): 388-396. PMID: 17684210.	Does not answer question; does not examine relationship between beans and peas and health.
Bes-Rastrollo M, Wedick NM, Martinez-Gonzalez MA, Li TY, Sampson L, Hu FB. Prospective study of nut consumption, long-term weight change and obesity risk in women. *Am J Clin Nutr.* 2009 Jun; 89 (6): 1, 913-1, 919. Epub 2009 Apr 29. PMID: 19403639; PMCID: PMC2683001.	Does not answer question; does not examine relationship between beans and peas and health.

Bourdon I, Olson B, Backus R, Richter BD, Davis PA, Schneeman BO. Beans, as a source of dietary fiber, increase cholecystokinin and apolipoprotein b48 response to test meals in men. *J Nutr*. 2001 May; 131 (5): 1, 485-1, 490. PMID: 11340104.	Examines postprandial response.
Duranti M. Grain legume proteins and nutraceutical properties. *Fitoterapia.* 2006 Feb; 77 (2): 67-82. Epub 2006 Jan 6. Review. PMID: 16406359.	Study design is narrative review.
Ejigui J, Savoie L, Marin J, Desrosiers T. Improvement of the nutritional quality of a traditional complementary porridge made of fermented yellow maize (Zea mays): Effect of maize-legume combinations and traditional processing methods. *Food Nutr Bull.* 2007 Mar; 28 (1): 23-34. PMID: 17718009.	Does not answer question; does not examine relationship between beans and peas and health.
Griel AE, Eissenstat B, Juturu V, Hsieh G, Kris-Etherton PM. Improved diet quality with peanut consumption. *J Am Coll Nutr*. 2004 Dec; 23 (6): 660-668. PMID: 15637214.	Does not answer question; does not examine relationship between beans and peas and health.
Hovey AL, Jones GP, Devereux HM, Walker KZ. Whole cereal and legume seeds increase faecal short chain fatty acids compared to ground seeds. *Asia Pac J Clin Nutr.* 2003; 12 (4): 477-482. PMID: 14672874.	Sample size less than inclusion criteria.
Jenkins DJ, Hu FB, Tapsell LC, Josse AR, Kendall CW. Possible benefit of nuts in type 2 diabetes. *J Nutr.* 2008 Sep; 138 (9): 1, 752S-1, 756S. PMID: 18716181.	Study design is narrative review.
Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. Nut and peanut butter consumption and risk of type 2 diabetes in women. *JAMA*. 2002 Nov 27; 288 (20): 2, 554-2, 560. PMID: 12444862.	Does not answer question; does not examine relationship between beans and peas and health.
Johnson SK, Chua V, Hall RS, Baxter AL. Lupin kernel fibre foods improve bowel function and beneficially modify some putative faecal risk factors for colon cancer in men. *Br J Nutr*. 2006 Feb; 95 (2): 372-378. PMID: 16469156.	Does not meet inclusion criteria for food form.
Johnson SK, Thomas SJ, Hall RS. Palatability and glucose, insulin and satiety responses of chickpea flour and extruded chickpea flour bread eaten as part of a breakfast. *Eur J Clin Nutr*. 2005 Feb; 59 (2): 169-176. PMID: 15483639.	Does not meet inclusion criteria for food form.
Kris-Etherton PM, Hu FB, Ros E, Sabaté J. The role of tree nuts and peanuts in the prevention of coronary heart disease: Multiple potential mechanisms. *J Nutr.* 2008 Sep; 138 (9): 1, 746S-1, 751S. Review. PMID: 18716180.	Study design is narrative review.
Larkin TA, Astheimer LB, Price WE. Dietary combination of soy with a probiotic or prebiotic food significantly reduces total and LDL cholesterol in mildly hypercholesterolaemic subjects. *Eur J Clin Nutr*. 2009 Feb; 63 (2): 238-245. Epub 2007 Oct 17. PMID: 17940545.	Participants were hypercholesterolemic.

Lee YP, Puddey IB, Hodgson JM. Protein, fibre and blood pressure: Potential benefit of legumes. *Clin Exp Pharmacol Physiol.* 2008 Apr; 35 (4): 473-476. Review. PMID: 18307744.	Study design is narrative review.
Li TY, Brennan AM, Wedick NM, Mantzoros C, Rifai N, Hu FB. Regular consumption of nuts is associated with a lower risk of cardiovascular disease in women with type 2 diabetes. *J Nutr*. 2009 Jul; 139 (7): 1, 333-1, 338. Epub 2009 May 6. PMID: 19420347; PMCID: PMC2696988.	Participants diagnosed with type 2 diabetes.
Lichtenstein AH, Matthan NR. The effect of soybean-based foods on plasma lipid and lipoprotein concentrations. *Am J Clin Nutr.* 2007 Oct; 86 (4): 1, 253; author reply 1, 253-1, 254. PMID: 17921413.	Publication is letter to the editor.
Lokko P, Lartey A, Armar-Klemesu M, Mattes RD. Regular peanut consumption improves plasma lipid levels in healthy Ghanaians. *Int J Food Sci Nutr*. 2007 May; 58 (3): 190-200. PMID: 17514537.	Does not answer question; does not examine relationship between beans and peas and health.
Masini E, Bani D, Marzocca C, Mateescu MA, Mannaioni PF, Federico R, Mondovì B. Pea seedling histaminase as a novel therapeutic approach to anaphylactic and inflammatory disorders. A plant histaminase in allergic asthma and ischemic shock. *ScientificWorldJournal*. 2007 Jun 12; 7: 888-902. Review. PMID: 17619775.	Does not include selected outcome in analyses.
Mattes RD, Kris-Etherton PM, Foster GD. Impact of peanuts and tree nuts on body weight and healthy weight loss in adults. *J Nutr*. 2008 Sep; 138 (9): 1, 741S-1, 745S. PMID: 18716179.	Study design is narrative review.
Nasca MM, Zhou JR, Welty FK. Effect of soy nuts on adhesion molecules and markers of inflammation in hypertensive and normotensive postmenopausal women. *Am J Cardiol.* 2008 Jul 1; 102 (1): 84-86. Epub 2008 Apr 16. PMID: 18572041.	Does not include selected outcome in analyses.
Noel SE, Newby PK, Ordovas JM, Tucker KL. A traditional rice and beans pattern is associated with metabolic syndrome in Puerto Rican older adults. *J Nutr.* 2009 Jul; 139 (7): 1, 360-1, 367. Epub 2009 May 20. PMID: 19458029; PMCID: PMC2696989.	Examines the relationship between dietary patterns, not specifically beans and peas, and health outcomes.
Nöthlings U, Schulze MB, Weikert C, Boeing H, van der Schouw YT, Bamia C, Benetou V, Lagiou P, Krogh V, Beulens JW, Peeters PH, Halkjaer J, Tjønneland A, Tumino R, Panico S, Masala G, Clavel-Chapelon F, de Lauzon B, Boutron-Ruault MC, Vercambre MN, Kaaks R, Linseisen J, Overvad K, Arriola L, Ardanaz E, Gonzalez CA, Tormo MJ, Bingham S, Khaw KT, Key TJ, Vineis P, Riboli E, Ferrari P, Boffetta P, Bueno-de-Mesquita HB, van der A DL, Berglund G, Wirfält E, Hallmans G, Johansson I, Lund E, Trichopoulo A. Intake of vegetables, legumes fruit, and risk for all-cause, cardiovascular and cancer mortality in a European diabetic population. *J Nutr*. 2008 Apr; 138 (4): 775-781. PMID: 18356334.	Participants diagnosed with diabetes .

Okamoto K, Horisawa R. Soy products and risk of an aneurysmal rupture subarachnoid hemorrhage in Japan. *Eur J Cardiovasc Prev Rehabil.* 2006 Apr; 13 (2): 284-287. PMID: 16575286.	Does not include selected outcome in analyses.
Oosthuizen W, Scholtz CS, Vorster HH, Jerling JC, Vermaak WJ. Extruded dry beans and serum lipoprotein and plasma haemostatic factors in hyperlipidaemic men. *Eur J Clin Nutr.* 2000 May; 54 (5): 373-379. PMID: 10822283.	Participants diagnosed with hyperlipidemia.
Qin LQ, Xu JY, Wang PY, Hoshi K. Soyfood intake in the prevention of breast cancer risk in women: A meta-analysis of observational epidemiological studies. *J Nutr Sci Vitaminol* (Tokyo). 2006 Dec; 52 (6): 428-436. PMID: 17330506.	Does not include selected outcome in analyses.
Ridges L, Sunderland R, Moerman K, Meyer B, Astheimer L, Howe P. Cholesterol lowering benefits of soy and linseed enriched foods. *Asia Pac J Clin Nutr*. 2001; 10 (3): 204-211. PMID: 11708310.	Participants were hypercholesterolemic.
Rivas M, Garay RP, Escanero JF, Cia P Jr, Cia P, Alda JO. Soy milk lowers blood pressure in men and women with mild to moderate essential hypertension. *J Nutr.* 2002 Jul; 132 (7): 1, 900-1, 902. PMID: 12097666.	Participants diagnosed with hypertension.
Salas-Salvadó J, Bulló M, Pérez-Heras A, Ros E. Dietary fibre, nuts and cardiovascular diseases. *Br J Nutr.* 2006 Nov; 96 Suppl 2: S46-S51. Review. Erratum in: *Br J Nutr*. 2008 Feb; 99 (2): 447-448. PMID: 17125533.	Study design is narrative review.
Schäfer G, Schenk U, Ritzel U, Ramadori G, Leonhardt U. Comparison of the effects of dried peas with those of potatoes in mixed meals on postprandial glucose and insulin concentrations in patients with type 2 diabetes. Am *J Clin Nutr.* 2003 Jul; 78 (1): 99-103. PMID: 12816777.	Participants diagnosed with type 2 diabetes.
Sirtori CR, Eberini I, Arnoldi A. Hypocholesterolaemic effects of soya proteins: Results of recent studies are predictable from the Anderson meta-analysis data. *Br J Nutr.* 2007 May; 97 (5): 816-822. Review. PMID: 17408521.	Does not meet inclusion criteria for food form.
Taku K, Umegaki K, Sato Y, Taki Y, Endoh K, Watanabe S. Soy isoflavones lower serum total and LDL cholesterol in humans: A meta-analysis of 11 randomized controlled trials. *Am J Clin Nutr*. 2007 Apr; 85 (4): 1, 148-1, 156. Erratum in: *Am J Clin Nutr.* 2007 Sep; 86 (3): 809. PMID: 17413118.	Does not meet inclusion criteria for food form.
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CHAPTER 12. DIETARY PROTEIN PATTERNS – VEGETARIAN DIET

HOW DO THE HEALTH OUTCOMES OF A VEGETARIAN DIET COMPARE TO THAT OF A DIET WHICH CUSTOMARILY INCLUDES ANIMAL PRODUCTS?

Conclusion statement

Limited evidence is available documenting that vegetarian diets protect against cancer. However, it suggests that vegetarian, including vegan diets, are associated with lower body mass index and blood pressure. Vegan diets may increase risk of osteoporotic fractures.

Grade

Limited

Evidence summary overview

Eighteen studies published since 2000 were reviewed that represented eight countries (Alewaeters, 2005; Appleby, 2002; Appleby, 2007; Baines, 2007; Chen, 2008; Dos Santos Silva, 2002; Grant, 2008; Hung, 2006; Key, 2009a; Key, 2009b; Newby, 2005; Nakamoto, 2008; Rosell, 2006; Spencer, 2003; Teixeira, 2007; Thorpe, 2008; Wang, 2008d; Yen, 2008). Most studies in this review were of a weaker design, including cross-sectional and case-control studies. Only five articles were prospective cohort studies and no randomized controlled trials (RCTs) were identified. Six articles provided results from the EPIC study from the United Kingdom and four studies were conducted in Taiwan. Other countries represented were the US, Australia, Japan, Sweden, Belgium and Brazil. Vegetarian diets varied greatly among countries and classifications of plant-based diets were inconsistent among studies. However, all studies compared the health outcomes observed between individuals who regularly consumed animal products to those who occasionally, rarely or never consumed animal products.

In the EPIC cohort, vegetarian, particularly vegan, diets were associated with lower body mass index (BMI) and lower levels of obesity than diets that included meat (Spencer, 2003). Similar results were found in the Swedish Mammography Cohort (Newby, 2005). Rosell et al, (2006) reported on five-year changes in weight in the EPIC cohort by dividing participants into groups based on their eating patterns. Specifically, they examined whether participants maintained the same diet (e.g., vegan) over time, or reverted from a vegan or vegetarian diet to a diet containing meat, or converted from eating meat to a vegetarian or vegan diet. Among those who had not changed their eating patterns over time, the largest weight gain was seen in meat-eaters. The smallest weight gain was observed in participants who converted to a vegetarian or vegan diet, and the highest weight gains were among participants classified as reverted, but mean weight gains were not different than weight gains in meat eaters.

Meat eaters had the highest prevalence of hypertension (HTN) and vegans the lowest in the EPIC cohort (Appleby, 2002), and vegetarians had lower blood pressure (BP) than omnivores in small studies in Taiwan (Chen, 2008) and Brazil (Teixeira, 2007). Studies from Taiwan and Brazil also showed improvement in cardiovascular

biomarkers, such as total cholesterol (TC), between individuals consuming vegetarian compared to omnivorous diets (Chen, 2008; Teixeira, 2007; Yen, 2008).

Vegans were found to have a higher risk of fractures than vegetarians and meat eaters in the EPIC cohort, which was related to the lower mean calcium intake in this group (Appleby, 2007). However, those on a vegetarian diet in Taiwan did not differ from non-vegetarians in bone mineral density (BMD) or risk of osteoporosis (Wang, 2008d). In a review of women from the Adventist Health Study (Thorpe, 2008), greater intake of foods rich in protein, whether from animal or plant sources, was associated with reduced wrist fractures.

Data on cancer are inconsistent with one recent study finding more colorectal cancer in vegetarians compared to meat eaters (Key, 2009a). However, the risk of female breast, prostate, ovarian and lung cancer were not significantly (NS) different between vegetarians and non-vegetarians.

Overall, Key and colleagues (2009b) found no differences in mortality rates between vegetarians and non-vegetarians in the EPIC cohort.

Evidence summary paragraphs

United Kingdom (Oxford cohort of the European Prospective Investigation into Cancer and Nutrition)

Appleby et al, 2002 (neutral quality). This cross-sectional study was designed to compare the prevalence of HTN and mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) among 11,004 participants (2,351 men, 8,653 women) from the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford). At baseline, all participants completed a detailed lifestyle questionnaire, including a semi-quantitative food frequency questionnaire (FFQ). Blood pressure was measured at their general practice. No standard method of BP measurement was specified and only single measurements were taken. Age at BP measurement ranged from 20 to 78 years (median=48 years in men and 46 years in women). Participants were 4,737 meat eaters, 1,728 fish eaters, 3,800 vegetarians and 739 vegans. Meat eaters had the highest mean energy intake, and consumed more protein, fat and saturated fat and less carbohydrate and polyunsaturated fat, than the other diet groups. Vegans consumed less saturated fat and calcium, had a higher P/S ratio compared with the other diet groups, and also had the lowest intakes of sodium from food. Meat eaters were the most likely and vegans the least likely, to use salt in cooking and at the table. There were significant differences in the age-adjusted prevalence of self-reported HTN among meat eaters, fish eaters, vegetarians and vegans for both men and women. Meat eaters had the highest and vegans the lowest prevalence of HTN, with fish eaters and vegetarians taking intermediate values. Among participants with no self-reported HTN, there were statistically significant variations in age-adjusted mean SBP and DBP between the four diet groups for both men and women, with meat eaters having the highest values and vegans the lowest values. The differences in age-adjusted mean BP between meat eaters and vegans among participants with no self-reported HTN were 4.2 and 2.6mmHg SBP and 2.8 and 1.7mmHg DBP for men and women, respectively. About half of the variation in BP was attributable to differences in body mass index (BMI), with non-dietary and macronutrient factors also accounting for some of the variation.

Spencer et al, 2003 (neutral quality). This cross-sectional study was designed to assess differences in BMI among participants from the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford). Participants were 57,498 men and women recruited between 1993 and 1999. Participants completed a validated semi-quantitative FFQ and provided self-reported height and weight. After applying exclusions due to ineligibility, recording error, missing or extreme values, and history of health conditions, 37,875 participants (8,871 men and 29,004 women) were included in analyses. Participants were primarily white adults between 20 and 97 years. Using answers from four questions, participants were divided into four diet groups: Meat eaters (eat meat), fish eaters (eat fish but not meat), vegetarians (do not eat meat or fish but do eat milk products or eggs) and vegans (eat no animal products). Meat-eaters had the highest intakes of energy, protein, total fat, saturated fat and monounsaturated fat and vegans had the highest intakes of fiber and polyunsaturated fats. Age-adjusted mean BMI was significantly different between the four diet groups: Highest in the meat-eaters (24.41kg/m^2 in men, 23.52kg/m^2 in women) and lowest in the vegans (22.49kg/m^2 in men, 21.98kg/m^2 in women); similar and intermediate for fish-eaters (23.30kg/m^2 in men, 22.66kg/m^2 in women) and vegetarians (23.37kg/m^2 in men, 22.71 in women). Prevalence of obesity was significantly lower in vegans than other diet groups; obesity rates significantly lower in vegetarians and fish-eaters than meat-eaters. After adjusting for all lifestyle and dietary factors included in this study, statistically significant differences in mean BMI between diet groups remained. High percent protein intake and low fiber intakes were the dietary factors most strongly associated with higher BMI between and within diet groups. The authors concluded that vegan diets, and to a less extent vegetarian diets and diets that include fish, are associated with lower BMI and lower levels of obesity than diets which include meat. However, they noted self-reported data and the use of a FFQ as limitations.

Rosell et al, 2006 (neutral quality). This prospective cohort was designed to assess changes in weight over five years among participants in the Oxford arm of the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford). Participants were 21,966 (5,373 men and 16,593 women) healthy adults aged 20-69 years at baseline who completed assessments between 1994 and 1999 and follow-up between 2000 and 2003 (median=5.3 years). Participants completed a FFQ and reported their height and weight. Participants were divided into six groups: Meat eaters (ate meat at both time points), fish eaters (ate fish but not meat at both time points), vegetarians (did not eat meat or fish but did eat diary or eggs at both time points), vegans (ate no animal products at either time point), reverted (those who changed diet in one or more steps in the direction of vegan to vegetarian to fish-eater to meat-eater) and converted (those who changed diet in one or more steps in the opposite direction). Mean annual weight gain was approximately 400g per year. Differences were observed between the diet groups. A significantly smaller weight gain was observed among male and female vegans and female fish-eaters, compared to meat eaters. Among those who had not changed their eating patterns over time, the largest weight gain was seen in meat-eaters. The smallest weight gain was observed in people classified as converted. The highest weight gains were among men and women classified as reverted, but mean weight gains were not significantly different than weight gains in meat eaters. The lowest weight gain among this health-conscious cohort was seen among those individuals who had changed their diet to contain fewer

animal foods. Additional analyses are reported on weight gain and non-dietary behaviors including physical activity and smoking.

Appleby et al, 2007 (neutral quality). This study was a prospective cohort study designed to examine fracture risk among meat eaters (N=19,249), fish eaters (N=4,901), vegetarians (N=9,420) and vegans (N=1,126) from the European Prospective Investigation into Cancer and Nutrition-Oxford (EPIC-Oxford) study. Of the 34,696 participants, 7,947 were men and 26,749 were women. Mean age at recruitment was 46.6 years. At baseline, participants completed a lifestyle and FFQ, including questions relating to height and weight, smoking habits, alcohol consumption, physical activity at work and during leisure time and marital status. Women were also asked about their reproductive history and use of hormone replacement therapy. Five years later, participants were sent a follow-up questionnaire that asked whether they had suffered any fractured bones over the previous six years and to report the bones affected and the cause. Incident fracture was defined as one occurring after the date of recruitment and involving bones other than the digits or ribs. Over an average of 5.2 years of follow-up, 343 men and 1,555 women reported one or more fractures. Fracture risk was similar for meat eaters, fish eaters and vegetarians; compared with meat eaters, fracture incidence rate ratios in men and women combined adjusted for sex, age and non-dietary factors were 1.01 (95% CI: 0.88-1.17) for fish eaters, 1.00 (95% CI: 0.89-1.13) for vegetarians and 1.30 (95% CI: 1.02-1.66) for vegans. Mean calcium intakes were also similar for meat eaters, fish eaters and vegetarians, but were considerably lower for vegans. Percent of subjects consuming <700mg per day of calcium was 15.0 for meat eaters, 15.9 for fish eaters, 18.6 for vegetarians and 76.1 for vegans. The authors concluded that the higher fracture risk in the vegans appeared to result from their lower mean calcium intake.

Key et al, 2009a (positive quality). This study was a prospective cohort study designed to compare cancer incidence among participants in the European Prospective Investigation into Cancer and Nutrition-Oxford (EPIC-Oxford) study. Cancer incidence was followed through nationwide cancer registries to December 2005. Using answers from four questions, participants were divided into four diet groups: Meat eaters (eat meat), fish eaters (eat fish but not meat), vegetarians (do not eat meat or fish but do eat milk products or eggs) and vegans (eat no animal products). The overall cancer incidence in this cohort was lower than the national average. The analyses comparing vegetarian and non-vegetarian cancer incidence rates were restricted to 52,706 participants aged 20-89 years at recruitment with known smoking characteristics and diet group and no history of cancer at baseline (except non-melanoma skin cancer). Because of the small number of cancers among vegans, vegans were included in the vegetarian category for analyses. The risk of colorectal cancer was significantly higher among vegetarians than non-vegetarians (IRR: 1.49; 95% CI: 1.09, 2.03). The risk of female breast, prostate, ovarian and lung cancer were not significantly (NS) different between vegetarians and non-vegetarians. The risk of all malignant neoplasms was NS lower in vegetarians than in non-vegetarians (IRR: 0.93; 95% CI: 0.83, 1.04). The risk of all malignant neoplasms was significantly lower among fish eaters than meat eaters (IRR: 0.83; 95% CI: 0.71, 0.96). Meat intake among the meat eaters was moderate (78.1g per day in men and 69.7g per day in women). Fruit and vegetable intake was less than 20% higher among vegetarians than non-vegetarians. A possible limitation of the study is the accuracy of the assessment of diet classification.

Key et al, 2009b (positive quality). This study was a prospective cohort study designed to compare mortality from major causes of death among participants in the European Prospective Investigation into Cancer and Nutrition-Oxford (EPIC-Oxford) study. Death information was obtained from the United Kingdom's National Health Service Central Register. Using answers from four questions, participants were divided into four diet groups: Meat eaters (eat meat), fish eaters (eat fish but not meat), vegetarians (do not eat meat or fish but do eat milk products or eggs), and vegans (eat no animal products). Among 64,234 participants with known diet group, 2,965 died before age 90 by 30 June 2007. The death rate among participants was lower than the national average. The standardized mortality ratio for all causes of death was 52% (95% CI: 50%, 54%) and was identical between vegetarians and non-vegetarians. The analyses comparing diet groups were limited to 47,254 participants after applying exclusions for missing data and previous myocardial infarction (MI), stroke or malignant cancer (excluding non-melanoma skin cancer). Because of small number of deaths among vegans, vegans were included with vegetarians in the analyses. Comparisons between diet groups showed NS differences in mortality rates, but the authors stated that the study was not large enough to exclude small or moderate difference for specific causes of death. The authors also noted that the average meat intake among the meat eaters was moderate (79g per day in men, 67g per day in women) and differences in fruit and vegetable intake between vegetarians and non-vegetarians was also moderate (<20%). Subsequently, the low intake of meat and high intake of fruits and vegetables among non-vegetarians in this cohort could reduce the chance of observing differences in mortality rates.

Taiwan

Hung et al, 2006 (neutral quality). This case-control study was designed to examine the effects of a Taiwanese vegetarian diet on hormonal secretion and glycemic control among female adults. Participants were 49 Buddhist lacto-vegetarians and 49 age-matched omnivores. The typical Taiwanese vegetarian diet consists mainly of rice, grains, fruits, vegetables, soybeans and soy products. The Western vegetarian diet contains more nuts, seeds, dairy and eggs. Dietary intakes were measured and hormone blood levels analyzed. Vegetarians consumed significantly less total fat (mean [SE]: 38.7 [2.65] vs. 49.9 [2.48] grams per day), saturated fat (mean [SE]: 8.34 [0.92] vs. 16.21 [1.10] grams per day) and protein (mean [SE]: 46.8 [2.23] vs. 64.5 [3.17] grams per day), but more fiber (mean [SE]: 6.57 [0.50] vs. 4.27 [0.45] grams per day) than omnivores. Total energy, carbohydrate and unsaturated fat intakes did not differ significantly. Percent of energy from protein, total fat, saturated fat and polyunsaturated fat were 12.2, 22.7, 4.9 and 11.5, respectively, for vegetarians; and 15.2, 26.4, 8.6 and 9.5, respectively, for omnivores. Vegetarians had significantly lower mean weight (mean [SE]: 51.5 [0.90] vs. 55.4 [0.85] kg) and waist circumference (WC) (mean [SE]: 64.2 [0.70] vs. 66.9 [0.67] cm), but BMI was NS different. Vegetarians had significantly lower fasting serum insulin (mean [SE]: 37.2 [1.81] vs. 56.6 [3.67] pmol/L), plasma glucose (mean [SE]: 4.7 [0.05] vs. 4.9 [0.05] mmol/L), insulin: glucagon ratio (mean [SE]: 0.37 [0.02] vs. 0.56 [0.05]) and HOMA-IR (mean [SE]: 1.09 [0.06] vs. 1.73 [0.11]) than omnivores. Body mass index and diet were independent predictors for insulin resistance and contributed 18 and 15% of the variation in insulin resistance, respectively. No significant difference in glucagon, beta-cell function, serum T3, free T4, TSH levels, or T3:T4 ratio was observed between groups. Young, female

Taiwanese vegetarians had lower glucose and insulin and higher insulin sensitivity than omnivores.

Chen et al, 2008 (positive quality). This cohort study was designed to compare the cardiovascular risk profile of healthy Taiwanese vegetarians to omnivores. Participants were 99 vegetarians (34 male, 65 female; mean [SD] age=51.24 [8.88] years) and 99 omnivores (53 male, 46 female; 49.38 [9.60] years) who had undergone a general health exam at the Buddhist Dalin Tzu-Chi General Hospital. Participants completed questionnaires regarding past medical history and dietary preferences. Vegetarians were lacto-ovo vegetarians practicing for at least one year. After a 12-hour fast, venous blood samples were obtained; weight, height and BP were also measured. Differences in dietary intake between groups were not reported. Vegetarians had significantly lower TC, LDL-C, SBP and DBP than omnivores. There was NS difference in age, BMI, blood glucose, white blood cell count, triglyceride or HDL-C between the two diet groups. The authors concluded that Taiwanese vegetarians had a better cardiovascular risk profile than omnivores.

Wang et al, 2008 (positive quality). This cross-sectional analysis explored the effects of vegetarian and non-vegetarian diets on bone mineral density (BMD) and incidence of osteoporosis in adult Taiwanese men and women. Participants were 1,865 adult male and female participants who underwent a routine exam at a regional teaching hospital. Participants self-reported their dietary preference as vegetarian for at least five years (383 men, 489 women) or non-vegetarian (464 men, 529 women). Bone mineral density was measured using dual-energy X-ray absorptiometry (DXA) at the right femoral neck in men and between L-2 and L-4 vertebrae in women. Classifications of osteopenia and osteoporosis were based on World Health Organization (WHO) criteria. Bone mineral density gradually declined with increasing age in men, and declined precipitously in women after the fifth decade, but there were no statistical differences in BMD observed between vegetarians and non-vegetarians of either sex. The proportion of participants with osteopenia and osteoporosis were also comparable between diet groups of both sexes. The authors concluded that there was an age-related decline in BMD, but a Taiwanese vegetarian diet did not appear to affect this decline. (Note: Dietary intake was not measured, but authors stated that the Taiwanese vegetarian diet typically contains large amounts of soybean products instead of milk, cheese and eggs.)

Yen et al, 2008 (positive quality). This cross-sectional study conducted in Taiwan, assessed and compared dietary intake and nutritional status of vegetarian and omnivorous pre-school children and their parents. Fifty-six omnivores (28 children and one of their parents) and 42 vegetarians (21 children and one of their parents) were included in the analysis. Among the preschool vegetarians, 18 were lacto-ovo vegetarians and three were ovo-vegetarians. Among the vegetarian parents, 16 were lacto-ovo vegetarians, two were ovo-vegetarians, one was lacto-vegetarian, and two were vegans. Anthropometric measurements were taken and fasting venous blood samples were obtained. Nutrient intake was recorded using three-day diet records. There were no differences between omnivores and vegetarians in terms of height, weight, BMI, weight-for-height index and triceps skinfold thickness values in both parent and child groups. All mean hematologic and biochemical nutrient status indices were within the reference range. However, both vegetarian parents and children had significantly lower mean TC and serum ferritin concentrations than those of

omnivorous parents and children. Omnivorous children also had significantly higher HDL-C concentrations than vegetarian children. Most subjects had nutrient intakes above the Taiwan Dietary Reference Intakes (DRI). However, both vegetarians and omnivores in both parent and child groups had mean calcium consumption less than 75% of the Taiwan DRI. The authors concluded that vegetarian and omnivorous pre-school children had normal growth and adequate nutritional status. However, parents and children in both diet groups had inadequate calcium intakes.

United States

Thorpe et al, 2008 (positive quality). This cohort study was designed to examine the effects of meat consumption and a vegetarian diet on risk of low-energy wrist fracture in a cohort of peri- and post-menopausal women. Study participants (N=1865) were white female Seventh-day Adventists in the Adventist Health Study. Participants completed two lifestyle surveys 25 years apart (1976 and 2002). The survey included 65 semi-quantitative food items and data on fractures due to minor trauma at the wrist. The 25-year period-incidence rate for wrist fracture was 3.7 per 1,000 person-years. The group at highest risk for fracture were those who never ate meat and were also in the lowest category of vegetable protein intake. Among vegetarians, increasing vegetable protein intake reduced risk of fracture. Similarly, among those with the lowest vegetable protein consumption, consuming meat decreased risk of fracture. Vegetarians consumed more beans, nuts and meat analogues than non-vegetarians whereas cheese intake was higher for non-vegetarians. Higher consumption frequencies of foods rich in protein were associated with reduced wrist fractures. Vegetarian women were not at higher risk for wrist fracture than non-vegetarian women. The authors concluded that adequate protein intake is attainable in a vegetarian diet.

Australia

Baines et al, 2007 (positive quality). This cross-sectional study was designed to explore differences in sociodemographic characteristics, health status, and health service use among 9,113 young women (22-27 years old) in the Australian Longitudinal Study on Women's Health. Participants completed a survey that included items related to general health and well-being, health service use and health behaviors. All variables were self-reported. Participants were asked if they exclude red meat (beef, lamb, pork), fish or poultry from their diet. Non-vegetarians (87%) reported including red meat in their diet, semi-vegetarians (10%) excluded red meat from their diet and vegetarians (3%) excluded meat, poultry and fish from their diet. Vegetarians and semi-vegetarians had lower mean BMI than non-vegetarians (22.2, 23.0 and 23.7kg/m^2, respectively) and tended to exercise more. The groups did not differ in their self-reported physical health; however, semi-vegetarians and vegetarians had poorer mental health, with 21-22% reporting depression compared with 15% of non-vegetarians ($P<0.001$). Significantly more vegetarians and semi-vegetarians reported (a) ever being diagnosed with low iron, iron deficiency or anemia, (b) constipation or other bowel problems, and (c) irregular periods than non-vegetarians.

Grant et al, 2008 (neutral quality). This cross-sectional analysis investigated possible relationships between nutrition and lifestyle behaviors and selected markers of health in 14 to 15-year-old Australian adolescents from Adventist secondary schools. 215 participants were recruited; complete data obtained for 207 participants (83 boys, 124

girls). Blood was drawn after a 12-hour overnight fast; height, weight and waist circumference (WC) were measured. Participants completed a school physical activity and nutrition survey. Participants were classified as vegetarian (N=53; 17 boys, 36 girls) if they reported consuming meat less than once a week, chicken less than once a week, and fish less than once a week; no participants were vegan. All other participants were classified as non-vegetarian (N=160; 69 boys, 91 girls). Participants following a vegetarian diet had significantly lower serum vitamin B_{12} (P<0.001), TC/HDL-C ratio (P<0.01), LDL-C (P<0.01), WC (P<0.01) and BMI (P<0.05) compared to non-vegetarians. No significant differences were observed between vegetarians and non-vegetarians in triglycerides, HDL-C, SBP, DBP or blood glucose. The authors concluded that a vegetable-rich diet may be an effective strategy for combating lifestyle diseases in adolescents.

Japan

Nakamoto et al, 2008 (neutral quality). This cross-sectional study conducted in Japan, investigated the nutritional characteristics of 75 healthy middle-aged vegetarians compared with 50 age- and sex-matched non-vegetarians. Of the vegetarians, 27 (nine men, 18 women) were lacto-ovo vegetarians and 48 (11 men, 37 women) were semi-vegetarians with the occasional intake of meat and seafood. Biochemical and anthropometric measurements were obtained from a medical examination. In men, vegetarians had significantly lower BMI, DBP, SBP and serum triacylglyceride than non-vegetarians. No significant difference in TC was observed in men. In women, vegetarians had significantly lower SBP and serum triacylglyceride than non-vegetarians. No significant differences in BMI, TC, or DBP were observed in women. Differences in dietary intake between vegetarians and non-vegetarians were also reported. Information on dietary intake (using three-day food record) was collected for 20 vegetarian men, 50 vegetarian women and 32 non-vegetarian men; the number of food records collected from non-vegetarian women was so small that their dietary intake data was dismissed. Vegetarian men had significantly higher intakes of calcium, iron and dietary fiber and significantly lower vitamin B_{12} and cholesterol than non-vegetarian men. The authors concluded that vegetarians had better characteristics from the standpoint of lifestyle related diseases, but cautioned that some nutrient intakes may be low in vegetarian men.

Sweeden

Newby et al, 2005 (neutral quality). This cross-sectional study was designed to examine the BMI and risk of overweight and obesity among self-defined omnivorous (consume all foods), semi-vegetarian (mostly lacto-vegetarian with some fish or eggs), lacto-vegetarian (no meat, poultry, fish or eggs) and vegan (no meat, poultry, fish, eggs or dairy) women. Participants were 55,459 healthy women from the Swedish Mammography Cohort who completed a FFQ, self-reported their height and weight, and identified their diet group. The majority of the participants were omnivores. Only 1.73% were semi-vegetarian, 0.29% were lacto-vegetarian and 0.15% were vegan. The omnivores had significantly higher energy, protein, saturated fat, and monounsaturated fat intakes and significantly lower carbohydrate and fiber intake than the three vegetarian groups. Omnivores had the highest intake of refined grains and animal products and the lowest intake of fruits and vegetables. The prevalence of overweight and obesity (BMI≥25kg/m^2) was 40% among omnivores, 29% among semi-vegetarians and vegans, and 25% among lacto-vegetarians. In multivariate, adjusted

linear regression analyses, the semi-vegetarian, lacto-vegetarian, and vegan women had significantly lower BMI than omnivorous women. In multivariate, adjusted logistic regression analyses, all three vegetarian groups also had a significantly lower risk of overweight or obesity than the omnivores. Semi-vegetarian women also had a lower risk of obesity than omnivorous women. Self-identified semi-vegetarian, lacto-vegetarian and vegan women had a smaller BMI and lower risk of overweight and obesity than omnivorous women. Physical activity was not accounted for in analyses.

Belgium

Alewaeters et al, 2005 (neutral quality). This cross-sectional study was designed to report BMI and health behaviors of a vegetarian population as compared to a reference Belgian population. Vegetarian participants were 326 adults (120 men and 206 women) who were vegetarians for more than one year. Classification as vegetarian was confirmed by reviewing responses to a survey on dietary habits. The vegetarian group included vegans and those who consumed eggs or milk products. Vegetarians had a lower mean BMI compared to the reference population. The BMI of female vegetarians was significantly lower than the reference female Belgian population (mean [SD]=22.1 [3.1] and 24.6 [4.8] kg/m^2, respectively). Similarly, the BMI of male vegetarians was significantly lower than the reference male Belgian population (mean [SD]=22.6 [3.6] and 25.7 [4.0] kg/m^2, respectively). Other variables including smoking, alcohol consumption, physical activity, medication use and health perception were also compared between the vegetarians and reference Belgian population.

Brazil

Teixeira et al, 2007 (neutral quality). This comparative observational study in Brazil was designed to describe and analyze the cardiovascular risk of vegetarian and omnivorous adults aged 35 to 64 years. Sixty-seven vegetarians (practicing at least five years) completed assessments in 2003-2004. A total of 134 omnivores that were matched for age, gender, race and socioeconomic status were selected from a database of participants in the MONICA Project/Vitoria (1999-2000). The same methodology was used for data collection at both time points. Questionnaires were administered during home visits. Blood was drawn after 12-hour fasting for determination of lipid profile and fasting plasma glucose. Most of the vegetarians (73%) were lacto-ovo vegetarians. Body mass index, waist-to-hip ratio (WHR), BP, TC, LDL-C, triglycerides and fasting blood glucose were significantly lower among vegetarians than omnivores. There was no difference in HDL-C levels. Using the Framingham algorithm, vegetarians had a significantly lower cardiovascular risk than omnivores. Possible confounding factors include differences in BMI between groups and higher levels of smoking and consumption of alcoholic beverages in the omnivore group.

South Asian Immigrants In England

Dos Santos Silva et al, 2002 (positive quality). The case-control study was designed to investigate the role of lifelong vegetarianism on the etiology of breast cancer in South Asian migrant women living in England. Cases (N=240) were women of South Asian ethnic origin, <75 years old, with newly diagnosed breast cancer, born in Indian sub-continent or in East Africa and living and reporting to the Thames and West Midlands cancer registries during the study period and alive at the time of reporting. Controls (N=480) were individually matched to the case on year of birth within five

years and were randomly selected from all South Asian female patients born in the Indian sub-continent or East Africa who were registered with the same general practitioner as the case at diagnosis. Home interviews were conducted and included completion of an FFQ specifically designed for South Asian populations residing in England. Among controls, lifelong vegetarians had a much higher median daily intake of vegetables (332g vs. 249g) and pulses, lentils and dhals (92g vs. 46g) than meat-eaters but similar consumption of fruit (1.6 servings vs. 1.6 servings) and bread (184g vs. 175g). Lifelong vegetarianism had a slight but not statistically significant reduction in the odds of breast cancer relative to lifelong meat eaters (OR=0.77, 95% CI: 0.50, 1.18). There was no linear trend in the odds of breast cancer with increasing meat intake, but there was a strong inverse linear trend with increasing intake of vegetables (P=0.005), pulses (P=0.007) and non-starch polysaccharides (P=0.02), but not with breads or fruits. The authors concluded that lifelong vegetarianism may be associated with a reduction in the risk of breast cancer through its association with a higher intake of vegetables and pulses.

Overview table

Author, Year, Study Design, Class, Rating	Population / Subjects	Study Methodology	Outcomes
Alewaeters K, Clarys P et al, 2005 Study Design: Cross-Sectional Study Class: D Neutral quality	N=326 vegetarians (120 men, 206 women) after exclusions. Participants were vegetarians >one year, ≥20 years of age and after looking at nutritional habits, did not eat meat including fish. Mean (SD) age: 42.3 (15.9) years for men; 37.0 (12.3) years for women. Reference Belgium population (N=9,659): Women N=4,993, age of 49.8 (18.0) years; men N=4,666, age of 48.0 (17.1) years. Location: Belgium.	Responses from 326 vegetarians were compared to the results from a survey of a representative sample of the Belgian population (N=9,659) conducted by the Belgian government. Vegetarians completed a self-administered questionnaire mainly comprised of questions from the National Health Survey (conducted in Belgium every five years) and self-reported their height and weight. Vegetarians were: 79.8% lacto-ovo-vegetarians 1.8% ovo-vegetarians 2.1% lacto-vegetarians 15% vegans.	BMI of female vegetarians was significantly lower than reference female Belgian population (mean [SD]=22.1 [3.1] and 24.6 [4.8] kg/m^2, respectively). BMI of male vegetarians was significantly lower than reference male Belgian population (mean [SD]=22.6 [3.6] and 25.7 [4.0] kg/m^2, respectively).

Appleby et al 2007 Study Design: Prospective Cohort Study Class: B Neutral quality	N=34,696 participants in the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford) (7,947 men and 26,749 women) Age: 20-89 years (mean age at recruitment 46.6 years). N=19,249 meat eaters, 4,901 fish eaters, 9,420 vegetarians and 1,126 vegans in the analysis. Location: United Kingdom.	Participants completed a lifestyle and FFQ at baseline. Asked four yes/no questions: 1) Do you eat meat? 2) Do you eat fish? 3) Do you eat dairy products? 4) Do you eat eggs? Categorized into four groups: 1) Meat eaters (eat meat) 2) Fish eaters (eat fish, but not meat) 3) Vegetarians (do not eat meat or fish, but do eat diary or eggs) 4) Vegans (eat no animal products). Participants were sent follow-up questionnaire five years later (mean follow-up=5.2 years) that asked whether they had suffered any fractured bones over the previous six years and to report the bones affected and cause. Incident fracture was defined as one occurring after the date of recruitment and involving bones other than the digits or ribs.	At follow-up, 343 men and 1,555 women reported one or more fractures. Most common fracture sites: Wrist/arm and ankle; 70% of fractures caused by falls. Fracture risk similar for meat eaters, fish eaters and vegetarians; compared with meat eaters, fracture incidence rate ratios in men/women combined adjusted for sex, age and non-dietary factors were 1.01 (95% CI: 0.88-1.17) for fish eaters, 1.00 (95% CI: 0.89-1.13) for vegetarians and 1.30 (95% CI: 1.02-1.66) for vegans. Mean calcium intakes were also similar for meat eaters, fish eaters and vegetarians, but were considerably ↓ for vegans. Subjects consuming <700mg per day of calcium: 15.0% for meat eaters 15.9% for fish eaters 18.6% for vegetarians 76.1% for vegans.

Appleby, Davey et al, 2002 Study Design: Cross-sectional Class: D Neutral quality	Participants in the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford). N=11,004 participants (2,351 men, 8,653 women) after exclusions: Date of BP measurement unknown or incomplete, >80 years, missing values of the BP measurements, BMI <15 or >60kg/m^2. N=4,737 meat eaters N=1,728 fish eaters N=3,800 vegetarians N=739 vegans. Age: At BP measurement ranged from 20 to 78 years (median 48 years men; 46 years women). Location: United Kingdom.	All participants completed a detailed lifestyle questionnaire, including a semi-quantitative FFQ. Asked four yes/no questions: 1) Do you eat meat? 2) Do you eat fish? 3) Do you eat dairy products? 4) Do you eat eggs? Categorized into four groups: Meat eaters (eat meat) Fish eaters (eat fish, but not meat) Vegetarians (do not eat meat or fish, but do eat diary or eggs) Vegans (eat no animal products). BP measured at their general practice. No standard method of BP measurement specified and only single measurements taken.	BMI was ↑ in the meat eaters than the vegans, with fish eaters and vegetarians having similar and intermediate values. Self-reported HTN was most common among meat eaters and least common among vegans. Age-adjusted prevalence for meat eaters, fish eaters, vegetarians and vegans, respectively, was 15.0%, 9.8%, 9.8% and 5.8% for men and 12.1%, 9.6%, 8.9% and 7.7% for women (each P<0.0005). The same pattern remained after further adjustment for BMI, although differences in prevalence of HTN between diet groups were smaller and of ↓ statistical significance (P=0.01 for men, P=0.07 for women). Significant differences in age-adjusted SBP and DBP between the diet groups for both men and women (each P<0.005). Meat eaters had the ↑ and vegans the ↓ adjusted mean values. Differences in age-adjusted mean BP between meat eaters and vegans among participants with no self-reported HTN were 4.2 and 2.6mmHg SBP and 2.8 and 1.7mmHg DBP for men and women, respectively; this variation was largely attributable to differences in BMI between groups.

Baines et al 2007 Study Design: Cross-sectional Analysis of Cohort Study Class: D Positive quality	N=9,113 women from the Australian Longitudinal Study on Women's Health. Age: 22-27 years. Location: Australia.	Self-reported survey. Participants asked: Do you exclude any of the following food groups from your diet? a) Red meat (beef, lamb, pork) b) Fish c) Poultry. Non-vegetarians (87%) reported including red meat in their diet; semi-vegetarians (10%) excluded red meat from their diet; vegetarians (3%) excluded meat, poultry and fish from their diet.	Vegetarians (mean=22.2, 95% CI: 21.7-22.7) and semi-vegetarians (mean=23.0, 95% CI: 22.7-23.3kg/m^2) had ↓ BMI than non-vegetarians (mean=23.7, 95% CI: 23.6-23.8kg/m^2) and tended to exercise more. Groups did not differ in self-reported physical health; however, semi-vegetarians and vegetarians had poorer mental health, with 21-22% reporting depression compared with 15% of non-vegetarians (P<0.001). Significantly more vegetarians (42.6%) and semi-vegetarians (38.9%) reported ever being diagnosed with low iron, iron deficiency or anemia than non-vegetarians (25.5%). Significantly more vegetarians (29.1%) and semi-vegetarians (27.5%) reported constipation or other bowel problems than non-vegetarians (22.7%). Significantly more vegetarians (27.5%) and semi-vegetarians (25.0%) reported irregular periods than non-vegetarians (18.7%).

Chen et al 2008 Study Design: Cohort study Class: B Positive quality	N=99 vegetarians (34 male, 65 female; mean [SD] age=51.24 [8.88] years). N=99 omnivores (53 male, 46 female; 49.38 [9.60] years). Location: Taiwan.	Participants had undergone general health exam at the Buddhist Dalin Tzu-Chi General Hospital. Questionnaires were completed regarding past medical history, dietary preferences and willingness to participate in the study and were enrolled if they met inclusion criteria. Patients with a history of DM, HTN, CVD, dyslipidemia, chronic gingivitis, rheumatoid arthritis or other connective tissue disease, CAD and fever or other infectious disease within three weeks before the start of the study were excluded. Vegetarians were lacto-ovo-vegetarians for ≥one year. After 12-hour fast, venous blood samples were obtained; weight, height and BP were also measured.	NS difference in age, BMI, blood glucose, white blood cell count, TG or HDL-C between the two groups. Vegetarians had significantly ↓ TC (mean [SD]: 184.74 [33.23] vs. 202.01 [41.05] mg/dL) and LDL-C (119.63 [31.59] vs. 135.89 [39.50] mg/dL) than omnivores. Vegetarians had significantly ↓ SBP (mean [SD]: 120.49 [15.63] vs. 125.55 [15.04]) and DBP (75.01 [11.90] vs. 78.76 [11.71]) than omnivores.

Dos Santos Silva et al 2002 Study Design: Case-Control Study Class: C Positive quality	N=240 cases with newly diagnosed breast cancer and 480 controls. Mean age: 51.45 years for cases; 51.87 years for controls. Location: England.	Cases were women of South Asian ethnic origin, <75 years old, with newly diagnosed breast cancer, born in Indian sub-continent or in East Africa and living and reported to the Thames and West Midlands cancer registries during the study period and alive at time of the reporting. Controls individually matched to the case on year of birth within five years and were randomly selected from all South Asian female patients born in the Indian sub-continent or East Africa who were registered with the same general practitioner as the case at diagnosis. Exclusion criteria: Previous diagnosis of any cancer, suffering from conditions requiring strict diets, or suffering from mental or psychiatric disorders. Home interviews conducted and included completion of an FFQ specifically designed for South Asian populations residing in England.	Among controls, lifelong vegetarians had a much ↑ median daily intake of vegetables (332g vs. 249g) and pulses, lentils and dhals (92g vs. 46g) than meat-eaters, but similar consumption of fruit (1.6 servings vs. 1.6 servings) and bread (184g vs. 175g). Lifelong vegetarianism had a slight, but not statistically significant ↓ in the odds of breast cancer relative to lifelong meat eaters (OR=0.77, 95% CI: 0.50, 1.18). No linear trend in the odds of breast cancer with ↑ meat intake, but a strong inverse linear trend with ↑ intake of vegetables (P=0.005), pulses (P=0.007) and non-starch polysaccharides (P=0.02), but not with breads or fruits.
Grant et al 2008 Study Design: Cross-Sectional Analysis of a Cohort Class: D Neutral quality	N=215 participants recruited; complete data existed for 207 participants (124 girls, 83 boys). Age: 14 to 15-year-old adolescents from Adventist secondary schools. Location: Australia	Blood drawn after a 12-hour overnight fast; height, weight and WC measured. Participants completed a school physical activity and nutrition survey. Vegetarians: N=53 (17 boys, 36 girls); diet was "vegetable-rich"; participants were classified as vegetarian if consumed meat <once a week, chicken <once a week, and fish <once a week; no participants were vegan. Non-vegetarians: N=160 (69 boys, 91 girls).	Vegetarians significantly lower values for the following variables than non-vegetarians (mean values): WC (69.2 vs. 73.5cm) BMI (20.5 vs. 21.9kg/m^2) TC/HDL-C ratio (2.7 vs. 2.9) LDL-C (2.1 vs. 2.3 mmol/L) Serum B_{12} (260 vs. 339 pmol/L). NS difference between vegetarians and non-vegetarians in TG, HDL-C, SBP, DBP or blood glucose.

Hung CJ, Huang PC et al, 2006 Study Design: Case Control Study Class: C Neutral quality	N=98 females (49 Buddhist lacto-vegetarians; 49 age-matched omnivores). Age: 31-45 years; pre-menopausal. Within 120% of IBW; no history of chronic disease (e.g., heart disease, DM, cancer, HTN, renal disease); and no alcohol intake or cigarette smoking. Among vegetarians, seven were vegans and 42 were lacto-vegetarians who consumed <240ml low-fat or skim milk daily; average vegetarian practice was eight years with minimum of two years. Location: Taiwan.	Dietary intake assessed using 24-hour recall supplemented with semi-quantitative FFQ. Nutrient data calculated using a database for Taiwan food composition. After an overnight fast of 10-11 hours, anthropometric measurements were performed and blood samples were collected.	Vegetarians consumed significantly ↓ total fat (mean [SE]: 38.7 [2.65] vs. 49.9 [2.48] g per day), saturated fat (mean [SE]: 8.34 [0.92] vs. 16.21 [1.10] g per day) and PRO (mean [SE]: 46.8 [2.23] vs. 64.5 [3.17] g per day), but more fiber (mean [SE]: 6.57 [0.50] vs. 4.27 [0.45] g per day) than omnivores. Total energy, CHO and unsaturated fat intakes NS different. Vegetarians had significantly ↓ mean weight (mean [SE]: 51.5 [0.90] vs. 55.4 [0.85] kg) and WC (mean [SE]: 64.2 [0.70] vs. 66.9 [0.67] cm), but BMI was NS different. Vegetarians had significantly ↓ mean weight (mean [SE]: 51.5 [0.90] vs. 55.4 [0.85] kg) and WC (mean [SE]: 64.2 [0.70] vs. 66.9 [0.67] cm), but BMI was NS different. Vegetarians had significantly ↓ fasting serum insulin (mean [SE]: 37.2 [1.81] vs. 56.6 [3.67] pmol/L), plasma glucose (mean [SE]: 4.7 [0.05] vs. 4.9 [0.05] mmol/L), insulin: glucagon ratio (mean [SE]: 0.37 [0.02] vs. 0.56 [0.05]) and HOMA-IR (mean [SE]: 1.09 [0.06] vs. 1.73 [0.11]) than omnivores. BMI and diet were independent predictors for insulin resistance and contributed 18 and 15% of the variation in insulin resistance, respectively. NS difference in glucagon, beta-cell function, serum T3, free T4, TSH levels, or T3:T4 ratio observed between groups.

Key TJ, Appleby PN et al, 2009 Study Design: Prospective Cohort Study Class: B Positive quality	Participants in the European Prospective Investigation into Cancer and Nutrition-Oxford (EPIC-Oxford) study. N=63,550 men and women included in the analyses comparing cancer incidence with national rates for England and Wales. N=52,706 men and women included in the analyses comparing vegetarians and non-vegetarians (32% vegetarians; 77% women). Age: 20-89 years at recruitment. Known smoking status; no history of cancer at baseline. Location: United Kingdom.	Prospective cohort study from 1990s to December 2005. Cancer incidence from nationwide cancer registries. Asked four yes/no questions: 1) Do you eat meat? 2) Do you eat fish? 3) Do you eat dairy products? 4) Do you eat eggs? Categorized into four groups: 1) Meat eaters (eat meat) 2) Fish eaters (eat fish, but not meat) 3) Vegetarians (do not eat meat or fish, but do eat diary or eggs) 4) Vegans (eat no animal products). Because of small number of cancers among vegans, vegans included with vegetarians in analyses.	N=2,179 incident cancers before age 90; overall cancer incidence ↓ than national average. Vegetarians to non-vegetarians: Risk of colorectal cancer significantly ↑ among vegetarians (IRR:1.49; 95% CI: 1.09, 2.03); risk at other cancer sites (female breast, prostate, ovarian, and lung) NS difference. Meat eaters, fish eaters and vegetarians: Colorectal cancer significantly ↑ in vegetarians than meat eaters (IRR: 1.39; 95% CI: 1.01, 1.91); risk of lung cancer significantly ↓ in fish eaters than meat eaters (IRR: 0.23; 95% CI: 0.06, 0.95); risk of all malignant neoplasms significantly ↓ among fish eaters than meat eaters (IRR: 0.83; 95% CI: 0.71, 0.96). Risk of all malignant neoplasms NS ↓ in vegetarians than non-vegetarians (IRR: 0.93; 95% CI: 0.83, 1.04); risk of all malignant neoplasms NS ↓ among vegetarians than meat eaters (IRR: 0.89; 95% CI: 0.80, 1.00).

Key TJ, Appleby PN et al, 2009 Study Design: Prospective cohort study Class: B Positive quality	Participants in the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford). N=64,234 participants aged 20-89 years included in the analyses comparing mortality with national rates for England and Wales. N=47,254 participants included in comparisons between diet groups (after applying exclusions for missing data, previous MI or stroke, or malignant cancer [excluding non-melanoma skin cancer]); 76% women, 34% vegetarians. Location: United Kingdom.	Participants recruited between 1993 and 1999. Self-reported dietary intake using a validated semi-quantitative FFQ. Death information from UK's National Health Service Central Register. Asked four yes/no questions: 1) Do you eat meat? 2) Do you eat fish? 3) Do you eat dairy products? 4) Do you eat eggs? Categorized into four groups: Meat eaters (eat meat) fish eaters (eat fish, but not meat) Vegetarians (do not eat meat or fish, but do eat diary or eggs) Vegans (eat no animal products). Because of small number of deaths among vegans, vegans included with vegetarians in analyses.	Among 64,234 participants, 2,965 had died before age 90 by 30 June 2007; death rate lower than average for the UK; standardized mortality ratio for all causes of death was 52% (95% CI: 50%, 54%) and was identical in vegetarians and non-vegetarians. Among 47,254 participants, there was NS difference in mortality rates between non-vegetarians and vegetarians or between meat eaters, fish eaters and vegetarians.

Nakamoto et al 2008 Study Design: Cross-sectional Study Class: D Neutral quality	N=75 healthy middle-aged vegetarians, compared with 50 age- and sex-matched non-vegetarians. Information on dietary intake was collected for: 20 vegetarian men (age, mean [SD]=45.2 [8.3] years) 50 vegetarian women (45.9 [8.8] years) 32 non-vegetarian men (44.2 [5.2] years) Number of food records collected from non-vegetarian women was so small that their dietary intake data was dismissed. Location: Japan.	Of the vegetarians, 27 (9 men, 18 women) were lacto-ovo-vegetarians and 48 (11 men, 37 women) were semi-vegetarians with the occasional intake of meat and seafood (none were vegan). Biochemical and anthropometric measurements were obtained from a medical examination. Participants kept a three-day food record; the average one-day intake over three days was used.	In men, vegetarians had significantly ↓ values than non-vegetarians for the following variables (mean values): BMI (21.4 vs. 23.2kg/m^2). DBP (71.7 vs. 83.3mmHg). SBP (118.3 vs. 129.4mmHg). Serum TG (119.6 vs. 228.8mg/dL). NS difference in TC. In women, vegetarians had significantly ↓ values than non-vegetarians for the following variables: SBP (111.7 vs. 118.4mmHg) Serum TG (85.9 vs. 133.7mg/dL). NS differences in TC, BMI or DBP. Differences in dietary intake between vegetarians and non-vegetarians men were also reported. For e.g., vegetarian men had significantly ↑ intakes of calcium, iron and dietary fiber and significantly ↓ vitamin B_{12} and cholesterol than non-vegetarian men.

Newby PK, Tucker KL et al, 2005 Study Design: Cross-Sectional Study Class: D Neutral quality	N=55,459 healthy women in Swedish Mammography Cohort after applying exclusions for missing or implausible values and history of angina, DM, CHD, cancer and stroke. Mean (SD) age: Four diet groups ranged from 51.1 (9.5) to 54.8 (9.5) years. Location: Sweden.	Cross-sectional study between 1987 and 1990. FFQ; self-reported height and weight. Women asked if they considered themselves: 1) Omnivores (consume all foods, N=54,257) 2) Semi-vegetarians (mostly lacto-vegetarian with some fish or eggs, N=960) 3) Lacto-vegetarians (no meat, poultry, fish or eggs, N=159) 4) Vegans (no meat, poultry, fish, eggs or dairy, N=83).	Prevalence of overweight and obesity (BMI≥25kg/m^2): 40% among omnivores 29% among semi-vegetarians and vegans 25% among lacto-vegetarians. In multivariate, adjusted linear regression analyses, semi-vegetarian (b= -1.13; 95% CI: -1.42, -0.84), lacto-vegetarian (b= -1.07; 95% CI: -1.81, -0.33) and vegan (b= -1.29; 95% CI: -2.33, -0.25) women had significantly ↓ BMI than omnivores. In multivariate, adjusted logistic regression analyses, semi-vegetarians (OR=0.52; 95% CI: 0.43, 0.62), lacto-vegetarians (OR=0.54; 95% CI: 0.35, 0.85) and vegans (OR=0.35; 95% CI: 0.18, 0.69) had a significantly ↓ risk of overweight or obesity than omnivores. Semi-vegetarians had a ↓ risk of obesity (OR=0.46; 95% CI: 0.31, 0.66) than omnivores.

Rosell M, Appleby P et al, 2006 Study Design: Prospective Cohort Study Class: B Positive quality	Participants in the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford). N=21,966 (5,373 men and 16,593 women) after applying exclusions for missing and extreme data, weight Δ >20kg, ≥70 years, suffered a stroke, heart attack, angina, malignant neoplasm or DM at baseline and if diet group was unclear. Mean (SD) age: 46.1 (11.5) years men; 43.1 (11.8) years women. Location. United Kingdom.	Prospective cohort; recruitment 1994 to 1999 and follow-up 2000 to 2003 (median duration 5.3 years, range 3.2-9.1 years). FFQ and self-reported height and weight. Asked four yes/no questions at baseline and follow-up: 1) Do you eat meat? 2) Do you eat fish? 3) Do you eat dairy products? 4) Do you eat eggs? Categorized into six groups based on responses: 1) Meat eaters (ate meat at both time points) 2) Fish eaters (ate fish, but not meat at both time points) 3) Vegetarians (did not eat meat or fish, but did eat diary or eggs at both time points) 4) Vegans (ate no animal products at either time point) 5) Reverted (Δ diet in one or more steps in the direction of vegan to vegetarian to fish-eater to meat-eater) 6) Converted (Δ their diet in one or more steps in the direction of meat-eater to fish-eater to vegetarian to vegan).	Mean (SD) annual weight gain was 389 (884)g in men and 398 (892)g in women. Differences in mean BMI between meat eaters, fish eaters, vegetarians and vegans at follow-up were similar to those seen at baseline. Compared with meat eaters, mean annual weight gain was significantly ↓ in vegans (284g in men and 303g in women, P<0.05 for both sexes) and fish-eaters (338g, P<0.001 for women only). Men and women classified as converted showed the smallest mean annual weight gain of 242 (95% CI: 133-351) and 301 (95% CI: 238-365)g, respectively. Highest weight gains were among men and women classified as reverted, but mean weight gains were NS different than weight gains in meat eaters.

Spencer EA, Appleby PN et al, 2003 Study Design: Cross-Sectional Study Class: D Neutral quality	Participants in the Oxford cohort of the European Prospective. Investigation into Cancer and Nutrition (EPIC-Oxford). N=57,498 men and women recruited. N=37,875 (8,871 men and 29,004 women, after applying exclusions due to ineligibility, recording error, missing or extreme values, or history of MI, stroke, angina, HBP, high cholesterol, DM, gallstones, polyps or cancer). Age: 20-97 years (median age=43 years men; 40 years women), primarily white. Location: United Kingdom.	Self-reported dietary intake using a validated semiquantitative FFQ. Asked four yes/no questions: 1) Do you eat meat? 2) Do you eat fish? 3) Do you eat dairy products? 4) Do you eat eggs? Categorized into four groups: Meat eaters (eat meat) Fish eaters (eat fish, but not meat) Vegetarians (do not eat meat or fish, but do eat diary or eggs) Vegans (eat no animal products). BMI calculated from self-reported weight to the nearest 0.1kg and height to the nearest cm. Questionnaires administered at baseline between 1993 and 1999.	Men (overall): Mean BMI=23.81kg/m^2; 8% underweight (BMI<20kg/m^2), 61% normal weight (BMI 20-24.9kg/m^2), 27% overweight (BMI 25-29.9kg/m^2) and 4% obese (BMI≥30kg/m^2). Women (overall): Mean BMI=23.05kg/m^2; 16% underweight, 63% normal weight, 17% overweight, and 5% obese. Age-adjusted mean BMI significantly different between four diet groups: Highest in the meat-eaters (24.41kg/m^2 in men, 23.52kg/m^2 in women) and ↓ in vegans (22.49kg/m^2 in men, 21.98kg/m^2 in women); similar and intermediate for fish-eaters (23.30kg/m^2 in men, 22.66kg/m^2 in women) and vegetarians (23.37kg/m^2 in men, 22.71 in women). Prevalence of obesity significantly ↓ in vegans than other diet groups; obesity rates significantly ↓ in vegetarians and fish-eaters than meat-eaters. After adjusting for all lifestyle and dietary factors included in this study, statistically significant differences in mean BMI between diet groups remained. High percent protein intake and low fiber intakes were the dietary factors most strongly associated with higher BMI between and within diet groups.

Teixeira Rde C, Molina Mdel C et al, 2007 Study Design: Prospective Cohort Study Class: B Neutral quality	N=67 vegetarians and 134 omnivores matched for age, gender, race, and socioeconomic status. Mean (SD) age: 47 (eight) years. Mostly white or of mixed race. Location: Brazil.	Vegetarians completed assessments in 2003-2004; omnivores were part of the MONICA Project/Vitoria conducted in 1999-2000; data collection methods were the same at both time points. Participants completed socioeconomic, health, eating habits and physical activity questionnaire during home visit. Blood drawn after 12-hour fast for determination of lipid profile and fasting plasma glucose. Vegetarians reported no meat intake in at least the last five years; omnivores reported that they did not refrain from eating meat. Mean (SD) duration of vegetarianism=19 (10) years: 73% lacto-ovo-vegetarians 3% lacto-vegetarians 10% pesco-vegetarians 14% strict vegetarians.	BMI significantly ↓ in vegetarians than omnivores, mean (SD)=22.6 (3.1) and 26.7 (5.1)kg/m^2, respectively. WHR significantly ↓ in vegetarians than omnivores, mean (SD)=0.82 (0.08) and 0.88 (0.09), respectively. Mean SBP and DBP significantly ↓ among vegetarians than omnivores, SBP: mean (SD)=108 (16) and 129 (19) mmHg, respectively; DBP: mean (SD)=71 (10) and 86 (13) mmHg, respectively. TC significantly ↓ among vegetarians than omnivores, mean (SD)=173 (36) and 225 (45) mg/dL, respectively. LDL-C significantly ↓ among vegetarians than omnivores, mean (SD)=106 (35) and 151 (43) mg/dL, respectively. TG significantly ↓ among vegetarians than omnivores, mean (SD)=113 (79) and 156 (127) mg/dL, respectively. HDL-C of vegetarians (mean (SD)=45.2 (10)) and omnivores (mean (SD)=45.7 (12)) did not differ significantly. Fasting plasma glucose significantly ↓ among vegetarians than omnivores, mean (SD)=82 (10) and 108 (37) mg/dL, respectively; those with levels above 125mg/dL= zero vegetarians and 14 omnivores. Total cardiovascular risk (using Framingham algorithm) significantly ↓ among vegetarians. Risk of CAD in ten years: Among vegetarians, 93% classified as low risk; 7% as medium risk. Among omnivores, 63% classified as low risk; 27% as medium risk; 10% as high risk.

Thorpe DL, Knutsen SF et al, 2008 Study Design: Prospective Cohort Study Class: B Positive quality	N=1,865 non-Hispanic White, Seventh-day Adventist women who were part of the Adventist Health Study. N=1,406 menopausal at baseline (including surgical menopause and early menopause) and 459 peri-menopausal. Location: United States.	Cohort study of women who completed two lifestyle surveys 25 years apart. In Adventist Health Study 1 (1976), participants completed a lifestyle survey. In Adventist Health Study 2 (2002), participants were recruited and 14 variables (e.g., name and date of birth) from the survey were used to match participants from AHS 1 to AHS 2. The survey included 65 semi-quantitative food items and data on fractures due to minor trauma at the wrist.	The 25-year period-incidence rate for wrist fracture was 3.7 per 1,000 person-years. Those at highest risk of fracture were those who never consume meat and were in the lowest category of vegetable protein intake. Among vegetarians, ↑ vegetable protein ↓ risk of fracture by 68% (HR=0.32, 95% CI 0.13-0.79) in the highest intake group. Among those with lowest vegetable PRO intake, ↑ meat intake ↓ risk of wrist fracture by 80% (HR=0.20, 95% CI 0.06-0.66) in the highest intake group. Six foods ↑ in protein were identified in the survey: Cheese, beans, nuts, meat analogues, vegetable protein analogues, meat and fruits and vegetables. Cheese and meat intake were protective against wrist fracture in a dose-response manner. Vegetable PRO food group intake did not show an independent effect on fracture risk. In vegetarians, risk of wrist fracture ↓ with frequency of consumption for each food ↑ in PRO. For non-vegetarians, risk tended to ↓ with meat consumption and ↑ with intake of each plant-based PRO food.

Wang et al 2008 Study Design: Cross-sectional Analysis of Retrospective Cohort Class: D Positive quality	N=1,865 adult male and female patients who underwent a routine exam at a regional teaching hospital. Specific age not specified, range of 21 years to 89 years. Exclusion criteria: Notable osteopathy, scoliosis or poor posture, degenerative Δ of the spinal cord and surgically or medically-induced menopause. Location: Taiwan.	Self-reported dietary preference as vegetarian (for at least five years) or non-vegetarian: 383 vegetarian men 464 non-vegetarian men 489 vegetarian women 529 non-vegetarian women. BMD measured using DXA at right femoral neck (men) and between L-2 and L-4 vertebrae (women). Classifications of osteopenia and osteoporosis based on WHO criteria. Dietary intake was not measured, but authors noted that the Taiwanese vegetarian diet typically contains large amounts of soybean products instead of milk, cheese and eggs.	BMD gradually ↓ with ↑ age in men and ↓ precipitously in women after the fifth decade, but there were no statistical differences in BMD observed between vegetarians and non-vegetarians of either sex. The proportion of participants with osteopenia and osteoporosis were also comparable between diet groups of both sexes.

Yen et al 2008 Study Design: Cross-sectional Study Class: D Positive quality	N=56 omnivores (28 children and one of their parents) and 42 vegetarians (21 children and one of their parents) were included in the analysis. Mean (SD) age and male/female: Omnivore parents: 35.9 (4.1) years, 9/19 Vegetarian parents: 34.8 (4.5) years, 4/17 Omnivore children: 5.0 (1.1) years, 15/13 Vegetarian children: 5.2 (1.5) years, 14/7. Location: Taiwan.	Anthropometric measurements were taken; BMI and weight-for-height index (WHI) were calculated. Nutrient intake was recorded using three-day dietary records. Fasting venous blood samples were obtained. Vegetarians: Among 21 preschool children 18 lacto-ovo-vegetarians Three ovo-vegetarians. Among 21 parents 16 lacto-ovo-vegetarians Two ovo-vegetarians One lacto-vegetarian Two vegans. Vegetarian parents and children had been following this diet practice for a mean of 8.8 and 4.5 years (range one to 35 and one to seven years, respectively).	No differences between omnivores and vegetarians in terms of height, weight, BMI, WHI and triceps skinfold thickness values in both parent and child groups. All mean hematologic and biochemical nutrient status indices were within the reference range; However, both vegetarian parents and children had significantly ↓ mean TC and serum ferritin concentrations than those of omnivorous parents and children: Parent TC for vegetarians and non-vegetarians, respectively: 159.4 vs. 187.2mg/dL. Child TC for vegetarians and non-vegetarians, respectively: 143.5 vs. 166.3mg/dL. Parent serum ferritin for vegetarians and non-vegetarians, respectively: 45.6 vs. 103.5ng/ml. Child serum ferritin for vegetarians and non-vegetarians, respectively: 26.6 vs. 38.7ng/ml. Omnivorous children had significantly ↑ HDL-C than vegetarian children (57.6 vs. 48.3mg/dL). Most subjects had nutrient intakes above the Taiwan DRI; however, vegetarians and omnivores in both parent and child groups had mean calcium consumption <75% of the Taiwan dietary intakes. Both omnivorous parents and their children had significantly ↑ fat and ↓ fiber intakes than vegetarian parents and children. Omnivorous children had significantly ↑ PRO and ↓ vitamin C intakes than vegetarian children, whereas omnivorous parents had significantly ↓ vitamin A and iron intakes than vegetarian parents.

Search plan and results

Inclusion criteria

- January 2000 to June 2009
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children two to 18 years; Adults: 19 and older
- *Populations:* Healthy, those with elevated chronic disease risk.

Exclusion criteria

- Medical treatment/therapy
- Diseased subjects (already diagnosed with CHD/CVD, hypertension, type 2 diabetes, osteoporosis, and/or osteopenia)
- Hospitalized patients
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: ("Vegetable Proteins"[Mesh] OR "Diet, Vegetarian"[Mesh] OR ("plant based" AND (diet OR diets OR food[mesh])))
  AND
  (Animal protein* OR “animal based” OR dairy OR meat[mesh] OR "Egg Proteins, Dietary"[Mesh] OR "Milk Proteins"[Mesh] OR "Fish Proteins"[Mesh])

Date searched: 06/04/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 230
- Total articles identified to review from electronic databases: 29
- Articles identified via handsearch or other means: 5
- Number of Primary Articles Identified: 18
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 18
- Number of Articles Reviewed but Excluded: 16

Included articles (References)

Primary Research Citations

2. Alewaeters K, Clarys P, Hebbelinck M, Deriemaeker P, Clarys JP.Cross-sectional analysis of BMI and some lifestyle variables in Flemish vegetarians compared with non-vegetarians. *Ergonomics.* 2005 Sep 15-Nov 15; 48 (11-14): 1, 433-1, 444. PMID: 16338711. (Hand search)
3. Appleby PN, Davey GK, Key TJ. Hypertension and blood pressure among meat eaters, fish eaters, vegetarians and vegans in EPIC-Oxford. *Public Health Nutr*.

2002 Oct; 5 (5): 645-654. PMID: 12372158. (Hand search)
4. Appleby P, Roddam A, Allen N, Key T. Comparative fracture risk in vegetarians and non-vegetarians in EPIC-Oxford. *Eur J Clin Nutr*. 2007 Dec; 61 (12): 1, 400-1, 406. Epub 2007 Feb 7. PMID: 17299475.
5. Baines S, Powers J, Brown WJ. How does the health and well-being of young Australian vegetarian and semi-vegetarian women compare with non-vegetarians? *Public Health Nutr.* 2007 May; 10 (5): 436-442. PMID: 17411462.
6. Chen CW, Lin YL, Lin TK, Lin CT, ChenBC, Lin CL. Total cardiovascular risk profile of Taiwanese vegetarians. *Eur J Clin Nutr*. 2008 Jan; 62 (1): 138-144. Epub 2007 Mar 14. PMID: 17356561.
7. Dos Santos Silva I, Mangtani P, McCormack V, Bhakta D, Sevak L, McMichael AJ. Lifelong vegetarianism and risk of breast cancer: A population-based case-control study among South Asian migrant women living in England. *Int J Cancer*. 2002 May 10; 99 (2): 238-244. PMID: 11979439.
8. Grant R, Bilgin A, Zeuschner C, Guy T, Pearce R, Hokin B, Ashton J. The relative impact of a vegetable-rich diet on key markers of health in a cohort of Australian adolescents. *Asia Pac J Clin Nutr.* 2008; 17 (1): 107-115. PMID: 18364335.
9. Hung CJ, Huang PC, Li YH, Lu SC, Ho LT, Chou HF. Taiwanese vegetarians have higher insulin sensitivity than omnivores. *Br J Nutr*. 2006 Jan; 95 (1): 129-135. PMID: 16441925 [PubMed - indexed for MEDLINE] (Hand search)
10. Key TJ, Appleby PN, Spencer EA, Travis RC, Roddam AW, Allen NE. Cancer incidence in vegetarians: Results from the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford). *Am J Clin Nutr*. 2009 May; 89 (5): 1, 620S-1, 626S. Epub 2009 Mar 11. PMID: 19279082.
11. Key TJ, Appleby PN, Spencer EA, Travis RC, Roddam AW, Allen NE. Mortality in British vegetarians: Results from the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford). *Am J Clin Nutr*. 2009 May; 89 (5): 1, 613S-1, 619S. Epub 2009 Mar 18. PMID: 19297458. (Hand search)
12. Newby PK, Tucker KL, Wolk A. Risk of overweight and obesity among semi vegetarian, lactovegetarian and vegan women. *Am J Clin Nutr.* 2005 Jun; 81 (6): 1, 267-1, 274. PMID: 15941875.
13. Nakamoto K, Watanabe S, Kudo H, Tanaka A. Nutritional characteristics of middle-aged Japanese vegetarians. *J Atheroscler Thromb*. 2008 Jun; 15 (3): 122-129. PMID: 18603818.
14. Rosell M, Appleby P, Spencer E, Key T. Weight gain over five years in 21, 966 meat-eating, fish-eating, vegetarian and vegan men and women in EPIC-Oxford. *Int J Obes* (Lond). 2006 Sep; 30 (9): 1, 389-1, 396. Epub 2006 Mar 14. PMID: 16534521.
15. Spencer EA, Appleby PN, Davey GK, Key TJ. Diet and body mass index in 38000 EPIC-Oxford meat-eaters, fish-eaters, vegetarians and vegans. *Int J Obes Relat Metab Disord*. 2003 Jun; 27 (6): 728-734. PMID: 12833118. (Hand search)
16. Teixeira Rde C, Molina Mdel C, Zandonade E, Mill JG. Cardiovascular risk in vegetarians and omnivores: A comparative study. *Arq Bras Cardiol*. 2007 Oct; 89 (4): 237-244. English, Portuguese. PMID: 17992380.
17. Thorpe DL, Knutsen SF, Beeson WL, Rajaram S, Fraser GE. Effects of meat consumption and vegetarian diet on risk of wrist fracture over 25 years in a

cohort of peri- and postmenopausal women. *Public Health Nutr*. 2008 Jun; 11 (6): 564-572. Epub 2007 Aug 9. PMID: 17686206.

18. Wang YF, Chiu JS, Chuang MH, Chiu JE, Lin CL. Bone mineral density of vegetarian and non-vegetarian adults in Taiwan. *Asia Pac J Clin Nutr.* 2008; 17 (1): 101-106. PMID: 18364334.
19. Yen CE, Yen CH, Huang MC, Cheng CH, Huang YC. Dietary intake and nutritional status of vegetarian and omnivorous preschool children and their parents in Taiwan. *Nutr Res*. 2008 Jul; 28 (7): 430-436. PMID: 19083442.

Excluded articles

Article	Reason for Exclusion
Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians and vegans. *Cancer Epidemiol Biomarkers Prev.* 2002 Nov; 11 (11): 1, 441-1, 448. PMID: 12433724.	Does not include body weight or incidence of disease in analyses.
Barr SI, Chapman GE. Perceptions and practices of self-defined current vegetarian, former vegetarian and non-vegetarian women. *J Am Diet Assoc*. 2002 Mar; 102 (3): 354-360. PMID: 11902368.	Does not include body weight or incidence of disease in analyses.
Bernstein AM, Treyzon L, Li Z. Are high-protein, vegetable-based diets safe for kidney function? A review of the literature. *J Am Diet Assoc*. 2007 Apr; 107 (4): 644-650. Review. PMID: 17383270.	Study design is narrative review.
Greene-Finestone LS, Campbell MK, Evers SE, Gutmanis IA. Attitudes and health behaviors of young adolescent omnivores and vegetarians: A school-based study. *Appetite.* 2008 Jul; 51 (1): 104-110. Epub 2007 Dec 28. PMID: 18249472.	Does not include body weight or incidence of disease in analyses.
Hossain MI, Islam MM, Wahed MA, Khatun M, Kabir I. Lentil-based high protein diet is comparable to animal-based diet in respect to nitrogen absorption and nitrogen balance in malnourished children recovering from shigellosis. *Asia Pac J Clin Nutr.* 2009; 18 (1): 8-14. PMID: 19329389.	Participants recovering from shigellosis (nutritional rehabilitation).
Jeejeebhoy KN. Vegetable proteins: Are they nutritionally equivalent to animal protein. *Eur J Gastroenterol Hepatol*. 2000 Jan; 12 (1): 1-2. PMID: 10656201.	Does not include body weight or incidence of disease in analyses.
Jenkins DJ, Kendall CW, Faulkner DA, Kemp T, Marchie A, Nguyen TH, Wong JM, de Souza R, Emam A, Vidgen E, Trautwein EA, Lapsley KG, Josse RG, Leiter LA, Singer W. Long-term effects of a plant-based dietary portfolio of cholesterol-lowering foods on blood pressure. *Eur J Clin Nutr*. 2008 Jun; 62 (6): 781-788. Epub 2007 Apr 25. PMID: 17457340.	Does not include comparison of vegetarian and non-vegetarian dietary patterns in analyses.
Key TJ, Appleby PN, Rosell MS. Health effects of vegetarian and vegan diets. *Proc Nutr Soc*. 2006 Feb; 65 (1): 35-41. Review. PMID: 16441942.	Study design is narrative review.

Kohlenberg-Mueller K, Raschka L. Calcium balance in young adults on a vegan and lactovegetarian diet. *J Bone Miner Metab.* 2003; 21 (1): 28-33. PMID: 12491091.	Sample size less than inclusion criteria.
Krajcovicova-Kudlackova M, Babinska K, Valachovicova M. Health benefits and risks of plant proteins. *Bratisl Lek Listy*. 2005; 106 (6-7): 231-234. Review. PMID: 16201743.	Study design is narrative review.
Lanou AJ. Should dairy be recommended as part of a healthy vegetarian diet? Counterpoint. *Am J Clin Nutr*. 2009 May; 89 (5): 1, 638S-1, 642S. Epub 2009 Mar 25. PMID: 19321571.	Study design is narrative review.
Merrill RM, Aldana SG. Consequences of a plant-based diet with low dairy consumption on intake of bone-relevant nutrients. *J Womens Health* (Larchmt). 2009 May; 18 (5): 691-698. PMID: 19368508.	Does not include comparison of vegetarian and non-vegetarian dietary patterns in analyses.
Perry CL, McGuire MT, Neumark-Sztainer D, Story M. Adolescent vegetarians: How well do their dietary patterns meet the healthy people 2010 objectives? *Arch Pediatr Adolesc Med.* 2002 May; 156 (5): 431-437. PMID: 11980547.	Does not include body weight or incidence of disease in analyses.
Walkowiak J, Wadolowska L, Szaflarska-Poplawska A, Lisowska A, Bugajewska A, Przyslawski J. The elimination of meat from the diet selectively decreases pancreatic elastase secretion. *Br J Nutr.* 2007 Jul; 98 (1): 154-158. Epub 2007 Mar 19. PMID: 17367570.	Does not include comparison of vegetarian and non-vegetarian dietary patterns in analyses.
Weaver CM. Should dairy be recommended as part of a healthy vegetarian diet? Point. *Am J Clin Nutr*. 2009 May; 89 (5): 1, 634S-1, 637S. Epub 2009 Mar 25. *Review.* PMID: 19321565.	Study design is narrative review.
Wells AM, Haub MD, Fluckey J, Williams DK, Chernoff R, Campbell WW. Comparisons of vegetarian and beef-containing diets on hematological indexes and iron stores during a period of resistive training in older men. *J Am Diet Assoc.* 2003 May; 103 (5): 594-601. PMID: 12728219; PMCID: PMC2495081.	Does not include body weight or incidence of disease in analyses.

CHAPTER 13. MILK AND MILK PRODUCTS – BODY WEIGHT

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF MILK AND MILK PRODUCTS AND BODY WEIGHT?

Conclusion statement

Strong evidence demonstrates that intake of milk and milk products provide no unique role in weight control.

Grade

Strong

Evidence summary overview

The Committee reviewed 18 studies conducted since 2004 that examined the link between the intake of milk and milk products and body weight and concluded that evidence supporting the hypothesis of a relationship between intake of milk and milk products and decreased body weight is not convincing. This conclusion is based on one systematic review (Lanou, 2008), one randomized controlled trial (RCT) (Bowen, 2005), four prospective cohort studies (Rajpathak, 2006; Rosell, 2006; Snijder, 2008; Vergnaud, 2008) and eight cross-sectional studies (Azadbakht, 2005; Beydoun, 2008; Brooks, 2006; Houston, 2008; Marques-Vidal, 2006; Mirmirin, 2005; Murakami, 2006; O'Neil 2009). The Committee also reviewed three studies that looked at energy intake as an outcome (Dove, 2009; Harper, 2007; Hollis, 2007) and one study (Olsen, 2007) that addressed pregnancy.

Lanou et al (2008) reviewed the body of evidence on the effect of dairy product or calcium intake, with or without energy restriction, on body weight or adiposity. Of the 49 randomized clinical trials reviewed, 42 found no effect on weight of dairy or calcium consumption and only four trials showed a potential effect of dairy products or calcium on weight loss. Of the 16 clinical trials, 15 showed no difference in body fat change between consumers of high and low levels of dairy or calcium. One study found greater fat loss among high-dairy consumers compared to low-dairy consumers. Overall, their review does not support a connection between dairy or calcium consumption and weight or fat loss.

In the Bowen et al (2005) RCT, the effects on weight, body composition, metabolic parameters and risk markers of two isocaloric, energy-restricted high-protein (PRO) diets that differed in dietary calcium and PRO source on weight loss and body composition in healthy, overweight adults were compared. The authors concluded that weight loss following energy-restricted, high-PRO diets is not affected by dietary calcium or PRO source.

The following four prospective cohort studies did not strongly support the hypothesis that increasing milk and milk products would result in a decrease in weight. Rajpathak et al (2006) evaluated the association between calcium and dairy intakes and 12-year weight change among men in the US. Their results indicate that increasing calcium or dairy consumption is not associated with lower long-term weight gain in men. Rosell et al (2006) examined the association between changes in dairy product consumption and self-reported weight change over nine years among women. They concluded that

the association between the intake of dairy products and weight gain differed according to the type of dairy product and the body weight status at baseline. Snijder et al (2008) investigated the association between dairy consumption and 6.4-year changes in weight and metabolic disturbances in an elderly Dutch population. They concluded that higher dairy consumption does not protect against weight gain and the development of metabolic disturbances over time. Vergnaud et al (2008) investigated the relationship between dairy consumption and calcium intake with six-year changes in body weight and waist circumference (WC) in a French population. The authors concluded that sex, overweight status at baseline and type of dairy product influences the associations between dairy product consumption and anthropometric changes. Eight cross-sectional studies (Azadbakht, 2005; Beydoun, 2008; Brooks, 2006; Houston, 2008; Marques-Vidal, 2006; Mirmirin, 2005; Murkami, 2006; O'Neil, 2009) were reviewed, and were more likely to support that calcium and dairy consumption was related to lower BMI.

Other studies included in the review measured whether consumption of milk or milk products was related to energy intake as an outcome. Dove et al (2009) concluded that consumption of skim milk, in comparison with a fruit drink, leads to increased perceptions of satiety and to decreased energy intake at a subsequent meal. Harper et al (2007) conducted a randomized cross-over design study to compare the effect on appetite and energy intake of consuming either a sugar-sweetened beverage (cola) or chocolate milk drink. The authors concluded that consuming chocolate milk increased subjective ratings of satiety and fullness compared with cola and decreased hunger and later consumption of food. However, this enhanced satiety did not translate into differences in ad libitum energy intake. Hollis and Mattes (2007) assessed the effect of daily intake of one or three portions of dairy foods on energy intake and appetite. The authors concluded that increasing dairy consumption from one to three portions each day led to increased energy intake. Thus, dairy foods may have some benefit for satiety when compared to fruit drinks, but increased consumption of any extra calories (vs. substitution), including dairy products, will lead to increased energy intake.

Olsen et al (2007) examined whether milk consumption during pregnancy is associated with greater infant size at birth in the Danish National Birth Cohort. Milk consumption was inversely associated with the risk of small-for-gestational age birth and directly with both large-for-gestational age birth and mean birth weight.

Evidence summary paragraphs

Systematic Review

Lanou et al, 2008 (neutral quality) performed a systematic review to evaluate the body of evidence on the effect of dairy product or calcium intake, with or without energy restriction, on body weight or adiposity. Forty-nine studies were identified using a MEDLINE search (keywords: milk, dairy, calcium, weight, body mass index (BMI), body fat) of clinical trials published between 1966 and 2007. Eighteen studies examined the effect of dairy products (seven studies; 330ml to four servings a day; three months to two years in length; N=28 to 757) or calcium (11 studies; 300 to 1,200mg calcium a day; six months to three years in length; N=84 to 162) in the absence of energy restriction in children and adolescents, and 20 studies examined the effect of dairy products (10 studies; 12 weeks to three years in length; N=34 to 204) or calcium (10 studies; 1,000 to 1,200mg calcium a day; four months to seven

years in length; N=37 to 36,282) in the absence of energy restriction in adults. Of these 38 studies, 37 showed no effect of dairy product or calcium intake in the absence of energy restriction on weight in adults or children. Eleven studies examined the effect of dairy products (500 to 2,400mg calcium a day or two to four servings a day; 12 to 48 weeks in length; N=29 to 72) or calcium (1,200mg to 1g calcium a day; one month to 25 weeks in length; N=62 to 100) with energy restriction in adults. Of these studies, seven found no effect and four found a significant positive association between dairy or calcium and weight loss. In summary, of the 49 RCTs reviewed, 42 found no effect on weight of dairy or calcium consumption, and only four trials showed a potential effect of dairy products or calcium on weight loss. In addition, 15 of 16 clinical trials showed no difference in body fat change between high and low consumers of dairy or calcium, while one study found greater fat loss among high-dairy consumers compared to low-dairy consumers. The authors conclude that the current evidence does not support the hypothesis that dairy or calcium consumption results in weight or fat loss.

Randomized Controlled Trial

Bowen et al, 2005 (positive quality) conducted an RCT in Australia to compare the effects on weight, body composition, metabolic parameters and risk markers of two isocaloric, energy-restricted high-PRO diets that differ in dietary calcium and PRO source on weight loss and body composition in healthy, overweight adults (N=50, 30 women and 20 men, ages 25 to 64 years). The intervention diets were a high dairy PRO/high-calcium (DP, 2,400mg calcium a day) diet and a high mixed PRO/moderate calcium (MP, 500mg calcium per day) diet followed for a 12-week energy restriction phase, followed by a four-week energy balance phase. After 16 weeks, subjects showed significant reductions in total weight (-9.7±3.8kg), fat mass (-8.3±0.4kg) and lean mass (-1.6±0.3kg), but there were no significant (NS) differences between the two diet groups. The authors concluded that weight loss following energy-restricted, high-protein diets is not affected by dietary calcium or PRO source.

Prospective Cohort Studies

Rajpathak et al, 2006 (positive quality) used data from a prospective cohort study (Health Professionals Follow-up Study) to evaluate the association between calcium and dairy intakes and 12-year weight change in US men. For this study, dietary intake during the preceding year was assessed in 1986 obtained using a food-frequency questionnaire (FFQ), which also collected information on the use of calcium and multivitamin supplements. Weight change follow-up was calculated using self-reported body weights given in 1986 and 1998. Data from 19,615 men (ages 40 to 75 years; mean BMI=25.2kg/m^2) was included in the final analysis. Results of a multivariate analysis adjusted for potential confounders showed that neither baseline nor change in total calcium intake was significantly associated with weight change. There was NS association between weight and dietary, dairy or supplemental calcium when each calcium source was evaluated separately. Men with the largest increase in total dairy intake gained slightly more weight (3.14±0.11kg) than did men with the largest decrease in dairy intake (2.57±0.13kg) ($P<0.001$). However, this association was primarily due to an increase in high-fat dairy intake ($P<0.001$), as low-fat dairy intake was not significantly associated with weight change ($P=0.19$). These results do not support the hypothesis that increasing calcium or dairy consumption is associated with lower long-term weight gain in men.

Rosell et al, 2006 (positive-quality), a prospective cohort study conducted in Sweden (Swedish Mammography Cohort), examined the association between changes in dairy product consumption and self-reported weight change over nine years. In 1987, dietary intake was measured with a 67-item FFQ, and in 1997 it was measured with an extended 96-item FFQ. 38,984 women completed the follow-up questionnaire; after application of exclusion criteria, 19,352 women (mean age 46.3±4.5 years at baseline) were included in the analysis. Women were divided into four dairy product consumption groups: 1) less than one serving a day, no change at follow-up; 2) less than one serving a day, increased to more than one serving a day at follow-up; 3) more than one serving a day, no change at follow-up; and 4) more than one serving a day, decreased to less than one serving a day at follow-up. Mean BMI at baseline was 23.7±3.5kg/m^2, and mean weight gain in the cohort was 0.33±0.63kg per year. Consistent consumption of more than one serving of dairy products per day was inversely associated with weight gain; odds ratios (OR) for consumption of less than one serving per day of whole milk and sour milk was 0.85 (95% CI: 0.73, 0.99) and of cheese was 0.70 (95% CI: 0.59, 0.84), while NS associations were seen for the other three intake groups. The authors concluded that the association between the intake of dairy products and weight gain differed according to the type of dairy product and to the body weight status at baseline.

Snijder et al, 2008 (positive quality), a prospective cohort study conducted in the Netherlands (Hoorn Study), investigated the association between dairy consumption and 6.4-year changes in weight and metabolic disturbances, based on data from a population-based cohort of white men and women aged 50 to 75 years. Average food intake was measured at baseline using a 92-item semi-quantitative FFQ. At baseline and follow-up, participants underwent an extensive physical examination and a blood sample was drawn for biochemical analyses of fasting glucose, post-load glucose, high-density lipoprotein (HDL-C) and low density lipoprotein cholesterol (LDL-C) and triglycerides (TG). During the physical examination, weight, waist circumference (WC) and blood pressure (BP) were measured. A total of 1,124 participants were included in the analysis. Linear regression analyses, using the continuous dairy variable as independent variable and the change in body composition or metabolic variables as dependent variables, revealed that baseline dairy composition was not associated with changes in body composition or metabolic variables, neither after adjustment for potential confounders. In subjects with BMI less than 25kg/m^2, higher dairy consumption was significantly associated with an increase in BMI, waist and weight (data not shown). The authors concluded that their results do not support the hypothesis that a higher dairy consumption protects against weight gain and development of metabolic disturbances in a Dutch elderly population.

Vergnaud et al, 2008 (positive quality), a prospective cohort study conducted in France, investigated the relationship between dairy consumption and calcium intake with six-year changes in body weight and WC. At total of 13,017 subjects were recruited in 1994 and 1995 to participate in the Supplementation en Vitamines et Mineraux Antioxidants (SU.VI.MAX) Study, an RCT of daily antioxidant supplementation. A total of 2,267 subjects (1,022 women, mean age 50.8±4.3 years, 1,245 men, mean age 51.5±4.44 years) were included in the analysis. Anthropometric measurements were taken at the first (1995 to 1996) and last (2001 to 2002) clinical examinations, and at least six 24-hour dietary records during the first 18 months were

evaluated. In overweight men only, six-year changes in weight and WC were inversely associated with the dairy product consumption, especially milk (P=0.02 for both weight and WC changes) and yogurt (P=0.01 for weight change, P=0.03 for WC change). Positive relations were found between milk consumption and WC change in overweight women, and between yogurt consumption and weight change in normal-weight women. The authors concluded that the associations between dairy product consumption and anthropometric changes differed according to sex, overweight status at baseline and type of dairy product.

Cross-Sectional Studies

Azadbakht et al, 2005 (positive quality), a cross-sectional study conducted in Tehran, Iran, ascertained the relation between dairy consumption and metabolic syndrome in a population-based sample of adults. A representative sample of 1,476 participants was randomly selected from the Tehran Lipid and Glucose Study, including 861 subjects aged 18 to 74 years. After application of exclusion criteria, 827 subjects (357 men, 470 women) were included in the analysis. Dairy consumption was assessed through a 168-item semi-quantitative FFQ, and subjects were categorized into quartiles of intake. Measurements relevant to the diagnosis of the metabolic syndrome were taken, such as height, weight, WC, BP and fasting blood samples for glucose and lipid concentrations. Mean consumption of milk, yogurt and cheese was 0.7±0.2, 1.06±0.6, and 0.9±0.3 servings per day, respectively; butter and ice cream were not included in the analysis due to their high fat content. Participants in the fourth quartile of dairy intake (more than 3.1 servings per day) had a lower BMI than did those in the three lower quartiles (P<0.01). Subjects in the highest quartile of dairy consumption had lower odds of having enlarged WC (OR by quartile: 1, 0.89, 0.74, 0.63, P for trend <0.001). These values became weaker after adjustment for calcium intake. The authors concluded that they found evidence of an inverse relation between dairy consumption and metabolic syndrome.

Beydoun et al, 2008 (positive quality), a cross-sectional analysis of merged National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2004 in the US, assessed the association between consumption of dairy and related nutrients and obesity, central obesity and the metabolic syndrome. Out of 17,061 subjects over age 18 years (8,970 women and 8,091 men) with complete demographic data, 4,519 subjects had complete data on dietary intake (assessed from 24-hour recall data) and metabolic outcomes, such as weight, height, WC, BP and laboratory values (fasting blood glucose (FBG), triacylglycerol (TG) stores and HDL-C). Sample sizes ranged from 4,519 for metabolic syndrome to 14,618 for obesity. Multivariate logistic regression models suggested that there was an overall net increase of 5% in prevalence of central obesity for each dairy serving among men (P<0.10). Whole milk was weakly and negatively associated with the prevalence of central obesity, whereas low-fat milk had the opposite effect (P<0.05 for both). Yogurt was associated with reduced BMI and waisWC (P<0.05 for both); in contrast, cheese was positively associated with BMI and WC (P<0.05 for both). In addition, large ethnic disparities existed for intakes of dairy and calcium, and for all metabolic outcomes, leading the authors to conclude that the health effects of dairy products and related nutrients are complex and may not be uniform across the population.

Brooks et al, 2006 (positive quality), a cross-sectional analysis of data from the Bogalusa Heart Study in the US, examined the association between intake of calcium

and dairy products and overweight and obesity in a biracial sample of 1,306 young adults (374 white males, 578 white females, 131 black males, 223 black females, mean age 29.7 years). Calcium intake and low-fat dairy product consumption was assessed through the Youth and Adolescent Questionnaire, a self-administered, semi-quantitative FFQ, and overweight status was measured through BMI, waist-hip ratio (WHR) and WC. Intakes of dairy products were significantly higher among blacks than whites (P<0.05), and females had significantly lower intakes of dairy products than males (P<0.05). No significant associations were found between dairy product consumption, calcium intake and overweight, defined by BMI or WC; however, in white males, there was a significant inverse association between calcium intake, low-fat dairy product consumption and WHR.

Houston et al, 2008 (positive quality), a cross-sectional study conducted in the US, examined the association between the frequency of cheese consumption and several cardiovascular risk factors, including measures of body fat, blood lipids, BP and blood glucose, using data from NHANES III. A total of 10,872 participants, aged 25 to 75 years, had complete data and were included in the analysis. Cheese consumption (combined full and low-fat) was assessed through FFQ asking one question about cheese and two questions about the consumption of foods containing large amounts of cheese. Body mass index and WC were significantly higher among men (P<0.05), but not among women, in the highest cheese consumption category (30 + servings a month) compared to non-consumers. More frequent cheese consumption was associated with a slightly worse body composition in men; however, there appeared to be less of an association between consumption and body composition in women.

Marques-Vidal et al, 2006 (neutral quality), a cross-sectional study conducted in Portugal, assessed the relationship between milk intake and BMI status using a representative population sample from the Portuguese National Health Interview Survey 1998 to 1999 database. Average daily milk intake was calculated by a FFQ that also assessed the average volume of one serving; height and weight were self-reported. A total of 37,513 subjects were included in the analysis (17,771 males, mean age 47.8 years and 19,742 females, mean age 50.3 years). In men, milk intake was inversely related to BMI (R=-0.10, P<0.001), whereas the relationship in women was weaker (R=-0.06, P<0.001). After adjustment for confounding variables, milk intake decreased with increasing BMI (P<0.001). The authors concluded that increased milk intake and possible calcium consumption is slightly but significantly inversely related to BMI.

Mirmirin et al, 2005 (neutral quality) analyzed data from a cross-sectional study to assess the relationship between consumption of dairy products and BMI in Tehranian adults. Daily dairy consumption was determined using 24-hour dietary recalls and a FFQ. Subjects were stratified into four quartiles based on dairy intake: 1) Less than 1.6 servings a day; 2) 1.6 to less than 2.2 servings a day; 3) 2.2 to less than three servings a day; and 4) more than three servings a day. The sample included 462 healthy subjects, 223 men (38±15 years; 24.8±4.6kg/m^2) and 239 women (32±13 years; 25.3±5.3kg/m^2). Mean consumption of dairy products was 3.7±1.0 and 2.9±1.2 servings per day in men and women, respectively. There was a significant inverse correlation between the servings of dairy consumed per day and BMI after controlling for age, physical activity, energy, carbohydrate (CHO), dietary fiber, PRO and fat intake (R=-0.38, P<0.05). Also, after adjustment for potential confounding variables,

men and women in the top quartile of dairy consumption had lower chances for being overweight (OR=0.78; 95% CI=0.43, 0.92 for men and OR=0.89; 95% CI=0.53, 0.95 for women) and obese (OR=0.73; 95% CI=0.40, 0.83 for men and OR=0.69; 95% CI=0.34, 0.80 for women) compared to those in the first quartile. These results suggest an inverse relationship between dairy consumption and BMI.

Murakami et al, 2006 (positive quality), analyzed data from a cross-sectional study to examine the associations between dairy product and calcium intake and BMI in young Japanese women. Dietary habits during the previous month were assessed by using a validated, self-administered diet history questionnaire (DHQ). Body weight and height were self-reported as part of the DHQ. Analyses included 1,905 women, ages 18 to 20 years, with a mean BMI of 20.8±2.6kg/m^2. Mean estimated intakes were 268±93mg per 1,000kcal for calcium and 80±63g per 1,000kcal for dairy products. There were NS associations between BMI and calcium or dairy product intake in this study. Therefore, intakes of calcium and dairy products may not necessarily be associated with BMI among young Japanese women. However, the population used in this study was relatively lean with a relatively low intake of calcium and dairy products.

O'Neil et al, 2009 (positive quality) used cross-sectional data to assess the association of milk and sweetened beverage consumption with weight, nutrient intake and dietary adequacy in a multiethnic population of Head Start mothers in the US. Dietary intake was assessed via three 24-hour dietary recalls, and nutrient intakes from foods and beverages were determined from the averages of the three days of dietary recalls. Height and weight was measured twice on each participant and BMI was calculated from these values. Subjects included 609 women (30.0±0.2 years; 30.8±0.3kg/m^2), 58% had completed high school or less and 46% were married. 33% were Hispanic, 43% were African American and 24% were white. Subjects were divided into groups based on beverage consumption: 1) Low milk, highly sweetened beverage (N=170); 2) High milk, low sweetened beverage (N=170); 3) Low milk, low sweetened beverage (N=134); 4) High milk, highly sweetened beverage (N=135). Mean BMI did not differ between the four beverage consumption groups. However, women in the high milk, low sweetened beverage group had higher mean intakes of vitamins A, D, and B_6; riboflavin; thiamin; folate; phosphorus; calcium; iron; magnesium; and potassium (P<0.0125) when compared with the other beverage consumption groups. Thus, Mean Adequacy Ratio (a measure of overall dietary adequacy) was highest in the high milk, low sweetened beverage (71.8±0.8) and lowest in the low milk, highly sweetened beverage (58.4±0.8) consumption groups (P<0.0125). In a multiethnic, low-income population of women, differing patterns of milk and sweetened beverage consumption were not associated with weight status.

Energy Intake as Outcome

Dove et al, 2009 (positive quality), a randomized study with crossover design conducted in Australia, investigated the effects of drinking skim milk in comparison with a fruit drink at breakfast on self-reported post-meal satiety and energy intake at lunch. Participants consumed 600ml (1,062kJ each) of either skim milk or fruit drink with a fixed-energy breakfast (1,923kJ). Participants completed visual analog scales (VAS) ratings of their satiety before breakfast (T=0), throughout the morning (T=30, 60, 120, 180, 210 and 240 minutes), and immediately after lunch (T=270 minutes). Lunch was provided four hours after breakfast (T=240 minutes). Thirty four subjects (13 men, 21 women; age 55.1±12.5 years; mean BMI=32.4±3.4kg/m^2) participated. Participants

consumed significantly less energy at lunch after consuming skim milk (mean: 2,432kJ; 95% CI: 2,160, 2,704kJ) than after consuming the fruit drink (mean: 2,658kJ; 95% CI: 2,386, 2,930kJ), with a mean difference of approximately 8.5% (P<0.05). Ratings of satiety were higher throughout the morning after consumption of skim milk than after consumption of the fruit drink (P<0.05) with the differences becoming larger over the four hours (P<0.05). The authors concluded that consumption of skim milk, in comparison with a fruit drink, leads to increased perceptions of satiety and to decreased energy intake at a subsequent meal.

Harper et al, 2007 (positive quality) conducted a randomized cross-over design study to compare the effect on appetite and energy intake of consuming either a sugar-sweetened beverage (cola) or chocolate milk drink. This study was conducted in Denmark. The test drinks were 500ml cola or chocolate milk (both 900kJ), and were ingested 30 minutes before an ad libitum lunch. Visual analogue scales were used to record subjective appetite ratings every 30 minutes on each of two test days. Energy intake at lunch was calculated using weighed food intakes. Subjects were 22 men with a mean age of 23±1.8 years, and a mean BMI of 22.2±1.5kg/m^2. Satiety and fullness ratings were significantly greater (P=0.0007, P=0.0004, respectively) 30 minutes after chocolate milk than after cola. Ratings of prospective consumption and hunger were significantly greater after cola than after chocolate milk, both immediately after preload intake (P=0.008, P=0.01, respectively) and 30 minutes afterwards (P=0.004, P=0.01, respectively). There was NS difference (P=0.42) in ad libitum lunch intake after ingestion of chocolate milk (3,145±1,268kJ) compared with cola (3,286±1,346kJ). The authors concluded that ingestion of chocolate milk increased subjective ratings of satiety and fullness compared with cola and decreased hunger and prospective consumption, but that this enhanced satiety did not translate into differences in ad libitum energy intake.

Hollis and Mattes, 2007 (neutral quality), a non-randomized crossover trial conducted in the US, assessed the effect of daily intake of one or three portions of dairy foods on energy intake and appetite. Subjects had seven days in the first treatment period of low or high dairy intake, a washout period of seven days and then seven days of the other treatment option; in the low-dairy phase, subjects could choose white or chocolate milk, yogurt or hard cheese, while in the high-dairy phase, subjects were required to have one serving of milk, one of yogurt, and one of hard cheese. Handheld devices were used to record appetite. Sixty subjects were enrolled in the study and 58 completed (28 males, 30 females, aged 18 to 50 years). Overall energy intake increased by 209kcal per day in the high-dairy treatment period [F (1, 52) = 28.088, P<0.05], but there were NS differences noted for hunger, satiety, desire to eat or thoughts of food in any treatment groups. The authors concluded that increasing dairy consumption from one to three portions each day led to increased energy intake.

Pregnancy

Olsen et al, 2007 (neutral quality), a prospective cohort study, conducted in Denmark, examined whether milk consumption during pregnancy is associated with greater infant size at birth in the Danish National Birth Cohort (1996 to 2002). Dietary intake was assessed through FFQs during one month of mid-pregnancy, and birth outcomes were ascertained through registry linkages. A total of 70,187 mothers completed the FFQ; after application of exclusion criteria, 50,117 mother-infant pairs were included in the analysis (mean age of mothers = 29.1±4.3 years). Mean consumption of milk was

3.1±2.0 glasses per day. Milk consumption was inversely associated with the risk of small-for-gestational age (SGA) birth and directly with both large-for-gestational age (LGA) birth and mean birth weight (P<0.001). Comparing women drinking more than six glasses of milk per day with those not drinking milk, the OR for SGA was 0.51 (95% CI: 0.39, 0.65) and for LGA was 1.59 (95% CI: 1.16, 2.16). The increment in mean birth weight was 108g (95% CI: 74, 143).

Overview table

Author, Year, Study Design, Class, Rating	Participants	Description of Study Design	Outcomes
Azadbakht L, Mirmiran P et al, 2005 Study Design: Cross-Sectional Study Class: D Positive quality	N=1,476 participants (representative sample) randomly selected from the Tehran Lipid and Glucose Study, including 861 subjects aged 18 to 74 years. Final N=827 (357 men, 470 women) after application of exclusion criteria. Location: Tehran, Iran.	Cross-sectional study that ascertained the relation between dairy consumption and metabolic syndrome in a population-based sample of adults. Dairy consumption was assessed through a 168-item semi-quantitative FFQ and subjects were categorized into quartiles of intake. Measurements relevant to the diagnosis of metabolic syndrome were taken, such as height, weight, WC, BP and fasting blood samples for glucose and lipid concentrations.	Mean consumption of milk, yogurt and cheese was 0.7±0.2, 1.06±0.6, and 0.9±0.3 servings per day, respectively (butter and ice cream not included in analysis due to ↑ fat content). Participants in the fourth quartile of dairy intake (more than 3.1 servings per day) had a lower BMI than did those in the three lower quartiles (P<0.01). Subjects in the highest quartile of dairy consumption had ↓ odds of having enlarged WC (OR by quartile: 1, 0.89, 0.74, 0.63, P<0.001). These values became weaker after adjustment for calcium intake.

Beydoun et al 2008 Study Design: Cross-sectional Study Class: D Positive quality	Out of 17,061 subjects >18 years (8,970 women and 8,091 men) with complete demographic data, 4,519 subjects had complete data on dietary intake and metabolic outcomes. Sample sizes ranged from 4,519 for metabolic syndrome to 14,618 for obesity. Location: United States.	Cross-sectional analysis of merged NHANES data from 1999 to 2004, assessed the association between consumption of dairy and related nutrients and obesity, central obesity and the metabolic syndrome. Included subjects had complete data on dietary intake (assessed from 24-hour recall data) and metabolic outcomes, such as weight, height, WC, BP and laboratory values (FBG, TG stores and HDL-C).	Multivariate logistic regression models suggested that there was an overall net increase of 5% in prevalence of central obesity for each dairy serving among men (P<0.10). Whole milk was weakly and negatively associated with the prevalence of central obesity, whereas low-fat milk had the opposite effect (P<0.05 for both). Yogurt was associated with ↓ BMI and WC (P<0.05 for both); in contrast, cheese was positively associated with BMI and WC (P<0.05 for both). In addition, large ethnic disparities existed for intakes of dairy and calcium, and for all metabolic outcomes, leading the authors to conclude that the health effects of dairy products and related nutrients are complex and may not be uniform across the population.
Bowen J, Noakes M et al, 2005 Study Design: Randomized Controlled Trial Class: A Positive quality	N=50 (30 women, 20 men). Age: 25 to 64 years. Location: Australia.	RCT to compare the effects of two isocaloric, energy-restricted high-PRO diets that differ in dietary calcium and PRO source on weight ↓ and body composition. The intervention diets were a high dairy PRO/high-calcium (DP, 2,400mg calcium a day) diet and a high mixed PRO/moderate calcium (MP, 500mg calcium a day) diet followed by a 12-week energy restriction phase, followed by a four-week energy balance phase.	After 16 weeks, subjects showed significant ↓ in total weight (-9.7±3.8kg), fat mass (-8.3±0.4 kg) and lean mass (-1.6±0.3kg), but NS differences between the two diet groups.

Brooks et al 2006 Study Design: Cross-sectional Study Class: D Positive quality	1,306 young adults from the Bogalusa Heart Study (374 white males, 578 white females; 131 black males, 223 black females). Mean age: 29.7 years. Location: United States.	Cross-sectional analysis of data from the Bogalusa Heart Study, examining the association between intake of calcium and dairy products and overweight and obesity in a biracial sample of young adults. Calcium intake and low-fat dairy product consumption was assessed through the Youth and Adolescent Questionnaire, a self-administered, semi-quantitative FFQ and overweight status was measured through BMI, WHR and WC.	Intakes of dairy products were significantly ↑ among blacks than whites (P<0.05), and females had significantly ↓ intakes of dairy products than males (P<0.05). NS associations were found between dairy product consumption, calcium intake and overweight, defined by BMI or WC; however, in white males, there was a significant inverse association between calcium intake, low-fat dairy product consumption and WHR.
Dove ER, Hodgson JM et al, 2009 Study Design: Randomized controlled trial with cross-over design Class: A Positive quality	N=34 (13 men, 21 women). Mean age: 55.1±12.5 years. Mean BMI: 32.4±3.4kg/m^2. Location: Australia.	RCT with cross-over design. Participants consumed 600ml (1,062kJ each) of either skim milk or fruit drink with a fixed-energy breakfast (1,923kJ). Satiety was measured using visual analog scales (VAS) at breakfast (T=0), throughout the morning (T=30, 60, 120, 180, 210 and 240 minutes), and immediately after lunch (T=270 minutes). Lunch was provided four hours after breakfast (T=240 minutes), from which subsequent energy intake was assessed.	Participants consumed significantly less energy at lunch after consuming skim milk (mean: 2432 kJ; 95% CI: 2160, 2704 kJ) than after consuming the fruit drink (mean: 2658 kJ; 95% CI: 2386, 2930 kJ), with a mean difference of ~8.5% (P<0.05). Ratings of satiety were higher throughout the morning after consumption of skim milk than after consumption of the fruit drink (P < 0.05), with the differences becoming larger over the four hours (P<0.05).

Harper A, James A et al, 2007 Study Design: Randomized crossover design Class: A Positive quality	N=22 men. Mean age: 23±1.8 years. Mean BMI: 22.2±1.5kg/m^2. Location: Denmark.	A randomized cross-over design study to compare the effect on appetite and energy intake of consuming either a sugar-sweetened beverage (cola) or chocolate milk drink. The test drinks were 500ml cola or chocolate milk (both 900kJ) and were ingested 30 minutes before an ad libitum lunch. Visual analogue scales were used to record satiety every 30 minutes on the test days. Energy intake at lunch was calculated using weighed food intakes.	Satiety and fullness ratings were significantly greater (P=0.0007, P=0.0004, respectively) 30 minutes after chocolate milk than after cola. Ratings of prospective consumption and hunger were significantly greater after cola than after chocolate milk, both immediately after preload intake (P=0.008, P=0.01, respectively) and 30 minutes afterwards (P=0.004, P=0.01, respectively). There was NS difference (P=0.42) in ad libitum lunch intake after ingestion of chocolate milk (3,145±1,268kJ) compared with cola (3,286±1,346kJ).
Hollis et al 2007 Study Design: Nonrandomized Crossover Trial Class: C Neutral quality	N=60 subjects enrolled. N=58 completed (28 males, 30 females). Age: 18 to 50 years. Location: United States.	Non-randomized crossover trial assessing the effect of daily intake of one or three portions of dairy foods on energy intake and appetite. Subjects had seven days in the first treatment period of low or high dairy intake, a washout period of seven days and then seven days of the other treatment option. In the low-dairy phase, subjects could choose white or chocolate milk, yogurt or hard cheese. While in the high-dairy phase, subjects were required to have one serving of milk, one of yogurt and one of hard cheese. Handheld devices were used to record appetite.	Overall energy intake ↑ by 209kcal per day in the high-dairy treatment period [F (1, 52) = 28.088, P<0.05], but NS differences noted in hunger, satiety, desire to eat or thoughts of food in any treatment groups. The authors concluded that increasing dairy consumption from one to three portions each day led to ↑ energy intake.

Houston et al 2008 Study Design: Cross-sectional Study Class: D Positive quality	10,872 NHANES III participants had complete data and were included in the analysis. Age: 25 to75 years. Location: United States.	Cross-sectional study examining the association between the frequency of cheese consumption and several CVD risk factors, including measures of body fat, blood lipids, BP and blood glucose, using data from NHANES III. Cheese consumption (combined full and low-fat) was assessed through FFQ asking one question about cheese and two questions about the consumption of foods containing large amounts of cheese.	BMI and WC were significantly higher among men (P<0.05), but not among women, in the highest cheese consumption category (30 + servings a month) compared to non-consumers. More frequent cheese consumption was associated with a slightly worse body composition in men; however, there appeared to be less of an association between consumption and body composition in women.
Lanou AJ and Barnard ND, 2008 Study Design: Meta-analysis or Systematic Review Class: M Neutral quality	18 studies examined the effect of dairy products (seven studies; 330ml to four servings a day; three months to two years in length; N=28 to 757) or calcium (11 studies; 300 to 1,200mg calcium a day; six months to three years in length; N=84 to 162) in the absence of energy restriction in children and adolescents. 20 studies examined the effect of dairy products (10 studies; 12 weeks to three years in length; N=34 to 204) or calcium (10 studies; 1,000 to 1,200mg calcium a day; four months to seven years in length; N=37 to 36,282) in the absence of energy restriction in adults. 11 studies examined the effect of dairy products (500 to 2,400mg calcium a day or two to four servings a day; 12 to 48 weeks in length; N=29 to 72) or calcium (1,200mg to 1g calcium a day; one month to 25 weeks in length; N=62 to 100) with energy restriction in adults.	A systematic review was done to evaluate the body of evidence on the effect of dairy product or calcium intake, with or without energy restriction, on body weight or adiposity. Studies were identified using a MEDLINE search (keywords: milk, dairy, calcium, weight, BMI, body fat) of clinical trials published between 1966 and 2007.	Of 38 studies, 37 showed no effect of dairy product or calcium intake in the absence of energy restriction on weight in adults or children. Of 11 studies, seven found no effect and four found a significant positive association between dairy or calcium and weight ↓ with energy restriction. 15 of 16 clinical trials showed no difference in body fat Δ between ↑ and ↓ consumers of dairy or calcium, while one study found ↑ fat loss among high-dairy consumers compared to low-dairy consumers.

Marques-Vidal et al 2006 Study Design: Cross-sectional Study Class: D Neutral quality	N=37,513 subjects (17,771 males, 19,742 females). Mean age: 47.8 years males; 50.3 years females. Location: Portugal.	Cross-sectional study assessing the relationship between milk intake and BMI status using a representative population sample from the Portuguese National Health Interview Survey 1998 to 1999 database. Average daily milk intake was calculated by a FFQ that also assessed the average volume of one serving; height and weight were self-reported.	In men, milk intake was inversely related to BMI (R=-0.10, P<0.001), whereas the relationship in women was weaker (R=-0.06, P<0.001). After adjustment for confounding variables, milk intake decreased with increasing BMI (P<0.001).
Mirmiran P, Esmaillzadeh A et al, 2005 Study Design: Cross sectional study Class: D Neutral quality	N=462 (223 men and 239 women). Age: 38±15 years men; 32±13 years women. BMI: 24.8±4.6kg/m^2 men; 25.3±5.3kg/m^2 women. Location: Tehran, Iran.	Daily dairy consumption was determined using 24-hour dietary recalls and a FFQ. Subjects were stratified into four quartiles based on dairy intake: 1) <1.6 2) 1.6 to <2.2 3) 2.2 <three 4) >three.	Mean consumption of dairy products was 3.7±1.0 and 2.9±1.2 servings per day in men and women, respectively. There was a significant inverse correlation between the servings of dairy consumed per day and BMI after controlling for age, physical activity, energy, CHO, dietary fiber, PRO and fat intake (R=-0.38, P<0.05). After adjustment for potential confounding variables, men and women in the top quartile of dairy consumption had lower chances for being overweight (OR=0.78; 95% CI=0.43, 0.92 for men and OR=0.89; 95% CI=0.53, 0.95 for women) and obese (OR=0.73; 95% CI=0.40, 0.83 for men and OR=0.69; 95% CI=0.34, 0.80 for women) compared to those in the first quartile.

Murakami K, Okubo H et al, 2006 Study Design: Cross-Sectional Study Class: D Positive quality	N=1,905 women. Age: 18 to 20 years. Mean BMI: 20.8±2.6kg/m^2. Location: Japan.	A cross-sectional analysis was done to examine the associations between dairy product and calcium intake and BMI in young Japanese women. Dietary habits during the previous month were assessed by using a validated, self-administered diet history questionnaire (DHQ). Body weight and height were self-reported as part of the DHQ. BMI was computed as weight (kg) divided by the square of height (m).	Mean estimated intakes were 268±93mg per 1,000kcal for calcium and 80±63g per 1,000kcal for dairy products. There were NS associations between BMI and calcium or dairy product intake in this study.
O'Neil CE, Nicklas TA et al, 2009 Study Design: Cross-Sectional Study Class: D Positive quality	N=609 women (33% Hispanic, 43% African American, 24% white). Age: 30.0±0.2 years. BMI: 30.8±0.3kg/m^2. 58% completed high school or less; 46% married. Subjects were divided into groups based on beverage consumption: 1) Low milk, high sweetened beverage (SB) (N=170) 2) High milk, low SB (N=170) 3) Low milk, low SB (N=134) 4) High milk, high SB (N=135). Location: United States.	Cross-sectional data was used to assess the association of milk and SB consumption with weight, nutrient intake and dietary adequacy in a multiethnic population of Head Start mothers. Dietary intake was assessed via three 24-hour dietary recalls. Height and weight was measured twice on each participant and BMI calculated as kg/m^2.	Mean BMI did not differ between the four beverage consumption groups. Women in the high milk, low SB group had ↑ mean intakes of vitamins A, D, and B_6; riboflavin; thiamin; folate; phosphorus; calcium; iron; magnesium; and potassium (P<0.0125), when compared with the other beverage consumption groups. Mean Adequacy Ratio (a measure of overall dietary adequacy) was highest in the high milk/low SB (71.8 ± 0.8) and lowest in the low milk/high SB (58.4 ± 0.8) consumption groups (P<0.0125).

Olsen SF et al 2007 Study Design: Prospective Cohort Study Class: B Neutral quality	N=70,187 mothers completed the FFQ. N=50,117 mother-infant pairs included in analysis after application of exclusion criteria. Mean age of mothers: 29.1±4.3 years. Location: Denmark.	Prospective cohort study examining whether milk consumption during pregnancy is associated with greater infant size at birth in the Danish National Birth Cohort (1996 to 2002). Dietary intake was assessed through FFQs during one month of mid-pregnancy; birth outcomes were ascertained through registry linkages.	Mean consumption of milk was 3.1±2.0 glasses per day. Milk consumption was inversely associated with the risk of SGA birth and directly with both LGA birth and mean birth weight (P<0.001). Comparing women drinking more than six glasses of milk per day with those not drinking milk, the OR for SGA was 0.51 (95% CI: 0.39, 0.65) and for LGA was 1.59 (95% CI: 1.16, 2.16). The increment in mean birth weight was 108g (95% CI: 74, 143).
Rajpathak SN, Rimm EB et al, 2006 Study Design: Prospective Cohort Study Class: B Positive quality	N=19,615 men. Age: 40 to 75 years. Mean BMI: 25.2 kg/m^2. Health Professionals Follow-up Study. Location: United States.	Data from a prospective cohort study to evaluate the association between calcium and dairy intakes and 12-year weight Δ in US men. Dietary intake during the preceding year was assessed in 1986 using a FFQ, which also collected information on the use of calcium and multivitamin supplements.	Results of a multivariate analysis adjusted for potential confounders showed that neither baseline nor Δ in total calcium intake was significantly associated with weight Δ. NS association between weight and dietary, dairy or supplemental calcium when each calcium source was evaluated separately. Men with the largest ↑ in total dairy intake gained slightly more weight (3.14±0.11kg) than did men with the largest ↓ in dairy intake (2.57±0.13kg) (P<0.001). This association was primarily due to an ↑ in high-fat dairy intake (P<0.001), as low-fat dairy intake was NS associated with weight Δ (P=0.19).

Rosell et al 2006 Study Design: Prospective Cohort Study Class: B Positive quality	N=19,352 women. Mean age: 46.3±4.5 years at baseline. Swedish Mammography Cohort. Location: Sweden.	Prospective cohort study examining the association between changes in dairy product consumption and self-reported weight Δ over nine years. In 1987, dietary intake was measured with a 67-item FFQ, and in 1997, it was measured with an extended 96-item FFQ. Women were divided into four dairy product consumption groups (serving per day): 1) <one, no Δ at follow-up 2) <one, ↑ to >one at follow-up 3) >one, no Δ at follow-up 4) >one, ↓ to <one at follow-up.	Mean BMI at baseline was 23.7±3.5kg/m^2 and mean weight ↑ in the cohort was 0.33±0.63kg per year. Consistent consumption of >one serving of dairy products per day was inversely associated with weight gain. OR for consumption of >one serving per day of whole milk and sour milk was 0.85 (95% CI: 0.73, 0.99) and of cheese was 0.70 (95% CI: 0.59, 0.84), while NS associations were seen for the other three intake groups. The authors concluded that the association between the intake of dairy products and weight gain differed according to the type of dairy product and to the body weight status at baseline.
Snijder et al 2008 Study Design: Prospective Cohort Study Class: B Positive quality	N=1,124 white men and women. Age: 50 to 75 years. Hoorn Study. Location: The Netherlands.	Prospective cohort study investigating the association between dairy consumption and 6.4-year Δ in weight and metabolic disturbances. Average food intake was measured at baseline using a 92-item semi-quantitative FFQ. At baseline and follow-up, participants underwent an extensive physical examination that included measurement of weight and WC.	Linear regression analyses, using the continuous dairy variable as independent variable and the change in body composition or metabolic variables as dependent variables, revealed that baseline dairy composition was not associated with Δ in body composition or metabolic variables, neither after adjustment for potential confounders. In subjects with BMI<25kg/m^2, higher dairy consumption was significantly associated with an ↑ in BMI, WC and weight (data not shown).

Vergnaud et al 2008 Study Design: Prospective Cohort Study Class: B Positive quality	N=2,267 subjects (1,022 women, 1,245 men) Mean age: 50.8±4.3 years women; 51.5±4.44 years men Supplementation en Vitamines et Mineraux Antioxidants (SU.VI.MAX) Study. Location: France.	Prospective cohort study investigating the relationship between dairy consumption and calcium intake with six-year Δ in body weight and WC. Anthropometric measurements were taken at the first (1995 to 1996) and last (2001 to 2002) clinical examinations and at least six 24-hour dietary records during the first 18 months were evaluated.	In overweight men only, six-year Δ in weight and WC were inversely associated with the dairy product consumption, especially milk (P=0.02 for both weight and WC Δ) and yogurt (P=0.01 for weight Δ, P=0.03 for WC Δ). Positive relations were found between milk consumption and WC Δ in overweight women, and between yogurt consumption and weight Δ in normal-weight women. The authors concluded that the associations between dairy product consumption and anthropometric changes differed according to sex, overweight status at baseline and type of dairy product.

Search plan and results

Inclusion criteria

- June 2004 to July 2009
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Adults 19 years and older (Energy Balance section addresses body weight measures for children)
- *Populations:* Healthy and those with elevated chronic disease risk.

Exclusion criteria

- Studies that only consider cancer outcomes
- Studies that considered milk and milk products as part of a larger dietary pattern
- Medical treatment/therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: ("Dairy Products"[mh]) AND ("Body Weights and Measures"[Mesh] OR

"Body Mass Index"[Mesh] OR "Adiposity"[mh] OR "Overweight"[mh] OR "Obesity"[mh] OR "Weight Gain"[mh] OR “body composition”[mh] OR “energy intake”[mh] OR caloric intake*) for adults

Date searched: 07/29/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 140
- Total articles identified to review from electronic databases: 42
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 17
- Number of Review Articles Identified: 1
- Total Number of Articles Identified: 18
- Number of Articles Reviewed but Excluded: 24

Included articles (References)

SYSTEMATIC REVIEW

1. Lanou AJ, Barnard ND. Dairy and weight loss hypothesis: An evaluation of the clinical trials. *Nutr Rev*. 2008 May; 66 (5): 272-279. Review. PMID: 18454813.

PRIMARY RESEARCH

Randomized Controlled Trial

1. Bowen J, Noakes M, Clifton PM. Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. *Int J Obes* (Lond). 2005 Aug; 29 (8): 957-965. PMID: 15711601.

Prospective Cohort Studies

1. Rajpathak SN, Rimm EB, Rosner B, Willett WC, Hu FB. Calcium and dairy intakes in relation to long-term weight gain in US men. *Am J Clin Nutr*. 2006 Mar; 83 (3): 559-566. PMID: 16522901.
2. Rosell M, Håkansson NN, Wolk A. Association between dairy food consumption and weight change over nine years in 19, 352 perimenopausal women. *Am J Clin Nutr*. 2006 Dec; 84 (6): 1, 481-1, 488. PMID: 17158433.
3. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity* (Silver Spring). 2008 Mar; 16 (3): 706-709. Epub 2008 Jan 17. PMID: 18239556.
4. Vergnaud AC, Péneau S, Chat-Yung S, Kesse E, Czernichow S, Galan P, Hercberg S, Bertrais S. Dairy consumption and six-year changes in body weight and waist circumference in middle-aged French adults. *Am J Clin Nutr*. 2008 Nov; 88 (5): 1, 248-1, 255. PMID: 18996859.

Cross-Sectional Studies

1. Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Tehranian adults. *Am J Clin Nutr*. 2005 Sep; 82 (3): 523-530. PMID: 16155263.
2. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y.

Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity and the metabolic syndrome. *Am J Clin Nutr.* 2008 Jun; 87 (6): 1, 914-1, 925. PMID: 18541585; Central PMCID: PMC2585752.

3. Brooks BM, Rajeshwari R, Nicklas TA, Yang SJ, Berenson GS. Association of calcium intake, dairy product consumption with overweight status in young adults (1995-1996): The Bogalusa Heart Study. *J Am Coll Nutr*. 2006 Dec; 25 (6): 523-532. PMID: 17229900.
4. Houston DK, Driver KE, Bush AJ, Kritchevsky SB. The association between cheese consumption and cardiovascular risk factors among adults. *J Hum Nutr Diet*. 2008 Apr; 21 (2): 129-140. PMID: 18339053.
5. Marques-Vidal P, Gonçalves A, Dias CM. Milk intake is inversely related to obesity in men and in young women: Data from the Portuguese Health Interview Survey 1998-1999. *Int J Obes* (Lond). 2006 Jan; 30 (1): 88-93. PMID: 16116492.
6. Mirmiran P, Esmaillzadeh A, Azizi F. Dairy consumption and body mass index: An inverse relationship. *Int J Obes* (Lond). 2005 Jan; 29 (1): 115-121. PMID: 15534616.
7. Murakami K, Okubo H, Sasaki S. No relation between intakes of calcium and dairy products and body mass index in Japanese women aged 18 to 20 years. *Nutrition*. 2006 May; 22 (5): 490-495. Epub 2006 Feb 24. PMID: 16500081.
8. O'Neil CE, Nicklas TA, Liu Y, Franklin FA. Impact of dairy and sweetened beverage consumption on diet and weight of a multiethnic population of Head Start mothers. *J Am Diet Assoc*. 2009 May; 109 (5): 874-882. PMID: 19394474.

Energy Intake as Outcome

1. Dove ER, Hodgson JM, Puddey IB, Beilin LJ, Lee YP, Mori TA. Skim milk compared with a fruit drink acutely reduces appetite and energy intake in overweight men and women. *Am J Clin Nutr*. 2009 Jul; 90 (1): 70-75. Epub 2009 May 27. PMID: 19474132.
2. Harper A, James A, Flint A, Astrup A. Increased satiety after intake of a chocolate milk drink compared with a carbonated beverage, but no difference in subsequent ad libitum lunch intake. *Br J Nutr*. 2007 Mar; 97 (3): 579-583. PMID: 17313721.
3. Hollis JH, Mattes RD. Effect of increased dairy consumption on appetitive ratings and food intake. *Obesity* (Silver Spring). 2007 Jun; 15 (6): 1, 520-1, 526. Erratum in: *Obesity* (Silver Spring). 2007 Oct; 15 (10): 2, 520. PMID: 17557989.

Pregnancy

1. Olsen SF, Halldorsson TI, Willett WC, Knudsen VK, Gillman MW, Mikkelsen TB, Olsen J; NUTRIX Consortium. Milk consumption during pregnancy is associated with increased infant size at birth: Prospective cohort study. *Am J Clin Nutr.* 2007 Oct; 86 (4): 1, 104-1, 110. PMID: 17921389.

Excluded articles

Article	Reason for Exclusion
Al-Zahrani MS. Increased intake of dairy products is related to lower periodontitis prevalence. *J Periodontol*. 2006 Feb; 77 (2): 289-294. PMID: 16460256.	Does not include body weight as an outcome.
Biong AS, Rebnord HM, Fimreite RL, Trygg KU, Ringstad J, Thelle DS, Pedersen JI. Intake of dairy fat and dairy products and risk of myocardial infarction: A case-control study. *Int J Food Sci Nutr.* 2008 Mar; 59 (2): 155-165. PMID: 17886080.	Does not include body weight in analyses.
Biong AS, Müller H, Seljeflot I, Veierød MB, Pedersen JI. A comparison of the effects of cheese and butter on serum lipids, haemostatic variables and homocysteine. *Br J Nutr*. 2004 Nov; 92 (5): 791-797. PMID: 15533268.	Does not include body weight in analyses.
Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake and the risk of gout in men. *N Engl J Med.* 2004 Mar 11; 350 (11): 1, 093-1, 103. PMID: 15014182.	Does not answer question: Does not examine relationship between milk product intake and body weight.
Eagan MS, Lyle RM, Gunther CW, Peacock M, Teegarden D. Effect of one-year dairy product intervention on fat mass in young women: six-month follow-up. *Obesity* (Silver Spring). 2006 Dec; 14 (12): 2, 242-2, 248. PMID: 17189552.	Included in Lanou, 2008.
Elwood PC, Pickering JE, Fehily AM. Milk and dairy consumption, diabetes and the metabolic syndrome: The Caerphilly prospective study. *J Epidemiol Community Health.* 2007 Aug; 61 (8): 695-698. PMID: 17630368.	Does not answer question: Does not examine relationship between milk product intake and body weight.
Engberink MF, Geleijnse JM, de Jong N, Smit HA, Kok FJ, Verschuren WM. Dairy intake, blood pressure, and incident hypertension in a general Dutch population. *J Nutr*. 2009 Mar; 139 (3): 582-587. Epub 2009 Jan 21. PMID: 19158223.	Does not answer question: Does not examine relationship between milk product intake and body weight.
Gunther CW, Legowski PA, Lyle RM, McCabe GP, Eagan MS, Peacock M, Teegarden D. Dairy products do not lead to alterations in body weight or fat mass in young women in a one-year intervention. *Am J Clin Nutr.* 2005 Apr; 81 (4): 751-756. PMID: 15817848. (Hand search)	Included in Lanou, 2008.
Harvey-Berino J, Gold BC, Lauber R, Starinski A. The impact of calcium and dairy product consumption on weight loss. *Obes Res*. 2005 Oct; 13 (10): 1, 720-1, 726. PMID: 16286519.	Included in Lanou, 2008.
Larsson SC, Bergkvist L, Wolk A. Milk and lactose intakes and ovarian cancer risk in the Swedish Mammography Cohort. *Am J Clin Nutr*. 2004 Nov; 80 (5): 1, 353-1, 357. PMID: 15531686.	Does not answer question: Does not examine relationship between milk product intake and body weight.

Liu S, Choi HK, Ford E, Song Y, Klevak A, Buring JE, Manson JE. A prospective study of dairy intake and the risk of type 2 diabetes in women. *Diabetes Care.* 2006 Jul; 29 (7): 1, 579-1, 584. PMID: 16801582.	Does not answer question: Does not examine relationship between milk product intake and body weight.
McGlynn KA, Sakoda LC, Rubertone MV, Sesterhenn IA, Lyu C, Graubard BI, Erickson RL. Body size, dairy consumption, puberty and risk of testicular germ cell tumors. *Am J Epidemiol.* 2007 Feb 15; 165 (4): 355-363. Epub 2006 Nov 16. PMID: 17110638.	Does not answer question: Does not examine relationship between milk product intake and body weight.
Peters ES, Luckett BG, Applebaum KM, Marsit CJ, McClean MD, Kelsey KT. Dairy products, leanness, and head and neck squamous cell carcinoma. *Head Neck.* 2008 Sep; 30 (9): 1, 193-1, 205. PMID: 18642285; PMCID: PMC2683246.	Does not answer question: does not examine relationship between milk product intake and body weight.
Ranganathan R, Nicklas TA, Yang SJ, Berenson GS. The nutritional impact of dairy product consumption on dietary intakes of adults (1995-1996): The Bogalusa Heart Study. *J Am Diet Assoc*. 2005 Sep; 105 (9): 1, 391-1, 400. PMID: 16129080.	Does not include body weight in analyses.
Rosado JL, Díaz M, González K, Griffin I, Abrams SA, Preciado R. The addition of milk or yogurt to a plant-based diet increases zinc bioavailability but does not affect iron bioavailability in women. *J Nutr.* 2005 Mar; 135 (3): 465-468. PMID: 15735079.	Does not include body weight in analyses.
Shahar DR, Abel R, Elhayany A, Vardi H, Fraser D. Does dairy calcium intake enhance weight loss among overweight diabetic patients? Diabetes Care. 2007 Mar; 30 (3): 485-489. PMID: 17327309.	Participants diagnosed with type 2 diabetes.
Snijder MB, van der Heijden AA, van Dam RM, Stehouwer CD, Hiddink GJ, Nijpels G, Heine RJ, Bouter LM, Dekker JM. Is higher dairy consumption associated with lower body weight and fewer metabolic disturbances? The Hoorn Study. *Am J Clin Nutr.* 2007 Apr; 85 (4): 989-995. PMID: 17413097.	Results reported based on the same dataset as Snijder, 2008.
Thompson WG, Rostad Holdman N, Janzow DJ, Slezak JM, Morris KL, Zemel MB. Effect of energy-reduced diets high in dairy products and fiber on weight loss in obese adults. *Obes Res*. 2005 Aug; 13 (8): 1, 344-1, 353. PMID: 16129716. (Hand search)	Included in Lanou, 2008.
Weyermann M, Brenner H, Rothenbacher D. Adipokines in human milk and risk of overweight in early childhood: A prospective cohort study. *Epidemiology*. 2007 Nov; 18 (6): 722-729. PMID: 18062063.	Evaluates break milk, not milk or milk products as defined by the Committee.
White KM, Bauer SJ, Hartz KK, Baldridge M. Changes in body composition with yogurt consumption during resistance training in women. *Int J Sport Nutr Exerc Metab.* 2009 Feb; 19 (1): 18-33. PMID: 19403951.	Does not answer question: Includes yogurt as part of resistance training intervention.

Wilkinson SB, Tarnopolsky MA, Macdonald MJ, Macdonald JR, Armstrong D, Phillips SM. Consumption of fluid skim milk promotes greater muscle protein accretion after resistance exercise than does consumption of an isonitrogenous and isoenergetic soy-protein beverage. *Am J Clin Nutr.* 2007 Apr; 85 (4): 1, 031-1, 040. PMID: 17413102.	Does not include body weight in analyses.
Woo J, Lau W, Xu L, Lam CW, Zhao X, Yu W, Xing X, Lau E, Kuhn-Sherlock B, Pocock N, Eastell R. Milk supplementation and bone health in young adult Chinese women. *J Womens Health (Larchmt).* 2007 Jun; 16 (5): 692-702. PMID: 17627404.	Evaluates milk supplement, not milk or milk products as defined by the Committee.
Wyatt HR, Jortberg BT, Babbel C, Garner S, Dong F, Grunwald GK, Hill JO.Weight loss in a community initiative that promotes decreased energy intake and increased physical activity and dairy consumption: Calcium Weighs-In. *J Phys Act Health.* 2008 Jan; 5 (1): 28-44. PMID: 18209252.	Dropout rate higher than inclusion criteria.
Zemel MB, Richards J, Milstead A, Campbell P. Effects of calcium and dairy on body composition and weight loss in African-American adults. *Obes Res.* 2005 Jul; 13 (7): 1, 218-1, 225. PMID: 16076991.	Included in Lanou, 2008.

CHAPTER 14. MILK AND MILK PRODUCTS – BONE HEALTH

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF MILK AND MILK PRODUCTS AND BONE HEALTH?

Conclusion statement

Moderate evidence indicates that the intake of milk and milk products is linked to improved bone health in children. Limited evidence suggests a positive relationship between the intake of milk and milk products and bone health in adults, but results are inconsistent due to variability in outcomes considered.

Grade

Moderate

Evidence summary overview

Research since 2004 indicates that the intake of milk and milk products is linked to improved bone health in children. Results in adults are mixed. The conclusion reached for this question is based on a review of three systematic reviews or meta-analyses (Alvarez-Leon, 2006; Huncharek, 2008; Kanis, 2005), three primary research studies conducted since the reviews (Budek, 2007; Kristensen, 2005; McCabe, 2004), one longitudinal study (Rockell, 2005), one case-control study (Konstantynowicz, 2007) and one cross-sectional study (Al-Zahrani, 2006), all published since 2004.

The results of the systematic reviews and meta-analyses are inconsistent when children and adults are considered together. In a meta-analysis focused on children, Huncharek et al, (2008) examined the relationship between dairy and calcium intake and bone mineral content. Their review of 21 studies concluded that increased dairy/calcium intake, with or without vitamin D supplementation, results in significantly higher total body and lumbar spine bone mineral content among children with low baseline intakes of dairy, calcium, and/or vitamin D. In a small, short-term study among pre-pubertal boys consuming equal amounts of protein, Budek et al, (2007) found that a high intake of milk, but not meat, decreased bone turnover. However, the relevance of reduced turnover for peak bone mass is unclear.

A longitudinal study conducted in New Zealand (Rockell, 2005), assessed two-year changes in bone and body composition in young children with a history of prolonged milk avoidance. The authors concluded that young milk avoiders demonstrated persistent height reduction, overweight and osteopenia at the ultradistal radius and lumbar spine over two years of follow-up.

Alvarez-Leon et al, (2006) reviewed literature on the associations between the consumption of dairy products and health outcomes, including two review papers on bone health. They concluded that there is weak evidence of the protective capacity of dairy products on bone health, noting that limitations in studies examining this relationship make it difficult to make firm conclusions about the effect of dairy products on bone health.

Kanis et al, (2005) reviewed six prospectively studied cohorts from European, Australian and Canadian research. They examined calcium intake, measured by milk

consumption, and its association with the risk of fracture. They found no significant relationship between low intake of calcium and fracture risk. This study did not include other sources of dietary calcium besides milk and did not account for variations in vitamin D intake or sunlight exposure. Therefore, the authors caution that these findings should not be misinterpreted as suggesting that calcium is not causally related to fracture risk nor that calcium does not play a role in fracture prevention.

Results from three intervention studies supported the role of dairy products in bone health. McCabe et al, (2004) found that calcium supplementation protected study participants from bone loss and that higher dairy product consumption was associated with greater hip bone mineral density (BMD) in men, but not in women. In a small study of Caucasian males who replaced milk with cola beverages in their diet for 10 days, Kristensen et al, (2005) concluded that replacement of cola for milk results in a low calcium intake, which may negatively affect bone health.

In summary, these reviews support that calcium and milk and milk products play an important role in bone mineral content in children. Results from adult trials are mixed.

Evidence summary paragraphs

Systematic Reviews / Meta-Analyses:

Alvarez-Leon et al, 2006 (positive quality) systematically reviewed papers on the associations between consumption of dairy products and health outcomes, including cancer, bone health and cardiovascular disease. Relevant articles were obtained through searching the MEDLINE database (from 1966 to January 2005) using the search terms: ‘Dairy products’, defined as ‘raw and processed or manufactured milk, and milk-derived products’ including butter, cheese, ice cream, margarine and milk and cultured milk products (yoghurt). This search revealed 85,000 articles. After excluding studies, and including only meta-analyses and systematic reviews, the final sample consisted of 14 meta-analyses and systematic reviews. This final sample consisted of six papers on dairy products and cancer, six papers on dairy products and cardiovascular disease (CVD) and two papers on dairy products and bone health. Evidence from these papers was summarized and evaluated. Weinsier and Krumdieck (2000) reviewed 12 articles. Among the 12 articles, there were six that found no effect between the intake of dairy products and bone health, five found a positive effect and one found a negative effect. Women under 30 years seemed to gain the most benefit. Cumming and Nevitt (1997) found 14 studies that evaluated calcium (Ca) supplements (four randomized trials, three non-randomized trials and seven observational epidemiological studies) and 23 observational studies that evaluated dietary Ca (non-randomized trials). The main conclusion emphasized by the authors was that increased Ca intake among postmenopausal women appeared to be associated with a small reduction in risk of fracture, with about a 30% reduction in fracture risk among those taking higher amounts of Ca (1g daily as a supplement). The authors concluded that there is weak evidence of a protective capacity of dairy products on bone health.

Huncharek et al, 2008 (positive quality) conducted a meta-analysis to determine the relationship between dairy and calcium intake and bone mineral content (BMC) in children. A search was done using the search terms bone/bones, dairy products, calcium and calcium/dietary to identify relevant studies published between 1966 and 2006. The search identified 1,200 studies, and after inclusion/exclusion criteria were applied, 21 studies with 3,821 subjects (83% female) ages four to 17.3 years were

included in the meta-analysis. Data were pooled from randomized controlled trials (RCTs) and observational studies using the primary outcomes of summary mean difference BMC. Sensitivity analyses were employed to evaluate any observed statistical heterogeneity and to examine the influence of specific study characteristics on the summary estimate of effect. Combining data from 21 RCTs using total body bone mineral content (TB-BMC) as the outcome of interest, yielded a non-statistically significant increase in BMC of 2g (supplemented vs. controls). However, sensitivity tests revealed that baseline calcium intake could be accounting for the statistical heterogeneity. Therefore, when results from three studies utilizing low intake subjects were pooled, increased dairy/calcium intake was significantly associated with a mean BMC increase of 49g. In addition, pooling data from two studies combining dairy/calcium and vitamin D supplementation showed a significant mean increase in lumbar spine BMC of 35g. These results suggest that increased dairy/calcium intake, with or without vitamin D supplementation, results in significantly higher total body and lumbar spine BMC among children with low baseline intakes of dairy, calcium and/or vitamin D.

Kanis et al, 2005 (positive quality) conducted a meta-analysis to quantify the fracture risk associated with a low dietary intake of milk and calcium, and to explore the dependence of this risk with age, sex and bone mineral density (BMD). Data from 39,563 adults (age range: 21-103 years) participating in six prospective cohort studies in Europe, Australia and Canada were used for the meta-analysis. There was no significant (NS) relationship between low intake of calcium and hip fracture risk in either sex at any age. For osteoporotic fractures, a small, but significant risk was found from the age of 80 years (RR=1.15; 95% CI: 1.02-1.30); however this association was no longer significant when adjusted for BMD. There was a weak but significant correlation between intake of milk and BMD (r=0.03643, P=4.5 x 10-10). The authors concluded that the main finding of the present study was that a low intake of calcium, as judged by the intake of milk, does not confer a substantial increase in fracture risk. This study did not include other sources of dietary calcium besides milk, and did not account for variations in vitamin D intake or sunlight exposure. Therefore, the authors caution that these findings not be misinterpreted as suggesting no causative role of calcium in the causation of fractures, nor a role for calcium nutrition in their prevention.

Primary Research:

Trials:

Budek et al, 2007 (positive quality) conducted a non-randomized trial to compare the short-term effect of high milk and a high meat intake, identical in the amount of protein, on bone formation, bone resorption and weight in pre-pubertal boys. The study was conducted in Denmark. Male subjects (N=24, 12 per group) aged eight years participated in a seven-day trial. Subjects were instructed to consume either 1.5 liter of skimmed milk per day or 250g of low-fat meat per day for seven days. Each treatment was designed to add approximately 53g of protein to the diet. Otherwise, subjects were instructed to maintain their normal dietary intake during the study. Three-day weighted food records (two weekdays and one weekend day) were kept for the three days preceding the intervention and for the last three days of the study. Measures of bone formation/resorption and weight were obtained between 8 and 10 a.m. on day zero (baseline) and day seven (end of intervention). At baseline, the groups did not differ with respect to serum concentrations of bone markers. After seven days,

serum osteocalcin (s-OC) (P<0.003) and serum C-terminal telopeptides of type I collagen (s-CTX) (P<0.04) were significantly reduced in the milk group compared to the meat group. While serum bone-specific alkaline phosphate (s-BAP) decreased in both groups, there were no significant differences between the groups. Boys in the milk group increased body weight by 0.54kg compared with the boys in the meat group, that did not exhibit a change in body weight (P=0.003).

Kristensen et al, 2005 (neutral quality), a randomized crossover trial conducted in Denmark, investigated the short-term effects of replacing milk with cola beverages in young men on a low-calcium diet in order to study the effect on calcium homeostasis and bone turnover. 2.5 liters of either cola or semi-skimmed milk were consumed each day in two 10-day experimental periods separated by a 10-day washout period. During the two diet periods, the same low-calcium diet was given to the subjects; all meals were provided. 11 Caucasian males, aged 22-29 years, were enrolled and completed the study. An increase in serum phosphate (P<0.001), 1,25(OH)2D (P<0.001), PTH (P=0.046) and osteocalcin (P<0.001) was observed in the cola period compared to the milk period and bone resorption was significantly increased following the cola period, seen as increased serum CTX (P<0.001) and urinary NTX (P<0.001) compared to the milk period. No changes were observed in serum concentrations of calcium or B-ALP. The authors concluded that the trend towards replacement of milk with cola and other soft drinks results in a low calcium intake, which may negatively affect bone health.

McCabe et al, 2004 (neutral quality) used both a RCT and a cross-sectional study to:

Examine the cross-sectional relationship between consumption of calcium and other nutrients from dairy products and bone mineral density (BMD) at the hip in elderly black and white men and women

Examine the impact of calcium supplement intake on the BMD loss in a longitudinal study of white men and women.

There were 289 white women and 116 white men who participated in the RCT, and their data was combined with data from 265 black women and 75 black men for the cross-sectional study; all subjects were ≥60 years of age. The study was conducted in the US. For the trial, subjects received daily placebo, 750mg Ca per day or 15 microgram 25-hydroxyvitamin D_3 per day for four years. For all subjects dietary intake data was collected using the National Cancer Institute's Health Habits and History questionnaire, and bone mineral density was assessed using dual energy X-ray absorptiometry (DEXA). For all participants, average total calcium intake from dairy was 436±289mg, with an additional 239±93mg coming from nondairy dietary sources. In the cross-sectional analysis, a partial positive correlation was found between total hip BMD and dairy calcium in men (P<0.05, r=0.23) but not in women (NS, r=0.02). The results of the RCT showed that the effect of calcium supplementation on femoral neck BMD depended on baseline dietary calcium intake (P<0.05). Those participants with deficient diets (<1.5 servings or <450mg Ca per day) at baseline who were treated with calcium had less change in femoral neck BMD compared to those treated with placebo. Also, the effect of calcium supplementation on femoral neck and hip BMD was evident in those that were less than 72 years old (P<0.05) at baseline, but not in those that were older than 72 years at baseline (NS). The authors concluded that the cross-sectional results indicated that higher dairy product consumption is associated

with greater hip bone mineral density in men, but not in women, and that long-term calcium supplementation protected both men and women from bone loss in the longitudinal study.

Longitudinal Study:

Rockell et al, 2005 (positive quality), a longitudinal study conducted in New Zealand, assessed two-year changes in bone and body composition in young children with a history of prolonged milk avoidance. The baseline visit consisted of 50 Caucasian children aged three to 10 years; 28 girls and 18 boys (mean age 8.1±2.0 years) completed the follow-up study. Calcium intake was assessed by food-frequency questionnaire (FFQ), as well as four-day diet records. Bone mineral density (BMD) and body composition were measured using DEXA. Thirteen children (28.3%) had history of fracture; five new fractures had occurred during the two-year follow-up. At follow-up, calcium intakes were positively correlated with Z scores for total body bone mineral content (r=0.34, P<0.023), total bone area (r=0.33, P<0.025), ultradistal radial bone mineral density (r=0.36, P<0.014) and 33% radial BMD (r=0.30, P<0.045). Every additional 100mg of calcium consumed was commensurate with a change of approximately 0.1 unit of Z score for these measurements. However, although some catch-up in height had taken place during the follow-up, the group remained significantly shorter than the reference population, with elevated body mass index (BMI). The authors concluded that young milk avoiders demonstrated persistent height reduction, overweight and osteopenia at the ultradistal radius and lumbar spine over two years of follow-up.

Case-Control Studies:

Konstantynowicz et al, 2007 (neutral quality), a case-control study conducted in Poland, examined the association between consumption of a milk-free diet and fracture risk, in 91 cases with fractures (57 boys and 34 girls, aged 2.5-20 years) and 273 age- and sex-matched controls without fractures (three per case, 171 boys and 102 girls). All children with cow's milk allergy were treated with a restrictive milk-free diet for 2.5 to 14 years. Weight, height, bone mineral density (BMD) and body composition were measured in all children, while calcium intake was assessed through 24-hour recall in a subset of 46 children. In girls, 29.4% of cases and 11.8% of controls had consumed a milk-free diet, producing an odds ratio (OR) for fracture associated with a milk-free diet of 4.6 (95% CI: 1.4, 15.5; P<0.01), while in boys, 23% of cases and 19% of controls had consumed a milk-free diet, producing an OR for fracture associated with a milk-free diet of 1.3 (95% CI: 0.6, 2.7; NS). No association was found between calcium intake, BMD or fracture prevalence in the sub-set of children, leading the authors to conclude that cow's milk allergy was associated with increased fracture risk in girls.

Cross-Sectional Study:

Al-Zahrani et al, 2006 (positive quality) conducted a cross-sectional study to examine whether or not there was an association between the intake of dairy products and periodontitis prevalence among adults (N=12,764; 6,549 females, 6,215 males) using National Health and Nutrition Examination Survey III (NHANES III) data. A 24-hour dietary recall collected information from participants regarding their intake of food and beverages (except for plain drinking water) for the past 24 hours, and the number of servings of dairy products was calculated. Mean intake of dairy products for the study

was 2.1 servings per day. Rates of periodontitis were significantly lower among individuals in the highest quintile of dairy intake (11.2±1.1%) compared to those in the lowest quintile of dairy intake (17.8±1.3%; P<0.01). Individuals in the highest quintile of dairy intake were 41% less likely to have periodontitis than those in the lowest quintile (OR: 0.80; 95% CI: 0.61, 1.07; P<0.05) (adjusted for age, gender, race/ethnicity, smoking, education, diabetes, poverty index; vitamin use, BMI, physical activity, time since the last dental visit, gingival bleeding and dental calculus). The authors concluded that a strong inverse association between intake of dairy products and prevalence of periodontitis was present, even after controlling for major risk factors of periodontitis.

Overview table

Author, Year, Study Design, Class, Rating	Participants	Description of Study Design	Outcomes
Al-Zahrani MS, 2006 Study Design: Cross-sectional study Class: D Positive quality	N=12,764 adults (6,549 females, 6,215 males) from NHANES III data. Location: United States.	Examined whether or not there was an association between the intake of dairy products and periodontitis prevalence using NHANES III data. A 24-hour dietary recall collected information from participants regarding their intake of food and beverages.	Rates of periodontitis were significantly ↓ among individuals in highest quintile of dairy intake (11.2±1.1%), compared to those in lowest quintile of dairy intake (17.8±1.3%; P<0.01). Individuals in highest quintile of dairy intake were 41% less likely to have periodontitis than those in the lowest quintile (OR: 0.80; 95% CI: 0.61, 1.07; P<0.05) (adjusted for age, gender, race/ethnicity, smoking, education, diabetes, poverty index; vitamin use, BMI, physical activity, time since the last dental visit, gingival bleeding and dental calculus).

Alvarez-León EE, Roman-Vinas B et al, 2006 Study Design: Meta-analysis or Systematic Review Class: M Positive quality	N=14 meta-analyses and systematic reviews: Six on dairy products and cancer. Six on dairy products and CVD Two on dairy products and bone health.	Relevant articles obtained through searching the MEDLINE database (from 1966 to January 2005) using the search terms: 'Dairy products', defined as 'raw and processed or manufactured milk, and milk-derived products' including butter, cheese, ice cream, margarine, and milk and cultured milk products (yoghurt). Weinsier and Krumdieck (2000) reviewed 12 articles. Among the 12 articles, six found no effect between intake of dairy products and bone health, five found a positive effect and one found a negative effect. Women <30 years seemed to gain the most benefit.	Cumming and Nevitt (1997) found fourteen studies that evaluated Ca supplements (four randomized trials, three non-randomized trials and seven observational epidemiological studies) and 23 observational studies that evaluated dietary Ca (non-randomized trials). Main conclusion emphasized by authors was that ↑ Ca intake among postmenopausal women appeared to be associated with a small ↓ in risk of fracture, with ~30% ↓ in fracture risk among those taking higher amounts of Ca (1g daily as a supplement). Authors concluded that there is weak evidence of a protective capacity of dairy products on bone health.
Budek AZ, Hoppe C et al, 2007 Study Design: Non-Randomized Controlled Trial Class: C Positive quality	N=24 males, aged eight years. N=12 per group. Location: Denmark.	Interventions per day for seven days: 1) 1.5L skimmed milk 2) 250g low-fat meat. Each added 53g of PRO to the diet. Serum bone-specific alkaline phosphate (s-BAP), serum C-terminal telopeptides of type I collagen (s-CTX), and serum osteocalcin (s-OC) were measured at baseline and on day seven.	s-OC (P<0.003) and s-CTX (P<0.04) were significantly ↓ in milk group compared to meat group. s-BAP ↓ in both groups, but there were NS differences between groups Boys in milk group ↑ body weight by 0.54kg compared with the boys in meat group, that did not exhibit a Δ body weight (P=0.003).

Huncharek M, Muscat J et al, 2008 Study Design: Meta-analysis or Systematic Review Class: M Positive quality	N=21 studies with 3,821 subjects (83% female). Age: Four to 17.3 years.	Search terms used: Bone/bones, dairy products, Ca and Ca/dietary to identify relevant studies published between 1966 and 2006. Data were pooled from RCTs and observational studies using the primary outcomes of summary mean difference bone mineral content (BMC).	Combining data from 21 RCTs using total body bone mineral content (TB-BMC) as the outcome of interest, yielded a non-statistically significant ↑ in BMC of 2g (supplemented vs. controls). Sensitivity tests revealed that baseline Ca intake could be accounting for statistical heterogeneity. When results from three studies utilizing ↓ intake subjects were pooled, ↑ dairy/Ca intake was significantly associated with a mean BMC ↑ of 49g. Pooling data from two studies combining dairy/Ca and vitamin D supplementation showed a significant mean ↑ in lumbar spine BMC of 35g.
Kanis JA, Johansson H et al, 2005 Study Design: Meta-analysis Class: M Positive quality	Data from 39,563 adults participating in six prospective cohort studies in Europe, Australia and Canada. Age range: 21-103 years.	Quantified fracture risk associated with a ↓ dietary intake of milk and Ca and to explore dependence of this risk with age, sex and BMD.	NS relationship between ↓ intake of Ca and hip fracture risk in either sex at any age. For osteoporotic fractures, a small, but significant risk was found from the age of 80 years (RR=1.15; 95% CI: 1.02-1.30); however association was no longer significant when adjusted for BMD. Weak, but significant correlation between intake of milk and BMD (r=0.03643, P=4.5 x 10-10).
Konstantynowicz et al 2007 Study Design: Case-Control Study Class: C Neutral quality	N=91 cases with fractures (57 boys and 34 girls, aged 2.5-20 years) and 273 age- and sex-matched controls without fractures (three per case, 171 boys and 102 girls). Location: Poland.	Examined association between consumption of a milk-free diet and fracture risk. All children with cow's milk allergy were treated with a restrictive milk-free diet for 2.5 to 14 years. Weight, height, BMD and body composition were measured in all children, while Ca intake was assessed through 24-hour recall in a sub-set of 46 children.	In girls, 29.4% of cases and 11.8% of controls had consumed a milk-free diet, producing an OR for fracture associated with a milk-free diet of 4.6 (95% CI: 1.4, 15.5, P<0.01), while in boys, 23% of cases and 19% of controls had consumed a milk-free diet, producing an OR for fracture associated with a milk-free diet of 1.3 (95% CI: 0.6, 2.7, NS). No association found between Ca intake, BMD or fracture prevalence in the subset of children, leading authors to conclude that cow's milk allergy was associated with ↑ fracture risk in girls.

Kristensen et al 2005 Study Design: Randomized Crossover Trial Class: A Neutral quality	11 Caucasian males enrolled and completed the study. Age: 22-29 years Location: Denmark.	Investigated the short-term effects of replacing milk with cola beverages in young men on a low-Ca diet in order to study effect on Ca homeostasis and bone turnover. 2.5L of either cola or semi-skimmed milk were consumed each day in two 10-day experimental periods separated by a 10-day washout period. During the two diet periods, same low-Ca diet was given to the subjects; all meals provided.	An ↑ in serum phosphate (P<0.001), 1,25(OH)2D (P<0.001), PTH (P=0.046) and osteocalcin (P<0.001) was observed in the cola period compared to milk period and bone resorption was significantly ↑ following the cola period, seen as ↑ serum CTX (P<0.001) and urinary NTX (P<0.001) compared to milk period. No Δ observed in serum concentrations of Ca or B-ALP. Authors concluded that the trend towards replacement of milk with cola and other soft drinks results in a low Ca intake, which may negatively affect bone health.
McCabe LD, Martin BR et al, 2004 Study Design: Cross-Sectional Study Class: D Neutral quality	N=289 white women and 116 white men who participated in the RCT. Their data were combined with data from 265 black women and 75 black men for the cross-sectional study. Age: All subjects ≥60 years of age. Location: United States.	Study examined: 1) Cross-sectional relationship between consumption of Ca and other nutrients from dairy products and BMD at the hip in elderly black and white men and women 2) Impact of Ca supplement intake on the BMD loss in a longitudinal study of white men and women. For the trial, subjects received daily placebo, 750mg Ca per day, or 15mcg 25-hydroxyvitamin D per day for four years. For all subjects, dietary intake data was collected using the National Cancer Institute's Health Habits and History questionnaire and BMD was assessed using DEXA.	For all participants, average total Ca intake from dairy was 436±289mg, with an additional 239±93mg coming from nondairy dietary sources. In the cross-sectional analysis, a partial positive correlation was found between total hip BMD and dairy Ca in men (P<0.05, r=0.23), but not in women (NS, r=0.02). Results of the RCT showed that effect of calcium supplementation on femoral neck BMD depended on baseline dietary Ca intake (P<0.05). Participants with deficient diets (<1.5 servings or <450mg Ca per day) at baseline who were treated with Ca had less Δ in femoral neck BMD compared to those treated with placebo. Effect of Ca supplementation on femoral neck and hip BMD was evident in those that were <72 years old (P<0.05) at baseline, but not in those that were >72 years at baseline (NS).

Rockell et al 2005 Study Design: Longitudinal Study Class: C Positive quality	N=50 Caucasian children (aged three to 10 years) at baseline. N=28 girls and 18 boys (mean age 8.1±2.0 years) completed follow-up study. Location: New Zealand.	Longitudinal study assessing two-year Δ in bone and body composition in young children with history of prolonged milk avoidance. Ca intake was assessed by FFQ, as well as four-day diet records. BMD and body composition were measured using DEXA.	13 children (28.3%) had history of fracture; five new fractures had occurred during the two-year follow-up. At follow-up, Ca intakes were positively correlated with Z scores for total body bone mineral content (r=0.34, P<0.023), total bone area (r=0.33, P<0.025), ultradistal radial BMD (r=0.36, P<0.014) and 33% radial BMD (r=0.30, P<0.045). Every additional 100mg of Ca consumed was commensurate with a Δ of ~0.1 unit of Z score for these measurements. However, although some catch-up in height had taken place during follow-up, the group remained significantly shorter than reference population, with ↑ BMI. Authors concluded that young milk avoiders demonstrated persistent height ↓, overweight and osteopenia at the ultradistal radius and lumbar spine over two years of follow-up.

Search plan and results

Inclusion criteria

- June 2004 to July 2009
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children, two to 18 years; adults, 19 years and older
- *Populations:* Healthy and those with elevated chronic disease risk.

Exclusion criteria

- Studies that only consider cancer outcomes
- Studies that considered milk and milk products as part of a larger dietary pattern
- Milk and milk products in forms not commonly consumed (e.g., enriched with additional calcium)
- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Animal studies

- In vitro studies
- Articles not peer reviewed (web sites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: ("Dairy Products"[mh]) AND ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mesh: NoExp] OR “heart diseases”[mh] OR “chronic disease”[mh] OR "Neoplasms"[majr] OR osteoporosis[mh] OR "Bone Density"[Mesh] OR "Fractures, Bone"[Mesh])

Date searched: 07/29/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 223
- Total articles identified to review from electronic databases: 95
- Articles identified via handsearch or other means: 3
- Number of Primary Articles Identified: 20
- Number of Review Articles Identified: 4
- Total Number of Articles Identified: 24
- Number of Articles Reviewed but Excluded: 74

Included articles (References)

What is the relationship between the intake of milk and milk products and bone health?

Systematic Reviews/Meta-analyses

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: A review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.
2. Huncharek M, Muscat J, Kupelnick B. Impact of dairy products and dietary calcium on bone-mineral content in children: Results of a meta-analysis. *Bone.* 2008 Aug; 43(2): 312-321. Epub 2008 Mar 15. PMID: 18539555.
3. Kanis JA, Johansson H, Oden A, De Laet C, Johnell O, Eisman JA, Mc Closkey E, Mellstrom D, Pols H, Reeve J, Silman A, Tenenhouse A. A meta-analysis of milk intake and fracture risk: low utility for case finding. *Osteoporos Int.* 2005 Jul; 16(7): 799-804. Epub 2004 Oct 21. PMID: 15502959.

Primary Research

Trials

1. Budek AZ, Hoppe C, Michaelsen KF, Mølgaard C. High intake of milk, but not meat, decreases bone turnover in prepubertal boys after 7 days. *Eur J Clin Nutr.* 2007 Aug; 61(8): 957-962. Epub 2007 Jan 17. PMID: 17228345.
2. Kristensen M, Jensen M, Kudsk J, Henriksen M, Mølgaard C. Short-term effects on bone turnover of replacing milk with cola beverages: A 10-day interventional study in young men. *Osteoporos Int.* 2005 Dec; 16(12): 1, 803-1, 808. Epub 2005 May 11. PMID: 15886860.
3. McCabe LD, Martin BR, McCabe GP, Johnston CC, Weaver CM, Peacock M. Dairy intakes affect bone density in the elderly. *Am J Clin Nutr.* 2004 Oct; 80(4): 1, 066-1, 074. PMID: 15447921.

Longitudinal Study

1. Rockell JE, Williams SM, Taylor RW, Grant AM, Jones IE, Goulding A. Two-year changes in bone and body composition in young children with a history of prolonged milk avoidance. *Osteoporos Int.* 2005 Sep; 16(9): 1, 016-1, 023. Epub 2004 Nov 23. PMID: 15565350.

Case-Control Study

1. Konstantynowicz J, Nguyen TV, Kaczmarski M, Jamiolkowski J, Piotrowska-Jastrzebska J, Seeman E. Fractures during growth: Potential role of a milk-free diet. *Osteoporos Int.* 2007 Dec; 18(12): 1, 601-1, 607. Epub 2007 May 22. PMID: 17516020.

Cross-Sectional Study

1. Al-Zahrani MS. Increased intake of dairy products is related to lower periodontitis prevalence. *J Periodontol.* 2006 Feb; 77(2): 289-294. PMID: 16460256. (Hand search)

What is the relationship between the intake of milk and milk products and cardiovascular disease?

Systematic Reviews/Meta-Analyses

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: A review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.
2. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

Primary Research

Case-Control Study

1. Kontogianni MD, Panagiotakos DB, Chrysohoou C, Pitsavos C, Stefanadis C. Modelling dairy intake on the development of acute coronary syndromes: The CARDIO2000 study. *Eur J Cardiovasc Prev Rehabil.* 2006 Oct; 13(5): 791-797. PMID: 17001220.

What is the relationship between the intake of milk and milk products and blood pressure?

Systematic Review

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: a review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.

Primary Research

Trial

1. Bowen J, Noakes M, Clifton PM.Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. *Int J Obes (Lond).* 2005 Aug; 29(8): 957-965. PMID:

15711601. (Hand search)

Prospective Cohort Studies

1. Alonso A, Beunza JJ, Delgado-Rodríguez M, Martínez JA, Martínez-González MA. Low-fat dairy consumption and reduced risk of hypertension: The Seguimiento Universidad de Navarra (SUN) cohort. *Am J Clin Nutr.* 2005 Nov; 82(5): 972-979. PMID: 16280427.
2. Engberink MF, Hendriksen MA, Schouten EG, van Rooij FJ, Hofman A, Witteman JC, Geleijnse JM. Inverse association between dairy intake and hypertension: The Rotterdam Study. *Am J Clin Nutr.* 2009 Jun; 89(6): 1, 877-1, 883. Epub 2009 Apr 15. PMID: 19369377.
3. Engberink MF, Geleijnse JM, de Jong N, Smit HA, Kok FJ, Verschuren WM. Dairy intake, blood pressure, and incident hypertension in a general Dutch population. *J Nutr.* 2009 Mar; 139(3): 582-587. Epub 2009 Jan 21. PMID: 19158223.
4. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.
5. Toledo E, Delgado-Rodríguez M, Estruch R, Salas-Salvadó J, Corella D, Gomez-Gracia E, Fiol M, Lamuela-Raventós RM, Schröder H, Arós F, Ros E, Ruíz-Gutiérrez V, Lapetra J, Conde-Herrera M, Sáez G, Vinyoles E, Martínez-González MA. Low-fat dairy products and blood pressure: Follow-up of 2290 older persons at high cardiovascular risk participating in the PREDIMED study. *Br J Nutr.* 2009 Jan; 101(1): 59-67. Epub 2008 May 20. PMID: 18492300.
6. Wang L, Manson JE, Buring JE, Lee IM, Sesso HD. Dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women. *Hypertension.* 2008 Apr; 51(4): 1, 073-1, 079. Epub 2008 Feb 7. PMID: 18259007.

Cross-Sectional Studies

1. Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Tehranian adults. *Am J Clin Nutr.* 2005 Sep; 82(3): 523-530. PMID: 16155263.
2. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. *Am J Clin Nutr.* 2008 Jun; 87(6): 1, 914-1, 925. PMID: 18541585; PMCID: PMC2585752. (Hand search)
3. Djoussé L, Pankow JS, Hunt SC, Heiss G, Province MA, Kabagambe EK, Ellison RC. Influence of saturated fat and linolenic acid on the association between intake of dairy products and blood pressure. *Hypertension.* 2006 Aug; 48(2): 335-341. Epub 2006 Jun 26. PMID: 16801477.
4. Houston DK, Driver KE, Bush AJ, Kritchevsky SB. The association between cheese consumption and cardiovascular risk factors among adults. *J Hum Nutr Diet.* 2008 Apr; 21(2): 129-140. PMID: 18339053.
5. Ruidavets JB, Bongard V, Simon C, Dallongeville J, Ducimetière P, Arveiler D, Amouyel P, Bingham A, Ferrières J. Independent contribution of dairy products and calcium intake to blood pressure variations at a population level. *J*

Hypertens. 2006 Apr; 24(4): 671-681. PMID: 16531795.

What is the relationship between the intake of milk and milk products and type 2 diabetes?

Meta-Analysis

1. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

What is the relationship between the intake of milk and milk products and metabolic syndrome?

Primary Research

Meta-Analysis

1. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

Prospective Cohort Study

1. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.

Cross-Sectional Studies

1. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. *Am J Clin Nutr.* 2008 Jun; 87(6): 1, 914-1, 925. PMID: 18541585; PMCID: PMC2585752. (Hand search)
2. Ruidavets JB, Bongard V, Dallongeville J, Arveiler D, Ducimetière P, Perret B, Simon C, Amouyel P, Ferrières J. High consumptions of grain, fish, dairy products and combinations of these are associated with a low prevalence of metabolic syndrome. *J Epidemiol Community Health.* 2007 Sep; 61(9): 810-817. PMID: 17699537.

What is the relationship between the intake of milk and milk products and serum cholesterol?

Primary Research

Trial

1. Bowen J, Noakes M, Clifton PM.Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. *Int J Obes (Lond).* 2005 Aug; 29(8): 957-965. PMID: 15711601. (Hand search)

Prospective Cohort Study

1. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.

Cross-Sectional Study

1. Houston DK, Driver KE, Bush AJ, Kritchevsky SB. The association between cheese consumption and cardiovascular risk factors among adults. *J Hum Nutr Diet.* 2008 Apr; 21(2): 129-140. PMID: 18339053.

Excluded articles

Article	Reason for Exclusion
Ahn J, Albanes D, Peters U, Schatzkin A, Lim U, Freedman M, Chatterjee N, Andriole GL, Leitzmann MF, Hayes RB; Prostate, Lung, Colorectal, and Ovarian Trial Project Team. Dairy products, calcium intake, and risk of prostate cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev.* 2007 Dec; 16(12): 2, 623-2, 630. PMID: 18086766.	Cancer outcomes excluded from NEL review.
Al Sarakbi W, Salhab M, Mokbel K. Dairy products and breast cancer risk: A review of the literature. *Int J Fertil Womens Med.* 2005 Nov-Dec; 50(6): 244-249. Review. PMID: 16526414.	Cancer outcomes excluded from NEL review.
Allen NE, Key TJ, Appleby PN, Travis RC, Roddam AW, Tjønneland A, Johnsen NF, Overvad K, Linseisen J, Rohrmann S, Boeing H, Pischon T, Bueno-de-Mesquita HB, Kiemeney L, Tagliabue G, Palli D, Vineis P, Tumino R, Trichopoulou A, Kassapa C, Trichopoulos D, Ardanaz E, Larrañaga N, Tormo MJ, González CA, Quirós JR, Sánchez MJ, Bingham S, Khaw KT, Manjer J, Berglund G, Stattin P, Hallmans G, Slimani N, Ferrari P, Rinaldi S, Riboli E. Animal foods, protein, calcium and prostate cancer risk: the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer.* 2008 May 6; 98(9): 1, 574-1, 581. Epub 2008 Apr 1. PMID: 18382426.	Does not answer question: examined relationship between milk protein intake and health.
Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Tehranian adults. *Am J Clin Nutr.* 2005 Sep; 82(3): 523-530. PMID: 16155263.	Included in blood pressure review, but excluded from metabolic syndrome review because included in Elwood, 2008.
Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: A systematic literature review and meta-analysis. *Cancer Causes Control.* 2007 Nov; 18(9): 967-988. Epub 2007 Jul 19. Review. PMID: 17638104; PMCID: PMC2592095.	Cancer outcomes excluded from NEL review.

Benito P, Caballero J, Moreno J, Gutiérrez-Alcántara C, Muñoz C, Rojo G, Garcia S, Soriguer FC. Effects of milk enriched with omega-3 fatty acid, oleic acid and folic acid in patients with metabolic syndrome. *Clin Nutr.* 2006 Aug; 25(4): 581-587. Epub 2006 May 15. PMID: 16701922.	Participants diagnosed with metabolic syndrome.
Biong AS, Rebnord HM, Fimreite RL, Trygg KU, Ringstad J, Thelle DS, Pedersen JI. Intake of dairy fat and dairy products, and risk of myocardial infarction: A case-control study. *Int J Food Sci Nutr.* 2008 Mar; 59(2): 155-165. PMID: 17886080.	Included in Elwood, 2008.
Biong AS, Veierød MB, Ringstad J, Thelle DS, Pedersen JI. Intake of milk fat, reflected in adipose tissue fatty acids and risk of myocardial infarction: A case-control study. *Eur J Clin Nutr.* 2006 Feb; 60(2): 236-244. PMID: 16267503.	Does not answer question: examined relationship between fatty acids in adipose tissue and myocardial infarction.
Chan JM, Wang F, Holly EA. Pancreatic cancer, animal protein and dietary fat in a population-based study, San Francisco Bay Area, California. *Cancer Causes Control.* 2007 Dec; 18(10): 1, 153-1, 167. Epub 2007 Sep 1. PMID: 17805983.	Cancer outcomes excluded from NEL review.
Cheng S, Lyytikäinen A, Kröger H, Lamberg-Allardt C, Alén M, Koistinen A, Wang QJ, Suuriniemi M, Suominen H, Mahonen A, Nicholson PH, Ivaska KK, Korpela R, Ohlsson C, Väänänen KH, Tylavsky F. Effects of calcium, dairy product, and vitamin D supplementation on bone mass accrual and body composition in 10- to 12-year-old girls: A two-year randomized trial. *Am J Clin Nutr.* 2005 Nov; 82(5): 1, 115-1, 126; quiz 1, 147-1, 148. PMID: 16280447.	Included in Huncharek, 2008.
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Daly RM, Brown M, Bass S, Kukuljan S, Nowson C. Calcium- and vitamin D3-fortified milk reduces bone loss at clinically relevant skeletal sites in older men: a 2-year randomized controlled trial. *J Bone Miner Res.* 2006 Mar; 21(3): 397-405. Epub 2005 Dec 19. PMID: 16491287.	Milk enriched with additional calcium and vitamin D_3.
Dixon LB, Pellizzon MA, Jawad AF, Tershakovec AM. Calcium and dairy intake and measures of obesity in hyper- and normocholesterolemic children. *Obes Res.* 2005 Oct; 13(10): 1, 727-1, 738. PMID: 16286520.	The relationship between milk product intake and adiposity in children is reviewed in the Energy Balance section.
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Du X, Zhu K, Trube A, Zhang Q, Ma G, Hu X, Fraser DR, Greenfield H. School-milk intervention trial enhances growth and bone mineral accretion in Chinese girls aged 10 to 12 years in Beijing. *Br J Nutr.* 2004 Jul; 92(1): 159-168. Erratum in: *Br J Nutr.* 2005 Apr; 93(4): 571-572. PMID: 15230999.	Milk enriched with additional calcium.
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Elwood PC, Pickering JE, Fehily AM, Hughes J, Ness AR. Milk drinking, ischaemic heart disease and ischaemic stroke I. Evidence from the Caerphilly cohort. *Eur J Clin Nutr.* 2004 May; 58(5): 711-717. PMID: 15116073.	Included in Elwood, 2008.
Elwood PC, Pickering JE, Hughes J, Fehily AM, Ness AR. Milk drinking, ischaemic heart disease and ischaemic stroke II. Evidence from cohort studies. *Eur J Clin Nutr.* 2004 May; 58(5): 718-724. Review. PMID: 15116074.	The most recent meta-analyses from these authors on these outcomes was included (Elwood, 2008).
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Genkinger JM, Hunter DJ, Spiegelman D, Anderson KE, Arslan A, Beeson WL, Buring JE, Fraser GE, Freudenheim JL, Goldbohm RA, Hankinson SE, Jacobs DR Jr, Koushik A, Lacey JV Jr, Larsson SC, Leitzmann M, McCullough ML, Miller AB, Rodriguez C, Rohan TE, Schouten LJ, Shore R, Smit E, Wolk A, Zhang SM, Smith-Warner SA. Dairy products and ovarian cancer: A pooled analysis of 12 cohort studies. *Cancer Epidemiol Biomarkers Prev.* 2006 Feb; 15(2): 364-372. PMID: 16492930.	Cancer outcomes excluded from NEL review.
Gibbons MJ, Gilchrist NL, Frampton C, Maguire P, Reilly PH, March RL, Wall CR. The effects of a high calcium dairy food on bone health in pre-pubertal children in New Zealand. *Asia Pac J Clin Nutr.* 2004; 13(4): 341-347. PMID: 15563438.	Drink was a high calcium supplement, not milk as defined by the Subcommittee.
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Huncharek M, Muscat J, Kupelnick B. Dairy products, dietary calcium and vitamin D intake as risk factors for prostate cancer: A meta-analysis of 26, 769 cases from 45 observational studies. *Nutr Cancer.* 2008; 60(4): 421-441. PMID: 18584476.	Cancer outcomes excluded from NEL review.
Kesse E, Bertrais S, Astorg P, Jaouen A, Arnault N, Galan P, Hercberg S. Dairy products, calcium and phosphorus intake, and the risk of prostate cancer: Results of the French prospective SU.VI.MAX (Supplémentation en Vitamines et Minéraux Antioxydants) study. *Br J Nutr.* 2006 Mar; 95(3): 539-545. PMID: 16512941.	Cancer outcomes excluded from NEL review.
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Lancaster KJ. Characteristics influencing daily consumption of fruits and vegetables and low-fat dairy products in older adults with hypertension. *J Nutr Elder.* 2004; 23(4): 21-33. PMID: 15233120.	Does not answer question; did not examine relationship between milk product intake and health; participants diagnosed with hypertension.
Larson NI, Neumark-Sztainer D, Harnack L, Wall M, Story M, Eisenberg ME. Calcium and dairy intake: Longitudinal trends during the transition to young adulthood and correlates of calcium intake. *J Nutr Educ Behav.* 2009 Jul-Aug; 41(4): 254-260. PMID: 19508930.	Does not answer question; did not examine relationship between milk product intake and health.
Larsson SC, Andersson SO, Johansson JE, Wolk A. Cultured milk, yogurt, and dairy intake in relation to bladder cancer risk in a prospective study of Swedish women and men. *Am J Clin Nutr.* 2008 Oct; 88(4): 1, 083-1, 087. PMID: 18842797.	Cancer outcomes excluded from NEL review.

Larsson SC, Bergkvist L, Rutegård J, Giovannucci E, Wolk A. Calcium and dairy food intakes are inversely associated with colorectal cancer risk in the Cohort of Swedish Men. *Am J Clin Nutr.* 2006 Mar; 83(3): 667-673; quiz 728-729. PMID: 16522915.	Cancer outcomes excluded from NEL review.
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Larsson SC, Bergkvist L, Wolk A. Milk and lactose intakes and ovarian cancer risk in the Swedish Mammography Cohort. *Am J Clin Nutr.* 2004 Nov; 80(5): 1, 353-1, 357. PMID: 15531686.	Cancer outcomes excluded from NEL review.
Larsson SC, Orsini N, Wolk A. Milk, milk products and lactose intake and ovarian cancer risk: A meta-analysis of epidemiological studies. *Int J Cancer.* 2006 Jan 15; 118(2): 431-441. PMID: 16052536.	Cancer outcomes excluded from NEL review.
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Liu S, Choi HK, Ford E, Song Y, Klevak A, Buring JE, Manson JE. A prospective study of dairy intake and the risk of type 2 diabetes in women. *Diabetes Care.* 2006 Jul; 29(7): 1, 579-1, 584. PMID: 16801582.	Included in Elwood, 2008.
Lorenz M, Jochmann N, von Krosigk A, Martus P, Baumann G, Stangl K, Stangl V. Addition of milk prevents vascular protective effects of tea. *Eur Heart J.* 2007 Jan; 28(2): 219-223. Epub 2007 Jan 9. PMID: 17213230.	Does not answer question; did not examine relationship between milk product intake and health.
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McCullough ML, Rodriguez C, Diver WR, Feigelson HS, Stevens VL, Thun MJ, Calle EE. Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev.* 2005 Dec; 14(12): 2, 898-2, 904. PMID: 16365007.	Cancer outcomes excluded from NEL review.

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Mitrou PN, Albanes D, Weinstein SJ, Pietinen P, Taylor PR, Virtamo J, Leitzmann MF. A prospective study of dietary calcium, dairy products and prostate cancer risk (Finland). *Int J Cancer.* 2007 Jun 1; 120(11): 2, 466-2, 473. PMID: 17278090.	Cancer outcomes excluded from NEL review.
Mizoue T, Kimura Y, Toyomura K, Nagano J, Kono S, Mibu R, Tanaka M, Kakeji Y, Maehara Y, Okamura T, Ikejiri K, Futami K, Yasunami Y, Maekawa T, Takenaka K, Ichimiya H, Imaizumi N. Calcium, dairy foods, vitamin D, and colorectal cancer risk: The Fukuoka Colorectal Cancer Study. *Cancer Epidemiol Biomarkers Prev.* 2008 Oct; 17(10): 2, 800-2, 807. PMID: 18843026.	Cancer outcomes excluded from NEL review.
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Nestel PJ, Chronopulos A, Cehun M. Dairy fat in cheese raises LDL cholesterol less than that in butter in mildly hypercholesterolaemic subjects. *Eur J Clin Nutr.* 2005 Sep; 59(9): 1, 059-1, 063. PMID: 16015270.	Participants diagnosed with hypercholesterolemia.
Park SY, Murphy SP, Wilkens LR, Stram DO, Henderson BE, Kolonel LN. Calcium, vitamin D, and dairy product intake and prostate cancer risk: The Multiethnic Cohort Study. *Am J Epidemiol.* 2007 Dec 1; 166(11): 1, 259-1, 269. Epub 2007 Oct 8. PMID: 17925283.	Cancer outcomes excluded from NEL review.
Park Y, Leitzmann MF, Subar AF, Hollenbeck A, Schatzkin A. Dairy food, calcium, and risk of cancer in the NIH-AARP Diet and Health Study. *Arch Intern Med.* 2009 Feb 23; 169(4): 391-401. PMID: 19237724.	Cancer outcomes excluded from NEL review.
Park Y, Mitrou PN, Kipnis V, Hollenbeck A, Schatzkin A, Leitzmann MF. Calcium, dairy foods, and risk of incident and fatal prostate cancer: the NIH-AARP Diet and Health Study. *Am J Epidemiol.* 2007 Dec 1; 166(11): 1, 270-1, 279. Epub 2007 Oct 12. PMID: 18000020.	Cancer outcomes excluded from NEL review.
Parodi PW. Dairy product consumption and the risk of breast cancer. *J Am Coll Nutr.* 2005 Dec; 24(6 Suppl): 556S-568S. Review. PMID: 16373955.	Cancer outcomes excluded from NEL review.
Qin LQ, Xu JY, Wang PY, Hashi A, Hoshi K, Sato A. Milk/dairy products consumption, galactose metabolism and ovarian cancer: Meta-analysis of epidemiological studies. *Eur J Cancer Prev.* 2005 Feb; 14(1): 13-19. PMID: 15677891.	Cancer outcomes excluded from NEL review.

Qin LQ, Xu JY, Wang PY, Tong J, Hoshi K. Milk consumption is a risk factor for prostate cancer in Western countries: Evidence from cohort studies. *Asia Pac J Clin Nutr.* 2007; 16(3): 467-476. PMID: 17704029.	Cancer outcomes excluded from NEL review.
Qin LQ, Xu JY, Wang PY, Kaneko T, Hoshi K, Sato A. Milk consumption is a risk factor for prostate cancer: Meta-analysis of case-control studies. *Nutr Cancer.* 2004; 48(1): 22-27. PMID: 15203374.	Cancer outcomes excluded from NEL review.
Rohrmann S, Platz EA, Kavanaugh CJ, Thuita L, Hoffman SC, Helzlsouer KJ. Meat and dairy consumption and subsequent risk of prostate cancer in a US cohort study. *Cancer Causes Control.* 2007 Feb; 18(1): 41-50. PMID: 17315319.	Cancer outcomes excluded from NEL review.
Snijder MB, van der Heijden AA, van Dam RM, Stehouwer CD, Hiddink GJ, Nijpels G, Heine RJ, Bouter LM, Dekker JM. Is higher dairy consumption associated with lower body weight and fewer metabolic disturbances? The Hoorn Study. *Am J Clin Nutr.* 2007 Apr; 85(4): 989-995. PMID: 17413097.	Same data set as Snijder, 2008.
Sun Q, Ma J, Campos H, Hu FB. Plasma and erythrocyte biomarkers of dairy fat intake and risk of ischemic heart disease. *Am J Clin Nutr.* 2007 Oct; 86(4): 929-937. PMID: 17921367.	Does not answer question; examined relationship between fatty acids and disease risk.
Taguchi H, Chen H, Yano R, Shoumura S. Comparative effects of milk and soymilk on bone loss in adult ovariectomized osteoporosis rat. *Okajimas Folia Anat Jpn.* 2006 Aug; 83(2): 53-59. PMID: 16944838.	Study tested animals.
Tricon S, Burdge GC, Jones EL, Russell JJ, El-Khazen S, Moretti E, Hall WL, Gerry AB, Leake DS, Grimble RF, Williams CM, Calder PC, Yaqoob P. Effects of dairy products naturally enriched with cis-9, trans-11 conjugated linoleic acid on the blood lipid profile in healthy middle-aged men. *Am J Clin Nutr.* 2006 Apr; 83(4): 744-753. PMID: 16600923.	Milk products enriched with cis-9, trans-11 conjugated linoleic acid.
Tseng M, Breslow RA, Graubard BI, Ziegler RG. Dairy, calcium, and vitamin D intakes and prostate cancer risk in the National Health and Nutrition Examination Epidemiologic Follow-up Study cohort. *Am J Clin Nutr.* 2005 May; 81(5): 1, 147-1, 154. PMID: 15883441.	Cancer outcomes excluded from NEL review.
van der Pols JC, Bain C, Gunnell D, Smith GD, Frobisher C, Martin RM. Childhood dairy intake and adult cancer risk: 65-year follow-up of the Boyd Orr cohort. *Am J Clin Nutr.* 2007 Dec; 86(6): 1, 722-1, 729. PMID: 18065592.	Cancer outcomes excluded from NEL review.

Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: A systematic review and meta-analysis. *Am J Public Health.* 2007 Apr; 97(4): 667-675. Epub 2007 Feb 28. Review. PMID: 17329656; PMCID: PMC1829363.	Does not answer question; did not examine relationship between milk product intake and health.
Warensjö E, Jansson JH, Berglund L, Boman K, Ahrén B, Weinehall L, Lindahl B, Hallmans G, Vessby B. Estimated intake of milk fat is negatively associated with cardiovascular risk factors and does not increase the risk of a first acute myocardial infarction. A prospective case-control study. *Br J Nutr.* 2004 Apr; 91(4): 635-642. PMID: 15035691.	Does not include milk product intake in analyses.
Xu JY, Qin LQ, Wang PY, Li W, Chang C. Effect of milk tripeptides on blood pressure: a meta-analysis of randomized controlled trials. *Nutrition.* 2008 Oct; 24(10): 933-940. Epub 2008 Jun 17. PMID: 18562172.	Does not answer question; did not examine relationship between milk product intake and health.
Zhang J, Kesteloot H. Milk consumption in relation to incidence of prostate, breast, colon, and rectal cancers: Is there an independent effect? Nu*tr Cancer.* 2005; 53(1): 65-72. PMID: 16351508.	Cancer outcomes excluded from NEL review.
Zhu K, Zhang Q, Foo LH, Trube A, Ma G, Hu X, Du X, Cowell CT, Fraser DR, Greenfield H. Growth, bone mass, and vitamin D status of Chinese adolescent girls three years after withdrawal of milk supplementation. *Am J Clin Nutr.* 2006 Mar; 83(3): 714-721. PMID: 16522922.	Milk enriched with additional calcium.

CHAPTER 15. MILK AND MILK PRODUCTS – CARDIOVASCULAR DISEASE

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF MILK AND MILK PRODUCTS AND CARDIOVASCULAR DISEASE?

Conclusion statement

Moderate evidence shows that intake of milk and milk products are inversely associated with cardiovascular disease.

Grade

Moderate

Evidence summary overview

Recent studies report that intake of milk and milk products are protective against cardiovascular disease (CVD). The conclusion reached for this question is based on review of two systematic reviews/meta-analyses (Alvarez-Leon, 2006; Elwood, 2008) and one case-control study (Kontogianni, 2006).

Alvarez-Leon et al (2006) systematically reviewed papers on the associations between consumption of dairy products and health outcomes, including CVD. The systematic review of these papers found an inverse association between the intake of dairy products and stroke.

Elwood et al (2008) performed a systematic review and meta-analysis to investigate the literature on milk and dairy consumption and risk of vascular disease. The final review included 15 prospective studies on ischemic heart disease (IHD) and stroke and four case-control studies on myocardial infarction (MI). The data showed a reduction in risk associated with the highest level of milk consumption for MI. There was also a reduction of about 10% to 15% in the incidence of IHD and a 20% reduction in stroke events in the individuals who had reported drinking the most milk, relative to those drinking the least milk within each cohort. The authors concluded that the data provides support for the beneficial effects of milk and dairy consumption on risk for CVD.

Finally, in a case-control study, Kontogianni et al (2006) examined the association between dairy consumption and the prevalence of a first, non-fatal event of an acute coronary syndrome in Greek adults. They reported an inverse relationship between dairy product consumption and the odds of having acute coronary syndrome. An increase of one portion of a dairy product per week was associated with a 12% lower likelihood of having acute coronary syndrome.

Evidence summary paragraphs

Systematic Reviews / Meta-Analyses:

Alvarez-Leon et al, 2006 (positive quality) systematically reviewed papers on the associations between consumption of dairy products and health outcomes, including cancer, bone health and CVD. Relevant articles were obtained through searching the MEDLINE database (from 1966 to January 2005) using the search terms: ‘dairy

products,' defined as 'raw and processed or manufactured milk, and milk-derived products' including butter, cheese, ice cream, margarine, and milk and cultured milk products (yoghurt). This search revealed 85,000 articles. After excluding studies, and including only meta-analysis and systematic reviews, the final sample consisted of 14 meta-analyses and systematic reviews. This final sample consisted of six papers on dairy products and cancer, six papers on dairy products and CVD [including hypertension (HTN), stroke and heart diseases] and two papers on dairy products and bone health. Evidence from these papers was summarized and evaluated. The systematic review found an inverse association between the intake of dairy products and stroke.

Elwood et al, 2008 (positive quality) performed a systematic review and meta-analysis to investigate the literature on milk and dairy consumption and risk of vascular disease and diabetes, examine the evidence related to consumption of whole vs. reduced fat milk and disease risk, and consider the likely effect of milk and dairy consumption on survival. The authors also reviewed a 2007 report by the World Cancer Research Fund to determine the impact of milk and dairy consumption on cancer risk. Using Cochrane systematic review methods, MEDLINE was searched up to June 2008 using key words milk/milk protein/dairy/dairy calcium and heart disease/coronary artery disease/myocardial infarction/ischaemic heart disease, stroke, and diabetes/metabolic syndrome. This search revealed 180 papers on milk and heart disease, 33 papers on milk and stroke, and 111 papers on milk and diabetes. Only studies that were done in human adults using population-based and prospective designs and reported baseline data on milk or dairy consumption, vascular disease outcome or incident diabetes were included in the final review. The final sample included 15 prospective studies on IHD and stroke, four prospective studies on diabetes, four case-control studies on metabolic syndrome and four case-control studies on MI. The data showed a reduction in risk associated with the highest level of milk consumption for MI (RR=0.83; 95% CI: 0.66, 0.99). There was also a reduction of about 10% to 15% in the incidence of IHD (RR=0.84; 95% CI: 0.76, 0.93) and a 20% reduction in stroke events in the subjects who had reported drinking the most milk, relative to those drinking the least milk within each cohort (RR=0.79; 95% CI: 0.75, 0.82). The authors concluded that taken together, these data provide support for the beneficial effects of milk and dairy consumption on health.

Case-Control Study:

Kontogianni et al, 2006 (neutral quality) used data from a case-control study to evaluate the association between dairy consumption and the prevalence of a first, non-fatal event of an acute coronary syndrome. Subjects were Greek adults [848 (700 male, 148 female) patients with an event of acute coronary syndrome and 1,078 (830 male, 248 female) population-based controls matched for age and sex]. Dietary intake was assessed using a semi-quantitative food-frequency questionnaire (FFQ), and multiple regression analysis estimated the odds ratio (OR) of having acute coronary syndrome by level of dairy intake, after adjusting for confounders. Levels of dairy intake were: No intake, five or less portions a week, six to eight portions a week and nine or more portions a week. Results showed an inverse relationship between dairy product consumption and odds of having acute coronary syndrome. An increase of one portion of dairy per week was associated with 12% lower likelihood of having acute coronary syndrome (0.88; 95% CI: 0.83, 0.93; P<0.0001). Cut-off analysis

showed that 7.4 portions of dairy a week was the optimal consumption amount to benefit people from having acute coronary syndrome.

Overview table

Author, Year, Study Design, Class, Rating	Participants	Description of Study Design	Outcomes
Alvarez-León EE, Roman-Vinas B et al, 2006 Study Design: Meta-analysis or Systematic Review Class: M Positive quality	N=14 meta-analyses and systematic reviews: Six on dairy products and cancer Six on dairy products and CVD Two on dairy products and bone health.	Relevant articles obtained through searching MEDLINE database (from 1966 to January 2005) using search terms: 'dairy products,' defined as 'raw and processed or manufactured milk, and milk-derived products' including butter, cheese, ice cream, margarine, and milk and cultured milk products (yoghurt).	Reviews on stroke and heart diseases were considered. Systematic review found inverse association between intake of dairy products and stroke.
Elwood PC, Givens DI et al, 2008 Study Design: Systematic review and meta-analysis Class: M Positive quality	Final N=15 prospective studies on ICD and stroke: Four prospective studies on diabetes Four case-control studies on metabolic syndrome Four case-control studies on MI.	MEDLINE searched up to June 2008 using key words milk/milk protein/dairy/dairy calcium and heart disease/coronary artery disease/myocardial infarction/ischaemic heart disease, stroke, and diabetes/metabolic syndrome.	Data showed a ↓ in risk associated with the highest level of milk consumption for MI (RR=0.83; 95% CI: 0.66, 0.99). Also a ↓ of ~10% to 15% in the incidence of IHD (RR=0.84; 95% CI: 0.76, 0.93) and a 20% ↓ in stroke events in subjects who had reported drinking the most milk, relative to those drinking the least milk within each cohort (RR=0.79; 95% CI: 0.75, 0.82).

Kontogianni MD, Panagiotakos DB et al, 2006 Study Design: Case Control Study Class: C Neural quality	N=848 (700 male, 148 female) patients with an event of acute coronary syndrome. N=1,078 (830 male, 248 female) population-based controls matched for age and sex. Location: Greece.	Dietary intake assessed using a semi-quantitative FFQ. Multiple regression analysis estimated the OR of having acute coronary syndrome by level of dairy intake, after adjusting for confounders. Levels of dairy intake were (portions per week): No intake ≤ Five Six to eight ≥ Nine.	An ↑ of one portion of dairy per week associated with 12% ↓ likelihood of having acute coronary syndrome (0.88; 95% CI: 0.83, 0.93; P<0.0001). Cut-off analysis showed that 7.4 portions of dairy a week was the optimal consumption amount to benefit people from having acute coronary syndrome.

Search plan and results

Inclusion criteria

- June 2004 to July 2009
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children, two to 18 years; adults, 19 years and older
- *Populations:* Healthy and those with elevated chronic disease risk.

Exclusion criteria

- Studies that only consider cancer outcomes
- Studies that considered milk and milk products as part of a larger dietary pattern
- Milk and milk products in forms not commonly consumed (e.g., enriched with additional calcium)
- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Animal studies
- In vitro studies
- Articles not peer reviewed (web sites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: ("Dairy Products"[mh]) AND ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mesh: NoExp] OR “heart diseases”[mh] OR

"chronic disease"[mh] OR "Neoplasms"[majr] OR osteoporosis[mh] OR "Bone Density"[Mesh] OR "Fractures, Bone"[Mesh])

Date searched: 07/29/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 223
- Total articles identified to review from electronic databases: 95
- Articles identified via handsearch or other means: 3
- Number of Primary Articles Identified: 20
- Number of Review Articles Identified: 4
- Total Number of Articles Identified: 24
- Number of Articles Reviewed but Excluded: 74

Included articles (References)

What is the relationship between the intake of milk and milk products and bone health?

Systematic Reviews/Meta-analyses

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: A review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.
2. Huncharek M, Muscat J, Kupelnick B. Impact of dairy products and dietary calcium on bone-mineral content in children: Results of a meta-analysis. *Bone.* 2008 Aug; 43(2): 312-321. Epub 2008 Mar 15. PMID: 18539555.
3. Kanis JA, Johansson H, Oden A, De Laet C, Johnell O, Eisman JA, Mc Closkey E, Mellstrom D, Pols H, Reeve J, Silman A, Tenenhouse A. A meta-analysis of milk intake and fracture risk: low utility for case finding. *Osteoporos Int.* 2005 Jul; 16(7): 799-804. Epub 2004 Oct 21. PMID: 15502959.

Primary Research

Trials

1. Budek AZ, Hoppe C, Michaelsen KF, Mølgaard C. High intake of milk, but not meat, decreases bone turnover in prepubertal boys after 7 days. *Eur J Clin Nutr.* 2007 Aug; 61(8): 957-962. Epub 2007 Jan 17. PMID: 17228345.
2. Kristensen M, Jensen M, Kudsk J, Henriksen M, Mølgaard C. Short-term effects on bone turnover of replacing milk with cola beverages: A 10-day interventional study in young men. *Osteoporos Int.* 2005 Dec; 16(12): 1, 803-1, 808. Epub 2005 May 11. PMID: 15886860.
3. McCabe LD, Martin BR, McCabe GP, Johnston CC, Weaver CM, Peacock M. Dairy intakes affect bone density in the elderly. *Am J Clin Nutr.* 2004 Oct; 80(4): 1, 066-1, 074. PMID: 15447921.

Longitudinal Study

1. Rockell JE, Williams SM, Taylor RW, Grant AM, Jones IE, Goulding A. Two-year changes in bone and body composition in young children with a history of prolonged milk avoidance. *Osteoporos Int.* 2005 Sep; 16(9): 1, 016-1, 023. Epub 2004 Nov 23. PMID: 15565350.

Case-Control Study

1. Konstantynowicz J, Nguyen TV, Kaczmarski M, Jamiolkowski J, Piotrowska-Jastrzebska J, Seeman E. Fractures during growth: Potential role of a milk-free diet. *Osteoporos Int.* 2007 Dec; 18(12): 1, 601-1, 607. Epub 2007 May 22. PMID: 17516020.

Cross-Sectional Study

1. Al-Zahrani MS. Increased intake of dairy products is related to lower periodontitis prevalence. *J Periodontol.* 2006 Feb; 77(2): 289-294. PMID: 16460256. (Hand search)

What is the relationship between the intake of milk and milk products and cardiovascular disease?

Systematic Reviews/Meta-Analyses

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: A review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.
2. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

Primary Research

Case-Control Study

1. Kontogianni MD, Panagiotakos DB, Chrysohoou C, Pitsavos C, Stefanadis C. Modelling dairy intake on the development of acute coronary syndromes: The CARDIO2000 study. *Eur J Cardiovasc Prev Rehabil.* 2006 Oct; 13(5): 791-797. PMID: 17001220.

What is the relationship between the intake of milk and milk products and blood pressure?

Systematic Review

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: a review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.

Primary Research

Trial

2. Bowen J, Noakes M, Clifton PM.Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. *Int J Obes (Lond).* 2005 Aug; 29(8): 957-965. PMID: 15711601. (Hand search)

Prospective Cohort Studies

1. Alonso A, Beunza JJ, Delgado-Rodríguez M, Martínez JA, Martínez-González MA. Low-fat dairy consumption and reduced risk of hypertension: The Seguimiento Universidad de Navarra (SUN) cohort. *Am J Clin Nutr.* 2005 Nov;

82(5): 972-979. PMID: 16280427.
2. Engberink MF, Hendriksen MA, Schouten EG, van Rooij FJ, Hofman A, Witteman JC, Geleijnse JM. Inverse association between dairy intake and hypertension: The Rotterdam Study. *Am J Clin Nutr.* 2009 Jun; 89(6): 1, 877-1, 883. Epub 2009 Apr 15. PMID: 19369377.
3. Engberink MF, Geleijnse JM, de Jong N, Smit HA, Kok FJ, Verschuren WM. Dairy intake, blood pressure, and incident hypertension in a general Dutch population. *J Nutr.* 2009 Mar; 139(3): 582-587. Epub 2009 Jan 21. PMID: 19158223.
4. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.
5. Toledo E, Delgado-Rodríguez M, Estruch R, Salas-Salvadó J, Corella D, Gomez-Gracia E, Fiol M, Lamuela-Raventós RM, Schröder H, Arós F, Ros E, Ruíz-Gutiérrez V, Lapetra J, Conde-Herrera M, Sáez G, Vinyoles E, Martínez-González MA. Low-fat dairy products and blood pressure: Follow-up of 2290 older persons at high cardiovascular risk participating in the PREDIMED study. *Br J Nutr.* 2009 Jan; 101(1): 59-67. Epub 2008 May 20. PMID: 18492300.
6. Wang L, Manson JE, Buring JE, Lee IM, Sesso HD. Dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women. *Hypertension.* 2008 Apr; 51(4): 1, 073-1, 079. Epub 2008 Feb 7. PMID: 18259007.

Cross-Sectional Studies

1. Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Tehranian adults. *Am J Clin Nutr.* 2005 Sep; 82(3): 523-530. PMID: 16155263.
2. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. *Am J Clin Nutr.* 2008 Jun; 87(6): 1, 914-1, 925. PMID: 18541585; PMCID: PMC2585752. (Hand search)
3. Djoussé L, Pankow JS, Hunt SC, Heiss G, Province MA, Kabagambe EK, Ellison RC. Influence of saturated fat and linolenic acid on the association between intake of dairy products and blood pressure. *Hypertension.* 2006 Aug; 48(2): 335-341. Epub 2006 Jun 26. PMID: 16801477.
4. Houston DK, Driver KE, Bush AJ, Kritchevsky SB. The association between cheese consumption and cardiovascular risk factors among adults. *J Hum Nutr Diet.* 2008 Apr; 21(2): 129-140. PMID: 18339053.
5. Ruidavets JB, Bongard V, Simon C, Dallongeville J, Ducimetière P, Arveiler D, Amouyel P, Bingham A, Ferrières J. Independent contribution of dairy products and calcium intake to blood pressure variations at a population level. *J Hypertens.* 2006 Apr; 24(4): 671-681. PMID: 16531795.

What is the relationship between the intake of milk and milk products and type 2 diabetes?

Meta-Analysis

1. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

What is the relationship between the intake of milk and milk products and metabolic syndrome?

Primary Research

Meta-Analysis

1. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

Prospective Cohort Study

1. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.

Cross-Sectional Studies

1. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. *Am J Clin Nutr.* 2008 Jun; 87(6): 1, 914-1, 925. PMID: 18541585; PMCID: PMC2585752. (Hand search)
2. Ruidavets JB, Bongard V, Dallongeville J, Arveiler D, Ducimetière P, Perret B, Simon C, Amouyel P, Ferrières J. High consumptions of grain, fish, dairy products and combinations of these are associated with a low prevalence of metabolic syndrome. *J Epidemiol Community Health.* 2007 Sep; 61(9): 810-817. PMID: 17699537.

What is the relationship between the intake of milk and milk products and serum cholesterol?

Primary Research

Trial

1. Bowen J, Noakes M, Clifton PM.Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. *Int J Obes (Lond).* 2005 Aug; 29(8): 957-965. PMID: 15711601. (Hand search)

Prospective Cohort Study

1. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.

Cross-Sectional Study

1. Houston DK, Driver KE, Bush AJ, Kritchevsky SB. The association between cheese consumption and cardiovascular risk factors among adults. *J Hum Nutr Diet.* 2008 Apr; 21(2): 129-140. PMID: 18339053.

Excluded articles

Article	Reason for Exclusion
Ahn J, Albanes D, Peters U, Schatzkin A, Lim U, Freedman M, Chatterjee N, Andriole GL, Leitzmann MF, Hayes RB; Prostate, Lung, Colorectal, and Ovarian Trial Project Team. Dairy products, calcium intake, and risk of prostate cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev.* 2007 Dec; 16(12): 2, 623-2, 630. PMID: 18086766.	Cancer outcomes excluded from NEL review.
Al Sarakbi W, Salhab M, Mokbel K. Dairy products and breast cancer risk: A review of the literature. *Int J Fertil Womens Med.* 2005 Nov-Dec; 50(6): 244-249. Review. PMID: 16526414.	Cancer outcomes excluded from NEL review.
Allen NE, Key TJ, Appleby PN, Travis RC, Roddam AW, Tjønneland A, Johnsen NF, Overvad K, Linseisen J, Rohrmann S, Boeing H, Pischon T, Bueno-de-Mesquita HB, Kiemeney L, Tagliabue G, Palli D, Vineis P, Tumino R, Trichopoulou A, Kassapa C, Trichopoulos D, Ardanaz E, Larrañaga N, Tormo MJ, González CA, Quirós JR, Sánchez MJ, Bingham S, Khaw KT, Manjer J, Berglund G, Stattin P, Hallmans G, Slimani N, Ferrari P, Rinaldi S, Riboli E. Animal foods, protein, calcium and prostate cancer risk: the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer.* 2008 May 6; 98(9): 1, 574-1, 581. Epub 2008 Apr 1. PMID: 18382426.	Does not answer question: examined relationship between milk protein intake and health.
Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Tehranian adults. *Am J Clin Nutr.* 2005 Sep; 82(3): 523-530. PMID: 16155263.	Included in blood pressure review, but excluded from metabolic syndrome review because included in Elwood, 2008.
Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: A systematic literature review and meta-analysis. *Cancer Causes Control.* 2007 Nov; 18(9): 967-988. Epub 2007 Jul 19. Review. PMID: 17638104; PMCID: PMC2592095.	Cancer outcomes excluded from NEL review.
Benito P, Caballero J, Moreno J, Gutiérrez-Alcántara C, Muñoz C, Rojo G, Garcia S, Soriguer FC. Effects of milk enriched with omega-3 fatty acid, oleic acid and folic acid in patients with metabolic syndrome. *Clin Nutr.* 2006 Aug; 25(4): 581-587. Epub 2006 May 15. PMID: 16701922.	Participants diagnosed with metabolic syndrome.
Biong AS, Rebnord HM, Fimreite RL, Trygg KU, Ringstad J, Thelle DS, Pedersen JI. Intake of dairy fat and dairy products, and risk of myocardial infarction: A case-control study. *Int J Food Sci Nutr.* 2008 Mar; 59(2): 155-165. PMID: 17886080.	Included in Elwood, 2008.

Biong AS, Veierød MB, Ringstad J, Thelle DS, Pedersen JI. Intake of milk fat, reflected in adipose tissue fatty acids and risk of myocardial infarction: A case-control study. *Eur J Clin Nutr.* 2006 Feb; 60(2): 236-244. PMID: 16267503.	Does not answer question: examined relationship between fatty acids in adipose tissue and myocardial infarction.
Chan JM, Wang F, Holly EA. Pancreatic cancer, animal protein and dietary fat in a population-based study, San Francisco Bay Area, California. *Cancer Causes Control.* 2007 Dec; 18(10): 1, 153-1, 167. Epub 2007 Sep 1. PMID: 17805983.	Cancer outcomes excluded from NEL review.
Cheng S, Lyytikäinen A, Kröger H, Lamberg-Allardt C, Alén M, Koistinen A, Wang QJ, Suuriniemi M, Suominen H, Mahonen A, Nicholson PH, Ivaska KK, Korpela R, Ohlsson C, Väänänen KH, Tylavsky F. Effects of calcium, dairy product, and vitamin D supplementation on bone mass accrual and body composition in 10- to 12-year-old girls: A two-year randomized trial. *Am J Clin Nutr.* 2005 Nov; 82(5): 1, 115-1, 126; quiz 1, 147-1, 148. PMID: 16280447.	Included in Huncharek, 2008.
Cho E, Smith-Warner SA, Spiegelman D, Beeson WL, van den Brandt PA, Colditz GA, Folsom AR, Fraser GE, Freudenheim JL, Giovannucci E, Goldbohm RA, Graham S, Miller AB, Pietinen P, Potter JD, Rohan TE, Terry P, Toniolo P, Virtanen MJ, Willett WC, Wolk A, Wu K, Yaun SS, Zeleniuch-Jacquotte A, Hunter DJ. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. *J Natl Cancer Inst.* 2004 Jul 7; 96(13): 1, 015-1.022. Erratum in: *J Natl Cancer Inst.* 2004 Nov 17; 96(22): 1, 724. PMID: 15240785.	Cancer outcomes excluded from NEL review.
Choi HK, Willett WC, Stampfer MJ, Rimm E, Hu FB. Dairy consumption and risk of type 2 diabetes mellitus in men: a prospective study. *Arch Intern Med.* 2005 May 9; 165(9): 997-1, 003. PMID: 15883237.	Included in Elwood, 2008.
Daly RM, Bass S, Nowson C. Long-term effects of calcium-vitamin-D3-fortified milk on bone geometry and strength in older men. *Bone.* 2006 Oct; 39(4): 946-953. Epub 2006 May 24. PMID: 16725396.	Milk enriched with additional calcium and vitamin D_3.
Daly RM, Brown M, Bass S, Kukuljan S, Nowson C. Calcium- and vitamin D3-fortified milk reduces bone loss at clinically relevant skeletal sites in older men: a 2-year randomized controlled trial. *J Bone Miner Res.* 2006 Mar; 21(3): 397-405. Epub 2005 Dec 19. PMID: 16491287.	Milk enriched with additional calcium and vitamin D_3.
Dixon LB, Pellizzon MA, Jawad AF, Tershakovec AM. Calcium and dairy intake and measures of obesity in hyper- and normocholesterolemic children. *Obes Res.* 2005 Oct; 13(10): 1, 727-1, 738. PMID: 16286520.	The relationship between milk product intake and adiposity in children is reviewed in the Energy Balance section.

Doornbos AM, Meynen EM, Duchateau GS, van der Knaap HC, Trautwein EA. Intake occasion affects the serum cholesterol lowering of a plant sterol-enriched single-dose yoghurt drink in mildly hypercholesterolaemic subjects. *Eur J Clin Nutr.* 2006 Mar; 60(3): 325-333. PMID: 16234829.	Participants diagnosed with hypercholesterolemia.
Du X, Zhu K, Trube A, Zhang Q, Ma G, Hu X, Fraser DR, Greenfield H. School-milk intervention trial enhances growth and bone mineral accretion in Chinese girls aged 10 to 12 years in Beijing. *Br J Nutr.* 2004 Jul; 92(1): 159-168. Erratum in: *Br J Nutr.* 2005 Apr; 93(4): 571-572. PMID: 15230999.	Milk enriched with additional calcium.
Elwood PC, Pickering JE, Fehily AM. Milk and dairy consumption, diabetes and the metabolic syndrome: The Caerphilly prospective study. *J Epidemiol Community Health.* 2007 Aug; 61(8): 695-698. PMID: 17630368.	Included in Elwood, 2008.
Elwood PC, Pickering JE, Fehily AM, Hughes J, Ness AR. Milk drinking, ischaemic heart disease and ischaemic stroke I. Evidence from the Caerphilly cohort. *Eur J Clin Nutr.* 2004 May; 58(5): 711-717. PMID: 15116073.	Included in Elwood, 2008.
Elwood PC, Pickering JE, Hughes J, Fehily AM, Ness AR. Milk drinking, ischaemic heart disease and ischaemic stroke II. Evidence from cohort studies. *Eur J Clin Nutr.* 2004 May; 58(5): 718-724. Review. PMID: 15116074.	The most recent meta-analyses from these authors on these outcomes was included (Elwood, 2008).
Elwood PC, Strain JJ, Robson PJ, Fehily AM, Hughes J, Pickering J, Ness A. Milk consumption, stroke, and heart attack risk: Evidence from the Caerphilly cohort of older men. *J Epidemiol Community Health.* 2005 Jun; 59(6): 502-505. PMID: 15911647; PMCID: PMC1757052.	Included in Elwood, 2008.
Fiorito LM, Mitchell DC, Smiciklas-Wright H, Birch LL. Dairy and dairy-related nutrient intake during middle childhood. *J Am Diet Assoc.* 2006 Apr; 106(4): 534-542. PMID: 16567149; PMCID: PMC2531148.	Does not answer question: did not examine relationship between milk product intake and health.
Gallus S, Bravi F, Talamini R, Negri E, Montella M, Ramazzotti V, Franceschi S, Giacosa A, La Vecchia C. Milk, dairy products and cancer risk (Italy). *Cancer Causes Control.* 2006 May; 17(4): 429-437. PMID: 16596295.	Cancer outcomes excluded from NEL review.
Gao X, LaValley MP, Tucker KL. Prospective studies of dairy product and calcium intakes and prostate cancer risk: a meta-analysis. *J Natl Cancer Inst.* 2005 Dec 7; 97(23): 1, 768-1, 777. Erratum in: *J Natl Cancer Inst.* 2006 Mar 1; 98(5): 366. PMID: 16333032.	Cancer outcomes excluded from NEL review.
Gardner CD, Messina M, Kiazand A, Morris JL, Franke AA. Effect of two types of soy milk and dairy milk on plasma lipids in hypercholesterolemic adults: A randomized trial. *J Am Coll Nutr.* 2007 Dec; 26(6): 669-677. PMID: 18187432.	Participants diagnosed with hypercholesterolemia.

Genkinger JM, Hunter DJ, Spiegelman D, Anderson KE, Arslan A, Beeson WL, Buring JE, Fraser GE, Freudenheim JL, Goldbohm RA, Hankinson SE, Jacobs DR Jr, Koushik A, Lacey JV Jr, Larsson SC, Leitzmann M, McCullough ML, Miller AB, Rodriguez C, Rohan TE, Schouten LJ, Shore R, Smit E, Wolk A, Zhang SM, Smith-Warner SA. Dairy products and ovarian cancer: A pooled analysis of 12 cohort studies. *Cancer Epidemiol Biomarkers Prev.* 2006 Feb; 15(2): 364-372. PMID: 16492930.	Cancer outcomes excluded from NEL review.
Gibbons MJ, Gilchrist NL, Frampton C, Maguire P, Reilly PH, March RL, Wall CR. The effects of a high calcium dairy food on bone health in pre-pubertal children in New Zealand. *Asia Pac J Clin Nutr.* 2004; 13(4): 341-347. PMID: 15563438.	Drink was a high calcium supplement, not milk as defined by the Subcommittee.
Hubner RA, Muir KR, Liu JF, Logan RF, Grainge MJ, Houlston RS; Members of UKCAP Consortium. Dairy products, polymorphisms in the vitamin D receptor gene and colorectal adenoma recurrence. *Int J Cancer.* 2008 Aug 1; 123(3): 586-593. PMID: 18470879.	Cancer outcomes excluded from NEL review.
Huncharek M, Muscat J, Kupelnick B. Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: A meta-analysis of 26, 335 cases from 60 observational studies. *Nutr Cancer.* 2009; 61(1): 47-69. PMID: 19116875.	Cancer outcomes excluded from NEL review.
Huncharek M, Muscat J, Kupelnick B. Dairy products, dietary calcium and vitamin D intake as risk factors for prostate cancer: A meta-analysis of 26, 769 cases from 45 observational studies. *Nutr Cancer.* 2008; 60(4): 421-441. PMID: 18584476.	Cancer outcomes excluded from NEL review.
Kesse E, Bertrais S, Astorg P, Jaouen A, Arnault N, Galan P, Hercberg S. Dairy products, calcium and phosphorus intake, and the risk of prostate cancer: Results of the French prospective SU.VI.MAX (Supplémentation en Vitamines et Minéraux Antioxydants) study. *Br J Nutr.* 2006 Mar; 95(3): 539-545. PMID: 16512941.	Cancer outcomes excluded from NEL review.
Kesse E, Boutron-Ruault MC, Norat T, Riboli E, Clavel-Chapelon F; E3N Group. Dietary calcium, phosphorus, vitamin D, dairy products and the risk of colorectal adenoma and cancer among French women of the E3N-EPIC prospective study. *Int J Cancer.* 2005 Oct 20; 117(1): 137-144. PMID: 15880532.	Cancer outcomes excluded from NEL review.
Kesse-Guyot E, Bertrais S, Duperray B, Arnault N, Bar-Hen A, Galan P, Hercberg S. Dairy products, calcium and the risk of breast cancer: Results of the French SU.VI.MAX prospective study. *Ann Nutr Metab.* 2007; 51(2): 139-145. Epub 2007 May 29. PMID: 17536191.	Cancer outcomes excluded from NEL review.
Koh KA, Sesso HD, Paffenbarger RS Jr, Lee IM. Dairy products, calcium and prostate cancer risk. *Br J Cancer.* 2006 Dec 4; 95(11): 1, 582-1, 585. Epub 2006 Nov 14. PMID: 17106437.	Cancer outcomes excluded from NEL review.

Koralek DO, Bertone-Johnson ER, Leitzmann MF, Sturgeon SR, Lacey JV Jr, Schairer C, Schatzkin A. Relationship between calcium, lactose, vitamin D, and dairy products and ovarian cancer. *Nutr Cancer.* 2006; 56(1): 22-30. PMID: 17176214.	Cancer outcomes excluded from NEL review.
Korpela R, Tuomilehto J, Högström P, Seppo L, Piironen V, Salo-Väänänen P, Toivo J, Lamberg-Allardt C, Kärkkäinen M, Outila T, Sundvall J, Vilkkilä S, Tikkanen MJ. Safety aspects and cholesterol-lowering efficacy of low fat dairy products containing plant sterols. *Eur J Clin Nutr.* 2006 May; 60(5): 633-642. PMID: 16404415.	Dairy products contained plant sterols.
Kurahashi N, Inoue M, Iwasaki M, Sasazuki S, Tsugane AS; Japan Public Health Center-Based Prospective Study Group. Dairy product, saturated fatty acid, and calcium intake and prostate cancer in a prospective cohort of Japanese men. *Cancer Epidemiol Biomarkers Prev.* 2008 Apr; 17(4): 930-937. PMID: 18398033.	Cancer outcomes excluded from NEL review.
Kuriki K, Hirose K, Matsuo K, Wakai K, Ito H, Kanemitsu Y, Hirai T, Kato T, Hamajima N, Takezaki T, Suzuki T, Saito T, Tanaka R, Tajima K. Meat, milk, saturated fatty acids, the Pro12Ala and C161T polymorphisms of the PPARgamma gene and colorectal cancer risk in Japanese. *Cancer Sci.* 2006 Nov; 97(11): 1, 226-1, 235. Epub 2006 Sep 5. PMID: 16965392.	Does not answer question: examined risk related to genetic polymorphisms.
Lancaster KJ. Characteristics influencing daily consumption of fruits and vegetables and low-fat dairy products in older adults with hypertension. *J Nutr Elder.* 2004; 23(4): 21-33. PMID: 15233120.	Does not answer question; did not examine relationship between milk product intake and health; participants diagnosed with hypertension.
Larson NI, Neumark-Sztainer D, Harnack L, Wall M, Story M, Eisenberg ME. Calcium and dairy intake: Longitudinal trends during the transition to young adulthood and correlates of calcium intake. *J Nutr Educ Behav.* 2009 Jul-Aug; 41(4): 254-260. PMID: 19508930.	Does not answer question; did not examine relationship between milk product intake and health.
Larsson SC, Andersson SO, Johansson JE, Wolk A. Cultured milk, yogurt, and dairy intake in relation to bladder cancer risk in a prospective study of Swedish women and men. *Am J Clin Nutr.* 2008 Oct; 88(4): 1, 083-1, 087. PMID: 18842797.	Cancer outcomes excluded from NEL review.
Larsson SC, Bergkvist L, Rutegård J, Giovannucci E, Wolk A. Calcium and dairy food intakes are inversely associated with colorectal cancer risk in the Cohort of Swedish Men. *Am J Clin Nutr.* 2006 Mar; 83(3): 667-673; quiz 728-729. PMID: 16522915.	Cancer outcomes excluded from NEL review.
Larsson SC, Bergkvist L, Wolk A. High-fat dairy food and conjugated linoleic acid intakes in relation to colorectal cancer incidence in the Swedish Mammography Cohort. *Am J Clin Nutr.* 2005 Oct; 82(4): 894-900. PMID: 16210722.	Cancer outcomes excluded from NEL review.

Larsson SC, Bergkvist L, Wolk A. Milk and lactose intakes and ovarian cancer risk in the Swedish Mammography Cohort. *Am J Clin Nutr.* 2004 Nov; 80(5): 1, 353-1, 357. PMID: 15531686.	Cancer outcomes excluded from NEL review.
Larsson SC, Orsini N, Wolk A. Milk, milk products and lactose intake and ovarian cancer risk: A meta-analysis of epidemiological studies. *Int J Cancer.* 2006 Jan 15; 118(2): 431-441. PMID: 16052536.	Cancer outcomes excluded from NEL review.
Lawlor DA, Ebrahim S, Timpson N, Davey Smith G. Avoiding milk is associated with a reduced risk of insulin resistance and the metabolic syndrome: Findings from the British Women's Heart and Health Study. *Diabet Med.* 2005 Jun; 22(6): 808-811. PMID: 15910636.	Included in Elwood, 2008.
Liu S, Choi HK, Ford E, Song Y, Klevak A, Buring JE, Manson JE. A prospective study of dairy intake and the risk of type 2 diabetes in women. *Diabetes Care.* 2006 Jul; 29(7): 1, 579-1, 584. PMID: 16801582.	Included in Elwood, 2008.
Lorenz M, Jochmann N, von Krosigk A, Martus P, Baumann G, Stangl K, Stangl V. Addition of milk prevents vascular protective effects of tea. *Eur Heart J.* 2007 Jan; 28(2): 219-223. Epub 2007 Jan 9. PMID: 17213230.	Does not answer question; did not examine relationship between milk product intake and health.
Ma D, Jones G. Soft drink and milk consumption, physical activity, bone mass, and upper limb fractures in children: a population-based case-control study. *Calcif Tissue Int.* 2004 Oct; 75(4): 286-291. Epub 2004 Jul 30. PMID: 15549642.	Does not answer question; examines relationship between soft drink intake and fracture risk.
Matsumoto M, Ishikawa S, Nakamura Y, Kayaba K, Kajii E. Consumption of dairy products and cancer risks. *J Epidemiol.* 2007 Mar; 17(2): 38-44. PMID: 17420611.	Cancer outcomes excluded from NEL review.
McCullough ML, Rodriguez C, Diver WR, Feigelson HS, Stevens VL, Thun MJ, Calle EE. Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev.* 2005 Dec; 14(12): 2, 898-2, 904. PMID: 16365007.	Cancer outcomes excluded from NEL review.
McGlynn KA, Sakoda LC, Rubertone MV, Sesterhenn IA, Lyu C, Graubard BI, Erickson RL. Body size, dairy consumption, puberty, and risk of testicular germ cell tumors. *Am J Epidemiol.* 2007 Feb 15; 165(4): 355-363. Epub 2006 Nov 16. PMID: 17110638.	Cancer outcomes excluded from NEL review.
Mitrou PN, Albanes D, Weinstein SJ, Pietinen P, Taylor PR, Virtamo J, Leitzmann MF. A prospective study of dietary calcium, dairy products and prostate cancer risk (Finland). *Int J Cancer.* 2007 Jun 1; 120(11): 2, 466-2, 473. PMID: 17278090.	Cancer outcomes excluded from NEL review.

Mizoue T, Kimura Y, Toyomura K, Nagano J, Kono S, Mibu R, Tanaka M, Kakeji Y, Maehara Y, Okamura T, Ikejiri K, Futami K, Yasunami Y, Maekawa T, Takenaka K, Ichimiya H, Imaizumi N. Calcium, dairy foods, vitamin D, and colorectal cancer risk: The Fukuoka Colorectal Cancer Study. *Cancer Epidemiol Biomarkers Prev.* 2008 Oct; 17(10): 2, 800-2, 807. PMID: 18843026.	Cancer outcomes excluded from NEL review.
Mommers M, Schouten LJ, Goldbohm RA, van den Brandt PA. Dairy consumption and ovarian cancer risk in the Netherlands Cohort Study on Diet and Cancer. *Br J Cancer.* 2006 Jan 16; 94(1): 165-170. PMID: 16306872.	Cancer outcomes excluded from NEL review.
Nestel PJ, Chronopulos A, Cehun M. Dairy fat in cheese raises LDL cholesterol less than that in butter in mildly hypercholesterolaemic subjects. *Eur J Clin Nutr.* 2005 Sep; 59(9): 1, 059-1, 063. PMID: 16015270.	Participants diagnosed with hypercholesterolemia.
Park SY, Murphy SP, Wilkens LR, Stram DO, Henderson BE, Kolonel LN. Calcium, vitamin D, and dairy product intake and prostate cancer risk: The Multiethnic Cohort Study. *Am J Epidemiol.* 2007 Dec 1; 166(11): 1, 259-1, 269. Epub 2007 Oct 8. PMID: 17925283.	Cancer outcomes excluded from NEL review.
Park Y, Leitzmann MF, Subar AF, Hollenbeck A, Schatzkin A. Dairy food, calcium, and risk of cancer in the NIH-AARP Diet and Health Study. *Arch Intern Med.* 2009 Feb 23; 169(4): 391-401. PMID: 19237724.	Cancer outcomes excluded from NEL review.
Park Y, Mitrou PN, Kipnis V, Hollenbeck A, Schatzkin A, Leitzmann MF. Calcium, dairy foods, and risk of incident and fatal prostate cancer: the NIH-AARP Diet and Health Study. *Am J Epidemiol.* 2007 Dec 1; 166(11): 1, 270-1, 279. Epub 2007 Oct 12. PMID: 18000020.	Cancer outcomes excluded from NEL review.
Parodi PW. Dairy product consumption and the risk of breast cancer. *J Am Coll Nutr.* 2005 Dec; 24(6 Suppl): 556S-568S. Review. PMID: 16373955.	Cancer outcomes excluded from NEL review.
Qin LQ, Xu JY, Wang PY, Hashi A, Hoshi K, Sato A. Milk/dairy products consumption, galactose metabolism and ovarian cancer: Meta-analysis of epidemiological studies. *Eur J Cancer Prev.* 2005 Feb; 14(1): 13-19. PMID: 15677891.	Cancer outcomes excluded from NEL review.
Qin LQ, Xu JY, Wang PY, Tong J, Hoshi K. Milk consumption is a risk factor for prostate cancer in Western countries: Evidence from cohort studies. *Asia Pac J Clin Nutr.* 2007; 16(3): 467-476. PMID: 17704029.	Cancer outcomes excluded from NEL review.
Qin LQ, Xu JY, Wang PY, Kaneko T, Hoshi K, Sato A. Milk consumption is a risk factor for prostate cancer: Meta-analysis of case-control studies. *Nutr Cancer.* 2004; 48(1): 22-27. PMID: 15203374.	Cancer outcomes excluded from NEL review.

Rohrmann S, Platz EA, Kavanaugh CJ, Thuita L, Hoffman SC, Helzlsouer KJ. Meat and dairy consumption and subsequent risk of prostate cancer in a US cohort study. *Cancer Causes Control.* 2007 Feb; 18(1): 41-50. PMID: 17315319.	Cancer outcomes excluded from NEL review.
Snijder MB, van der Heijden AA, van Dam RM, Stehouwer CD, Hiddink GJ, Nijpels G, Heine RJ, Bouter LM, Dekker JM. Is higher dairy consumption associated with lower body weight and fewer metabolic disturbances? The Hoorn Study. *Am J Clin Nutr.* 2007 Apr; 85(4): 989-995. PMID: 17413097.	Same data set as Snijder, 2008.
Sun Q, Ma J, Campos H, Hu FB. Plasma and erythrocyte biomarkers of dairy fat intake and risk of ischemic heart disease. *Am J Clin Nutr.* 2007 Oct; 86(4): 929-937. PMID: 17921367.	Does not answer question; examined relationship between fatty acids and disease risk.
Taguchi H, Chen H, Yano R, Shoumura S. Comparative effects of milk and soymilk on bone loss in adult ovariectomized osteoporosis rat. *Okajimas Folia Anat Jpn.* 2006 Aug; 83(2): 53-59. PMID: 16944838.	Study tested animals.
Tricon S, Burdge GC, Jones EL, Russell JJ, El-Khazen S, Moretti E, Hall WL, Gerry AB, Leake DS, Grimble RF, Williams CM, Calder PC, Yaqoob P. Effects of dairy products naturally enriched with cis-9, trans-11 conjugated linoleic acid on the blood lipid profile in healthy middle-aged men. *Am J Clin Nutr.* 2006 Apr; 83(4): 744-753. PMID: 16600923.	Milk products enriched with cis-9, trans-11 conjugated linoleic acid.
Tseng M, Breslow RA, Graubard BI, Ziegler RG. Dairy, calcium, and vitamin D intakes and prostate cancer risk in the National Health and Nutrition Examination Epidemiologic Follow-up Study cohort. *Am J Clin Nutr.* 2005 May; 81(5): 1, 147-1, 154. PMID: 15883441.	Cancer outcomes excluded from NEL review.
van der Pols JC, Bain C, Gunnell D, Smith GD, Frobisher C, Martin RM. Childhood dairy intake and adult cancer risk: 65-year follow-up of the Boyd Orr cohort. *Am J Clin Nutr.* 2007 Dec; 86(6): 1, 722-1, 729. PMID: 18065592.	Cancer outcomes excluded from NEL review.
Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: A systematic review and meta-analysis. *Am J Public Health.* 2007 Apr; 97(4): 667-675. Epub 2007 Feb 28. Review. PMID: 17329656; PMCID: PMC1829363.	Does not answer question; did not examine relationship between milk product intake and health.
Warensjö E, Jansson JH, Berglund L, Boman K, Ahrén B, Weinehall L, Lindahl B, Hallmans G, Vessby B. Estimated intake of milk fat is negatively associated with cardiovascular risk factors and does not increase the risk of a first acute myocardial infarction. A prospective case-control study. *Br J Nutr.* 2004 Apr; 91(4): 635-642. PMID: 15035691.	Does not include milk product intake in analyses.

Xu JY, Qin LQ, Wang PY, Li W, Chang C. Effect of milk tripeptides on blood pressure: a meta-analysis of randomized controlled trials. *Nutrition.* 2008 Oct; 24(10): 933-940. Epub 2008 Jun 17. PMID: 18562172.	Does not answer question; did not examine relationship between milk product intake and health.
Zhang J, Kesteloot H. Milk consumption in relation to incidence of prostate, breast, colon, and rectal cancers: Is there an independent effect? Nu*tr Cancer.* 2005; 53(1): 65-72. PMID: 16351508.	Cancer outcomes excluded from NEL review.
Zhu K, Zhang Q, Foo LH, Trube A, Ma G, Hu X, Du X, Cowell CT, Fraser DR, Greenfield H. Growth, bone mass, and vitamin D status of Chinese adolescent girls three years after withdrawal of milk supplementation. *Am J Clin Nutr.* 2006 Mar; 83(3): 714-721. PMID: 16522922.	Milk enriched with additional calcium.

CHAPTER 16. MILK AND MILK PRODUCTS – TYPE 2 DIABETES

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF MILK AND MILK PRODUCTS AND TYPE 2 DIABETES?

Conclusion statement

Moderate evidence shows that milk and milk products are associated with a lower incidence of type 2 diabetes in adults.

Grade

Moderate

Evidence summary overview

In a recent systematic review with meta-analysis (Elwood, 2008) of four prospective studies on diabetes, relative risk for type 2 diabetes (T2D) was estimated to be 10% lower in people who had a high milk intake relative to those with low consumption.

Evidence summary paragraphs

Elwood et al, 2008 (positive quality) performed a systematic review and meta-analysis to investigate the literature on milk and dairy consumption and risk of vascular disease and diabetes, examine the evidence related to consumption of whole vs. reduced fat milk and disease risk and consider the likely effect of milk and dairy consumption on survival. The authors also reviewed a 2007 report by the World Cancer Research Fund to determine the impact of milk and dairy consumption on cancer risk. Using Cochrane systematic review methods, MEDLINE was searched up to June 2008 using key words milk/milk protein/dairy/dairy calcium and heart disease/coronary artery disease/myocardial infarction/ischaemic heart disease, stroke and diabetes/metabolic syndrome. This search revealed 180 papers on milk and heart disease, 33 papers on milk and stroke and 111 papers on milk and diabetes. Only studies that were done in human adults using population-based and prospective designs and reported baseline data on milk or dairy consumption, vascular disease outcome or incident diabetes were included in the final review. The final sample included 15 prospective studies on ischaemic heart disease and stroke, four prospective studies on diabetes, four case-control studies on metabolic syndrome and four case-control studies on myocardial infarction. Relative risk for T2D was estimated to be 10% lower in people who had a high milk intake (RR=0.92; 95% CI: 0.86, 0.97).

Overview table

Author, Year, Study Design, Class, Rating	Description of Study Sample	Methodology	Outcomes
Elwood PC, Givens DI et al, 2008 Study Design: Systematic review and meta-analysis Class: M Positive quality	Final N=15 prospective studies on IHD and stroke: Four prospective studies on diabetes Four case-control studies on metabolic syndrome Four case-control studies on MI.	MEDLINE was searched up to June 2008 using key words: Milk/milk protein/dairy/dairy calcium and heart disease/coronary artery disease/myocardial infarction/ ischaemic heart disease, stroke and diabetes/metabolic syndrome.	RR for T2D estimated to be 10% lower in people who had a ↑ milk intake (RR=0.92; 95% CI: 0.86, 0.97).

Search plan and results

Inclusion criteria

- June 2004 to July 2009
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children, two to 18 years; adults, 19 years and older
- *Populations:* Healthy and those with elevated chronic disease risk.

Exclusion criteria

- Studies that only consider cancer outcomes
- Studies that considered milk and milk products as part of a larger dietary pattern
- Milk and milk products in forms not commonly consumed (e.g., enriched with additional calcium)
- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)

- Hospitalized patients
- Animal studies
- In vitro studies
- Articles not peer reviewed (web sites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: ("Dairy Products"[mh]) AND ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mesh: NoExp] OR “heart diseases”[mh] OR “chronic disease”[mh] OR "Neoplasms"[majr] OR osteoporosis[mh] OR "Bone Density"[Mesh] OR "Fractures, Bone"[Mesh])

Date searched: 07/29/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 223
- Total articles identified to review from electronic databases: 95
- Articles identified via handsearch or other means: 3
- Number of Primary Articles Identified: 20
- Number of Review Articles Identified: 4
- Total Number of Articles Identified: 24
- Number of Articles Reviewed but Excluded: 74

Included articles (References)

What is the relationship between the intake of milk and milk products and bone health?

Systematic Reviews/Meta-analyses

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: A review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.
2. Huncharek M, Muscat J, Kupelnick B. Impact of dairy products and dietary calcium on bone-mineral content in children: Results of a meta-analysis. *Bone.* 2008 Aug; 43(2): 312-321. Epub 2008 Mar 15. PMID: 18539555.
3. Kanis JA, Johansson H, Oden A, De Laet C, Johnell O, Eisman JA, Mc Closkey E, Mellstrom D, Pols H, Reeve J, Silman A, Tenenhouse A. A meta-analysis of milk intake and fracture risk: low utility for case finding. *Osteoporos Int.* 2005 Jul; 16(7): 799-804. Epub 2004 Oct 21. PMID: 15502959.

Primary Research

Trials

1. Budek AZ, Hoppe C, Michaelsen KF, Mølgaard C. High intake of milk, but not meat, decreases bone turnover in prepubertal boys after 7 days. *Eur J Clin Nutr.* 2007 Aug; 61(8): 957-962. Epub 2007 Jan 17. PMID: 17228345.
2. Kristensen M, Jensen M, Kudsk J, Henriksen M, Mølgaard C. Short-term effects on bone turnover of replacing milk with cola beverages: A 10-day interventional study in young men. *Osteoporos Int.* 2005 Dec; 16(12): 1, 803-1, 808. Epub 2005 May 11. PMID: 15886860.

3. McCabe LD, Martin BR, McCabe GP, Johnston CC, Weaver CM, Peacock M. Dairy intakes affect bone density in the elderly. *Am J Clin Nutr.* 2004 Oct; 80(4): 1, 066-1, 074. PMID: 15447921.

Longitudinal Study

1. Rockell JE, Williams SM, Taylor RW, Grant AM, Jones IE, Goulding A. Two-year changes in bone and body composition in young children with a history of prolonged milk avoidance. *Osteoporos Int.* 2005 Sep; 16(9): 1, 016-1, 023. Epub 2004 Nov 23. PMID: 15565350.

Case-Control Study

1. Konstantynowicz J, Nguyen TV, Kaczmarski M, Jamiolkowski J, Piotrowska-Jastrzebska J, Seeman E. Fractures during growth: Potential role of a milk-free diet. *Osteoporos Int.* 2007 Dec; 18(12): 1, 601-1, 607. Epub 2007 May 22. PMID: 17516020.

Cross-Sectional Study

1. Al-Zahrani MS. Increased intake of dairy products is related to lower periodontitis prevalence. *J Periodontol.* 2006 Feb; 77(2): 289-294. PMID: 16460256. (Hand search)

What is the relationship between the intake of milk and milk products and cardiovascular disease?

Systematic Reviews/Meta-Analyses

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: A review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.
2. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

Primary Research

Case-Control Study

1. Kontogianni MD, Panagiotakos DB, Chrysohoou C, Pitsavos C, Stefanadis C. Modelling dairy intake on the development of acute coronary syndromes: The CARDIO2000 study. *Eur J Cardiovasc Prev Rehabil.* 2006 Oct; 13(5): 791-797. PMID: 17001220.

What is the relationship between the intake of milk and milk products and blood pressure?

Systematic Review

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: a review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.

Primary Research

Trial

1. Bowen J, Noakes M, Clifton PM.Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. *Int J Obes (Lond).* 2005 Aug; 29(8): 957-965. PMID: 15711601. (Hand search)

Prospective Cohort Studies

1. Alonso A, Beunza JJ, Delgado-Rodríguez M, Martínez JA, Martínez-González MA. Low-fat dairy consumption and reduced risk of hypertension: The Seguimiento Universidad de Navarra (SUN) cohort. *Am J Clin Nutr.* 2005 Nov; 82(5): 972-979. PMID: 16280427.
2. Engberink MF, Hendriksen MA, Schouten EG, van Rooij FJ, Hofman A, Witteman JC, Geleijnse JM. Inverse association between dairy intake and hypertension: The Rotterdam Study. *Am J Clin Nutr.* 2009 Jun; 89(6): 1, 877-1, 883. Epub 2009 Apr 15. PMID: 19369377.
3. Engberink MF, Geleijnse JM, de Jong N, Smit HA, Kok FJ, Verschuren WM. Dairy intake, blood pressure, and incident hypertension in a general Dutch population. *J Nutr.* 2009 Mar; 139(3): 582-587. Epub 2009 Jan 21. PMID: 19158223.
4. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.
5. Toledo E, Delgado-Rodríguez M, Estruch R, Salas-Salvadó J, Corella D, Gomez-Gracia E, Fiol M, Lamuela-Raventós RM, Schröder H, Arós F, Ros E, Ruíz-Gutiérrez V, Lapetra J, Conde-Herrera M, Sáez G, Vinyoles E, Martínez-González MA. Low-fat dairy products and blood pressure: Follow-up of 2290 older persons at high cardiovascular risk participating in the PREDIMED study. *Br J Nutr.* 2009 Jan; 101(1): 59-67. Epub 2008 May 20. PMID: 18492300.
6. Wang L, Manson JE, Buring JE, Lee IM, Sesso HD. Dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women. *Hypertension.* 2008 Apr; 51(4): 1, 073-1, 079. Epub 2008 Feb 7. PMID: 18259007.

Cross-Sectional Studies

1. Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Tehranian adults. *Am J Clin Nutr.* 2005 Sep; 82(3): 523-530. PMID: 16155263.
2. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. *Am J Clin Nutr.* 2008 Jun; 87(6): 1, 914-1, 925. PMID: 18541585; PMCID: PMC2585752. (Hand search)
3. Djoussé L, Pankow JS, Hunt SC, Heiss G, Province MA, Kabagambe EK, Ellison RC. Influence of saturated fat and linolenic acid on the association between intake of dairy products and blood pressure. *Hypertension.* 2006 Aug; 48(2): 335-341. Epub 2006 Jun 26. PMID: 16801477.
4. Houston DK, Driver KE, Bush AJ, Kritchevsky SB. The association between cheese consumption and cardiovascular risk factors among adults. *J Hum Nutr Diet.* 2008 Apr; 21(2): 129-140. PMID: 18339053.

5. Ruidavets JB, Bongard V, Simon C, Dallongeville J, Ducimetière P, Arveiler D, Amouyel P, Bingham A, Ferrières J. Independent contribution of dairy products and calcium intake to blood pressure variations at a population level. *J Hypertens.* 2006 Apr; 24(4): 671-681. PMID: 16531795.

What is the relationship between the intake of milk and milk products and type 2 diabetes?

Meta-Analysis

1. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

What is the relationship between the intake of milk and milk products and metabolic syndrome?

Primary Research

Meta-Analysis

1. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

Prospective Cohort Study

1. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.

Cross-Sectional Studies

1. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. *Am J Clin Nutr.* 2008 Jun; 87(6): 1, 914-1, 925. PMID: 18541585; PMCID: PMC2585752. (Hand search)
2. Ruidavets JB, Bongard V, Dallongeville J, Arveiler D, Ducimetière P, Perret B, Simon C, Amouyel P, Ferrières J. High consumptions of grain, fish, dairy products and combinations of these are associated with a low prevalence of metabolic syndrome. *J Epidemiol Community Health.* 2007 Sep; 61(9): 810-817. PMID: 17699537.

What is the relationship between the intake of milk and milk products and serum cholesterol?

Primary Research

Trial

1. Bowen J, Noakes M, Clifton PM.Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. *Int J Obes (Lond).* 2005 Aug; 29(8): 957-965. PMID:

15711601. (Hand search)

Prospective Cohort Study

1. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.

Cross-Sectional Study

1. Houston DK, Driver KE, Bush AJ, Kritchevsky SB. The association between cheese consumption and cardiovascular risk factors among adults. *J Hum Nutr Diet.* 2008 Apr; 21(2): 129-140. PMID: 18339053.

Excluded articles

Article	Reason for Exclusion
Ahn J, Albanes D, Peters U, Schatzkin A, Lim U, Freedman M, Chatterjee N, Andriole GL, Leitzmann MF, Hayes RB; Prostate, Lung, Colorectal, and Ovarian Trial Project Team. Dairy products, calcium intake, and risk of prostate cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev.* 2007 Dec; 16(12): 2, 623-2, 630. PMID: 18086766.	Cancer outcomes excluded from NEL review.
Al Sarakbi W, Salhab M, Mokbel K. Dairy products and breast cancer risk: A review of the literature. *Int J Fertil Womens Med.* 2005 Nov-Dec; 50(6): 244-249. Review. PMID: 16526414.	Cancer outcomes excluded from NEL review.
Allen NE, Key TJ, Appleby PN, Travis RC, Roddam AW, Tjønneland A, Johnsen NF, Overvad K, Linseisen J, Rohrmann S, Boeing H, Pischon T, Bueno-de-Mesquita HB, Kiemeney L, Tagliabue G, Palli D, Vineis P, Tumino R, Trichopoulou A, Kassapa C, Trichopoulos D, Ardanaz E, Larrañaga N, Tormo MJ, González CA, Quirós JR, Sánchez MJ, Bingham S, Khaw KT, Manjer J, Berglund G, Stattin P, Hallmans G, Slimani N, Ferrari P, Rinaldi S, Riboli E. Animal foods, protein, calcium and prostate cancer risk: the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer.* 2008 May 6; 98(9): 1, 574-1, 581. Epub 2008 Apr 1. PMID: 18382426.	Does not answer question: examined relationship between milk protein intake and health.
Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Tehranian adults. *Am J Clin Nutr.* 2005 Sep; 82(3): 523-530. PMID: 16155263.	Included in blood pressure review, but excluded from metabolic syndrome review because included in Elwood, 2008.
Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: A systematic literature review and meta-analysis. *Cancer Causes Control.* 2007 Nov; 18(9): 967-988. Epub 2007 Jul 19. Review. PMID: 17638104; PMCID: PMC2592095.	Cancer outcomes excluded from NEL review.

Benito P, Caballero J, Moreno J, Gutiérrez-Alcántara C, Muñoz C, Rojo G, Garcia S, Soriguer FC. Effects of milk enriched with omega-3 fatty acid, oleic acid and folic acid in patients with metabolic syndrome. *Clin Nutr.* 2006 Aug; 25(4): 581-587. Epub 2006 May 15. PMID: 16701922.	Participants diagnosed with metabolic syndrome.
Biong AS, Rebnord HM, Fimreite RL, Trygg KU, Ringstad J, Thelle DS, Pedersen JI. Intake of dairy fat and dairy products, and risk of myocardial infarction: A case-control study. *Int J Food Sci Nutr.* 2008 Mar; 59(2): 155-165. PMID: 17886080.	Included in Elwood, 2008.
Biong AS, Veierød MB, Ringstad J, Thelle DS, Pedersen JI. Intake of milk fat, reflected in adipose tissue fatty acids and risk of myocardial infarction: A case-control study. *Eur J Clin Nutr.* 2006 Feb; 60(2): 236-244. PMID: 16267503.	Does not answer question: examined relationship between fatty acids in adipose tissue and myocardial infarction.
Chan JM, Wang F, Holly EA. Pancreatic cancer, animal protein and dietary fat in a population-based study, San Francisco Bay Area, California. *Cancer Causes Control.* 2007 Dec; 18(10): 1, 153-1, 167. Epub 2007 Sep 1. PMID: 17805983.	Cancer outcomes excluded from NEL review.
Cheng S, Lyytikäinen A, Kröger H, Lamberg-Allardt C, Alén M, Koistinen A, Wang QJ, Suuriniemi M, Suominen H, Mahonen A, Nicholson PH, Ivaska KK, Korpela R, Ohlsson C, Väänänen KH, Tylavsky F. Effects of calcium, dairy product, and vitamin D supplementation on bone mass accrual and body composition in 10- to 12-year-old girls: A two-year randomized trial. *Am J Clin Nutr.* 2005 Nov; 82(5): 1, 115-1, 126; quiz 1, 147-1, 148. PMID: 16280447.	Included in Huncharek, 2008.
Cho E, Smith-Warner SA, Spiegelman D, Beeson WL, van den Brandt PA, Colditz GA, Folsom AR, Fraser GE, Freudenheim JL, Giovannucci E, Goldbohm RA, Graham S, Miller AB, Pietinen P, Potter JD, Rohan TE, Terry P, Toniolo P, Virtanen MJ, Willett WC, Wolk A, Wu K, Yaun SS, Zeleniuch-Jacquotte A, Hunter DJ. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. *J Natl Cancer Inst.* 2004 Jul 7; 96(13): 1, 015-1.022. Erratum in: *J Natl Cancer Inst.* 2004 Nov 17; 96(22): 1, 724. PMID: 15240785.	Cancer outcomes excluded from NEL review.
Choi HK, Willett WC, Stampfer MJ, Rimm E, Hu FB. Dairy consumption and risk of type 2 diabetes mellitus in men: a prospective study. *Arch Intern Med.* 2005 May 9; 165(9): 997-1, 003. PMID: 15883237.	Included in Elwood, 2008.
Daly RM, Bass S, Nowson C. Long-term effects of calcium-vitamin-D3-fortified milk on bone geometry and strength in older men. *Bone.* 2006 Oct; 39(4): 946-953. Epub 2006 May 24. PMID: 16725396.	Milk enriched with additional calcium and vitamin D_3.

Daly RM, Brown M, Bass S, Kukuljan S, Nowson C. Calcium- and vitamin D3-fortified milk reduces bone loss at clinically relevant skeletal sites in older men: a 2-year randomized controlled trial. *J Bone Miner Res.* 2006 Mar; 21(3): 397-405. Epub 2005 Dec 19. PMID: 16491287.	Milk enriched with additional calcium and vitamin D_3.
Dixon LB, Pellizzon MA, Jawad AF, Tershakovec AM. Calcium and dairy intake and measures of obesity in hyper- and normocholesterolemic children. *Obes Res.* 2005 Oct; 13(10): 1, 727-1, 738. PMID: 16286520.	The relationship between milk product intake and adiposity in children is reviewed in the Energy Balance section.
Doornbos AM, Meynen EM, Duchateau GS, van der Knaap HC, Trautwein EA. Intake occasion affects the serum cholesterol lowering of a plant sterol-enriched single-dose yoghurt drink in mildly hypercholesterolaemic subjects. *Eur J Clin Nutr.* 2006 Mar; 60(3): 325-333. PMID: 16234829.	Participants diagnosed with hypercholesterolemia.
Du X, Zhu K, Trube A, Zhang Q, Ma G, Hu X, Fraser DR, Greenfield H. School-milk intervention trial enhances growth and bone mineral accretion in Chinese girls aged 10 to 12 years in Beijing. *Br J Nutr.* 2004 Jul; 92(1): 159-168. Erratum in: *Br J Nutr.* 2005 Apr; 93(4): 571-572. PMID: 15230999.	Milk enriched with additional calcium.
Elwood PC, Pickering JE, Fehily AM. Milk and dairy consumption, diabetes and the metabolic syndrome: The Caerphilly prospective study. *J Epidemiol Community Health.* 2007 Aug; 61(8): 695-698. PMID: 17630368.	Included in Elwood, 2008.
Elwood PC, Pickering JE, Fehily AM, Hughes J, Ness AR. Milk drinking, ischaemic heart disease and ischaemic stroke I. Evidence from the Caerphilly cohort. *Eur J Clin Nutr.* 2004 May; 58(5): 711-717. PMID: 15116073.	Included in Elwood, 2008.
Elwood PC, Pickering JE, Hughes J, Fehily AM, Ness AR. Milk drinking, ischaemic heart disease and ischaemic stroke II. Evidence from cohort studies. *Eur J Clin Nutr.* 2004 May; 58(5): 718-724. Review. PMID: 15116074.	The most recent meta-analyses from these authors on these outcomes was included (Elwood, 2008).
Elwood PC, Strain JJ, Robson PJ, Fehily AM, Hughes J, Pickering J, Ness A. Milk consumption, stroke, and heart attack risk: Evidence from the Caerphilly cohort of older men. *J Epidemiol Community Health.* 2005 Jun; 59(6): 502-505. PMID: 15911647; PMCID: PMC1757052.	Included in Elwood, 2008.
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Gallus S, Bravi F, Talamini R, Negri E, Montella M, Ramazzotti V, Franceschi S, Giacosa A, La Vecchia C. Milk, dairy products and cancer risk (Italy). *Cancer Causes Control.* 2006 May; 17(4): 429-437. PMID: 16596295.	Cancer outcomes excluded from NEL review.

Gao X, LaValley MP, Tucker KL. Prospective studies of dairy product and calcium intakes and prostate cancer risk: a meta-analysis. *J Natl Cancer Inst.* 2005 Dec 7; 97(23): 1, 768-1, 777. Erratum in: *J Natl Cancer Inst.* 2006 Mar 1; 98(5): 366. PMID: 16333032.	Cancer outcomes excluded from NEL review.
Gardner CD, Messina M, Kiazand A, Morris JL, Franke AA. Effect of two types of soy milk and dairy milk on plasma lipids in hypercholesterolemic adults: A randomized trial. *J Am Coll Nutr.* 2007 Dec; 26(6): 669-677. PMID: 18187432.	Participants diagnosed with hypercholesterolemia.
Genkinger JM, Hunter DJ, Spiegelman D, Anderson KE, Arslan A, Beeson WL, Buring JE, Fraser GE, Freudenheim JL, Goldbohm RA, Hankinson SE, Jacobs DR Jr, Koushik A, Lacey JV Jr, Larsson SC, Leitzmann M, McCullough ML, Miller AB, Rodriguez C, Rohan TE, Schouten LJ, Shore R, Smit E, Wolk A, Zhang SM, Smith-Warner SA. Dairy products and ovarian cancer: A pooled analysis of 12 cohort studies. *Cancer Epidemiol Biomarkers Prev.* 2006 Feb; 15(2): 364-372. PMID: 16492930.	Cancer outcomes excluded from NEL review.
Gibbons MJ, Gilchrist NL, Frampton C, Maguire P, Reilly PH, March RL, Wall CR. The effects of a high calcium dairy food on bone health in pre-pubertal children in New Zealand. *Asia Pac J Clin Nutr.* 2004; 13(4): 341-347. PMID: 15563438.	Drink was a high calcium supplement, not milk as defined by the Subcommittee.
Hubner RA, Muir KR, Liu JF, Logan RF, Grainge MJ, Houlston RS; Members of UKCAP Consortium. Dairy products, polymorphisms in the vitamin D receptor gene and colorectal adenoma recurrence. *Int J Cancer.* 2008 Aug 1; 123(3): 586-593. PMID: 18470879.	Cancer outcomes excluded from NEL review.
Huncharek M, Muscat J, Kupelnick B. Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: A meta-analysis of 26, 335 cases from 60 observational studies. *Nutr Cancer.* 2009; 61(1): 47-69. PMID: 19116875.	Cancer outcomes excluded from NEL review.
Huncharek M, Muscat J, Kupelnick B. Dairy products, dietary calcium and vitamin D intake as risk factors for prostate cancer: A meta-analysis of 26, 769 cases from 45 observational studies. *Nutr Cancer.* 2008; 60(4): 421-441. PMID: 18584476.	Cancer outcomes excluded from NEL review.
Kesse E, Bertrais S, Astorg P, Jaouen A, Arnault N, Galan P, Hercberg S. Dairy products, calcium and phosphorus intake, and the risk of prostate cancer: Results of the French prospective SU.VI.MAX (Supplémentation en Vitamines et Minéraux Antioxydants) study. *Br J Nutr.* 2006 Mar; 95(3): 539-545. PMID: 16512941.	Cancer outcomes excluded from NEL review.
Kesse E, Boutron-Ruault MC, Norat T, Riboli E, Clavel-Chapelon F; E3N Group. Dietary calcium, phosphorus, vitamin D, dairy products and the risk of colorectal adenoma and cancer among French women of the E3N-EPIC prospective study. *Int J Cancer.* 2005 Oct 20; 117(1): 137-144. PMID: 15880532.	Cancer outcomes excluded from NEL review.

Kesse-Guyot E, Bertrais S, Duperray B, Arnault N, Bar-Hen A, Galan P, Hercberg S. Dairy products, calcium and the risk of breast cancer: Results of the French SU.VI.MAX prospective study. *Ann Nutr Metab.* 2007; 51(2): 139-145. Epub 2007 May 29. PMID: 17536191.	Cancer outcomes excluded from NEL review.
Koh KA, Sesso HD, Paffenbarger RS Jr, Lee IM. Dairy products, calcium and prostate cancer risk. *Br J Cancer.* 2006 Dec 4; 95(11): 1, 582-1, 585. Epub 2006 Nov 14. PMID: 17106437.	Cancer outcomes excluded from NEL review.
Koralek DO, Bertone-Johnson ER, Leitzmann MF, Sturgeon SR, Lacey JV Jr, Schairer C, Schatzkin A. Relationship between calcium, lactose, vitamin D, and dairy products and ovarian cancer. *Nutr Cancer.* 2006; 56(1): 22-30. PMID: 17176214.	Cancer outcomes excluded from NEL review.
Korpela R, Tuomilehto J, Högström P, Seppo L, Piironen V, Salo-Väänänen P, Toivo J, Lamberg-Allardt C, Kärkkäinen M, Outila T, Sundvall J, Vilkkilä S, Tikkanen MJ. Safety aspects and cholesterol-lowering efficacy of low fat dairy products containing plant sterols. *Eur J Clin Nutr.* 2006 May; 60(5): 633-642. PMID: 16404415.	Dairy products contained plant sterols.
Kurahashi N, Inoue M, Iwasaki M, Sasazuki S, Tsugane AS; Japan Public Health Center-Based Prospective Study Group. Dairy product, saturated fatty acid, and calcium intake and prostate cancer in a prospective cohort of Japanese men. *Cancer Epidemiol Biomarkers Prev.* 2008 Apr; 17(4): 930-937. PMID: 18398033.	Cancer outcomes excluded from NEL review.
Kuriki K, Hirose K, Matsuo K, Wakai K, Ito H, Kanemitsu Y, Hirai T, Kato T, Hamajima N, Takezaki T, Suzuki T, Saito T, Tanaka R, Tajima K. Meat, milk, saturated fatty acids, the Pro12Ala and C161T polymorphisms of the PPARgamma gene and colorectal cancer risk in Japanese. *Cancer Sci.* 2006 Nov; 97(11): 1, 226-1, 235. Epub 2006 Sep 5. PMID: 16965392.	Does not answer question: examined risk related to genetic polymorphisms.
Lancaster KJ. Characteristics influencing daily consumption of fruits and vegetables and low-fat dairy products in older adults with hypertension. *J Nutr Elder.* 2004; 23(4): 21-33. PMID: 15233120.	Does not answer question; did not examine relationship between milk product intake and health; participants diagnosed with hypertension.
Larson NI, Neumark-Sztainer D, Harnack L, Wall M, Story M, Eisenberg ME. Calcium and dairy intake: Longitudinal trends during the transition to young adulthood and correlates of calcium intake. *J Nutr Educ Behav.* 2009 Jul-Aug; 41(4): 254-260. PMID: 19508930.	Does not answer question; did not examine relationship between milk product intake and health.
Larsson SC, Andersson SO, Johansson JE, Wolk A. Cultured milk, yogurt, and dairy intake in relation to bladder cancer risk in a prospective study of Swedish women and men. *Am J Clin Nutr.* 2008 Oct; 88(4): 1, 083-1, 087. PMID: 18842797.	Cancer outcomes excluded from NEL review.

Larsson SC, Bergkvist L, Rutegård J, Giovannucci E, Wolk A. Calcium and dairy food intakes are inversely associated with colorectal cancer risk in the Cohort of Swedish Men. *Am J Clin Nutr.* 2006 Mar; 83(3): 667-673; quiz 728-729. PMID: 16522915.	Cancer outcomes excluded from NEL review.
Larsson SC, Bergkvist L, Wolk A. High-fat dairy food and conjugated linoleic acid intakes in relation to colorectal cancer incidence in the Swedish Mammography Cohort. *Am J Clin Nutr.* 2005 Oct; 82(4): 894-900. PMID: 16210722.	Cancer outcomes excluded from NEL review.
Larsson SC, Bergkvist L, Wolk A. Milk and lactose intakes and ovarian cancer risk in the Swedish Mammography Cohort. *Am J Clin Nutr.* 2004 Nov; 80(5): 1, 353-1, 357. PMID: 15531686.	Cancer outcomes excluded from NEL review.
Larsson SC, Orsini N, Wolk A. Milk, milk products and lactose intake and ovarian cancer risk: A meta-analysis of epidemiological studies. *Int J Cancer.* 2006 Jan 15; 118(2): 431-441. PMID: 16052536.	Cancer outcomes excluded from NEL review.
Lawlor DA, Ebrahim S, Timpson N, Davey Smith G. Avoiding milk is associated with a reduced risk of insulin resistance and the metabolic syndrome: Findings from the British Women's Heart and Health Study. *Diabet Med.* 2005 Jun; 22(6): 808-811. PMID: 15910636.	Included in Elwood, 2008.
Liu S, Choi HK, Ford E, Song Y, Klevak A, Buring JE, Manson JE. A prospective study of dairy intake and the risk of type 2 diabetes in women. *Diabetes Care.* 2006 Jul; 29(7): 1, 579-1, 584. PMID: 16801582.	Included in Elwood, 2008.
Lorenz M, Jochmann N, von Krosigk A, Martus P, Baumann G, Stangl K, Stangl V. Addition of milk prevents vascular protective effects of tea. *Eur Heart J.* 2007 Jan; 28(2): 219-223. Epub 2007 Jan 9. PMID: 17213230.	Does not answer question; did not examine relationship between milk product intake and health.
Ma D, Jones G. Soft drink and milk consumption, physical activity, bone mass, and upper limb fractures in children: a population-based case-control study. *Calcif Tissue Int.* 2004 Oct; 75(4): 286-291. Epub 2004 Jul 30. PMID: 15549642.	Does not answer question; examines relationship between soft drink intake and fracture risk.
Matsumoto M, Ishikawa S, Nakamura Y, Kayaba K, Kajii E. Consumption of dairy products and cancer risks. *J Epidemiol.* 2007 Mar; 17(2): 38-44. PMID: 17420611.	Cancer outcomes excluded from NEL review.
McCullough ML, Rodriguez C, Diver WR, Feigelson HS, Stevens VL, Thun MJ, Calle EE. Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev.* 2005 Dec; 14(12): 2, 898-2, 904. PMID: 16365007.	Cancer outcomes excluded from NEL review.

McGlynn KA, Sakoda LC, Rubertone MV, Sesterhenn IA, Lyu C, Graubard BI, Erickson RL. Body size, dairy consumption, puberty, and risk of testicular germ cell tumors. *Am J Epidemiol.* 2007 Feb 15; 165(4): 355-363. Epub 2006 Nov 16. PMID: 17110638.	Cancer outcomes excluded from NEL review.
Mitrou PN, Albanes D, Weinstein SJ, Pietinen P, Taylor PR, Virtamo J, Leitzmann MF. A prospective study of dietary calcium, dairy products and prostate cancer risk (Finland). *Int J Cancer.* 2007 Jun 1; 120(11): 2, 466-2, 473. PMID: 17278090.	Cancer outcomes excluded from NEL review.
Mizoue T, Kimura Y, Toyomura K, Nagano J, Kono S, Mibu R, Tanaka M, Kakeji Y, Maehara Y, Okamura T, Ikejiri K, Futami K, Yasunami Y, Maekawa T, Takenaka K, Ichimiya H, Imaizumi N. Calcium, dairy foods, vitamin D, and colorectal cancer risk: The Fukuoka Colorectal Cancer Study. *Cancer Epidemiol Biomarkers Prev.* 2008 Oct; 17(10): 2, 800-2, 807. PMID: 18843026.	Cancer outcomes excluded from NEL review.
Mommers M, Schouten LJ, Goldbohm RA, van den Brandt PA. Dairy consumption and ovarian cancer risk in the Netherlands Cohort Study on Diet and Cancer. *Br J Cancer.* 2006 Jan 16; 94(1): 165-170. PMID: 16306872.	Cancer outcomes excluded from NEL review.
Nestel PJ, Chronopulos A, Cehun M. Dairy fat in cheese raises LDL cholesterol less than that in butter in mildly hypercholesterolaemic subjects. *Eur J Clin Nutr.* 2005 Sep; 59(9): 1, 059-1, 063. PMID: 16015270.	Participants diagnosed with hypercholesterolemia.
Park SY, Murphy SP, Wilkens LR, Stram DO, Henderson BE, Kolonel LN. Calcium, vitamin D, and dairy product intake and prostate cancer risk: The Multiethnic Cohort Study. *Am J Epidemiol.* 2007 Dec 1; 166(11): 1, 259-1, 269. Epub 2007 Oct 8. PMID: 17925283.	Cancer outcomes excluded from NEL review.
Park Y, Leitzmann MF, Subar AF, Hollenbeck A, Schatzkin A. Dairy food, calcium, and risk of cancer in the NIH-AARP Diet and Health Study. *Arch Intern Med.* 2009 Feb 23; 169(4): 391-401. PMID: 19237724.	Cancer outcomes excluded from NEL review.
Park Y, Mitrou PN, Kipnis V, Hollenbeck A, Schatzkin A, Leitzmann MF. Calcium, dairy foods, and risk of incident and fatal prostate cancer: the NIH-AARP Diet and Health Study. *Am J Epidemiol.* 2007 Dec 1; 166(11): 1, 270-1, 279. Epub 2007 Oct 12. PMID: 18000020.	Cancer outcomes excluded from NEL review.
Parodi PW. Dairy product consumption and the risk of breast cancer. *J Am Coll Nutr.* 2005 Dec; 24(6 Suppl): 556S-568S. Review. PMID: 16373955.	Cancer outcomes excluded from NEL review.
Qin LQ, Xu JY, Wang PY, Hashi A, Hoshi K, Sato A. Milk/dairy products consumption, galactose metabolism and ovarian cancer: Meta-analysis of epidemiological studies. *Eur J Cancer Prev.* 2005 Feb; 14(1): 13-19. PMID: 15677891.	Cancer outcomes excluded from NEL review.

Qin LQ, Xu JY, Wang PY, Tong J, Hoshi K. Milk consumption is a risk factor for prostate cancer in Western countries: Evidence from cohort studies. *Asia Pac J Clin Nutr.* 2007; 16(3): 467-476. PMID: 17704029.	Cancer outcomes excluded from NEL review.
Qin LQ, Xu JY, Wang PY, Kaneko T, Hoshi K, Sato A. Milk consumption is a risk factor for prostate cancer: Meta-analysis of case-control studies. *Nutr Cancer.* 2004; 48(1): 22-27. PMID: 15203374.	Cancer outcomes excluded from NEL review.
Rohrmann S, Platz EA, Kavanaugh CJ, Thuita L, Hoffman SC, Helzlsouer KJ. Meat and dairy consumption and subsequent risk of prostate cancer in a US cohort study. *Cancer Causes Control.* 2007 Feb; 18(1): 41-50. PMID: 17315319.	Cancer outcomes excluded from NEL review.
Snijder MB, van der Heijden AA, van Dam RM, Stehouwer CD, Hiddink GJ, Nijpels G, Heine RJ, Bouter LM, Dekker JM. Is higher dairy consumption associated with lower body weight and fewer metabolic disturbances? The Hoorn Study. *Am J Clin Nutr.* 2007 Apr; 85(4): 989-995. PMID: 17413097.	Same data set as Snijder, 2008.
Sun Q, Ma J, Campos H, Hu FB. Plasma and erythrocyte biomarkers of dairy fat intake and risk of ischemic heart disease. *Am J Clin Nutr.* 2007 Oct; 86(4): 929-937. PMID: 17921367.	Does not answer question; examined relationship between fatty acids and disease risk.
Taguchi H, Chen H, Yano R, Shoumura S. Comparative effects of milk and soymilk on bone loss in adult ovariectomized osteoporosis rat. *Okajimas Folia Anat Jpn.* 2006 Aug; 83(2): 53-59. PMID: 16944838.	Study tested animals.
Tricon S, Burdge GC, Jones EL, Russell JJ, El-Khazen S, Moretti E, Hall WL, Gerry AB, Leake DS, Grimble RF, Williams CM, Calder PC, Yaqoob P. Effects of dairy products naturally enriched with cis-9, trans-11 conjugated linoleic acid on the blood lipid profile in healthy middle-aged men. *Am J Clin Nutr.* 2006 Apr; 83(4): 744-753. PMID: 16600923.	Milk products enriched with cis-9, trans-11 conjugated linoleic acid.
Tseng M, Breslow RA, Graubard BI, Ziegler RG. Dairy, calcium, and vitamin D intakes and prostate cancer risk in the National Health and Nutrition Examination Epidemiologic Follow-up Study cohort. *Am J Clin Nutr.* 2005 May; 81(5): 1, 147-1, 154. PMID: 15883441.	Cancer outcomes excluded from NEL review.
van der Pols JC, Bain C, Gunnell D, Smith GD, Frobisher C, Martin RM. Childhood dairy intake and adult cancer risk: 65-year follow-up of the Boyd Orr cohort. *Am J Clin Nutr.* 2007 Dec; 86(6): 1, 722-1, 729. PMID: 18065592.	Cancer outcomes excluded from NEL review.

Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: A systematic review and meta-analysis. *Am J Public Health.* 2007 Apr; 97(4): 667-675. Epub 2007 Feb 28. Review. PMID: 17329656; PMCID: PMC1829363.	Does not answer question; did not examine relationship between milk product intake and health.
Warensjö E, Jansson JH, Berglund L, Boman K, Ahrén B, Weinehall L, Lindahl B, Hallmans G, Vessby B. Estimated intake of milk fat is negatively associated with cardiovascular risk factors and does not increase the risk of a first acute myocardial infarction. A prospective case-control study. *Br J Nutr.* 2004 Apr; 91(4): 635-642. PMID: 15035691.	Does not include milk product intake in analyses.
Xu JY, Qin LQ, Wang PY, Li W, Chang C. Effect of milk tripeptides on blood pressure: a meta-analysis of randomized controlled trials. *Nutrition.* 2008 Oct; 24(10): 933-940. Epub 2008 Jun 17. PMID: 18562172.	Does not answer question; did not examine relationship between milk product intake and health.
Zhang J, Kesteloot H. Milk consumption in relation to incidence of prostate, breast, colon, and rectal cancers: Is there an independent effect? Nu*tr Cancer.* 2005; 53(1): 65-72. PMID: 16351508.	Cancer outcomes excluded from NEL review.
Zhu K, Zhang Q, Foo LH, Trube A, Ma G, Hu X, Du X, Cowell CT, Fraser DR, Greenfield H. Growth, bone mass, and vitamin D status of Chinese adolescent girls three years after withdrawal of milk supplementation. *Am J Clin Nutr.* 2006 Mar; 83(3): 714-721. PMID: 16522922.	Milk enriched with additional calcium.

CHAPTER 17. MILK AND MILK PRODUCTS – BLOOD PRESSURE

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF MILK AND MILK PRODUCTS AND BLOOD PRESSURE?

Conclusion statement

A moderate body of evidence suggests an inverse relationship between the intake of milk and milk products and blood pressure.

Grade

Moderate

Evidence summary overview

Based on the current review of research of literature published since 2004, there is little evidence that supports an independent relationship between the intake of milk and milk products and blood pressure (BP). This conclusion is based on one systematic review (Alvarez-Leon, 2006), one randomized controlled trial (RCT) (Bowen, 2005), six prospective cohort studies (Alonso, 2005; Engberink, 2009a; Engberink, 2009b; Snijder, 2008; Toledo, 2009; Wang, 2008) and five cross-sectional studies (Azadbakht, 2005; Beydoun, 2008; Djousse, 2006; Houston, 2008; Ruidavets, 2006).

The systematic review by Alvarez-Leon et al (2006) concluded that an inverse association exists between the intake of dairy products and hypertension (HTN). In the Bowen et al (2005) RCT, the authors determined that weight loss following energy-restricted, high-protein diets is not affected by dietary calcium or protein source. Also, weight loss, not dietary calcium, was shown to improve BP.

Results were reviewed from six prospective studies conducted in the Netherlands, Spain and the US. In the Women's Health Study (Wang, 2008a), decreased risk of HTN was associated with low-fat dairy products, calcium and vitamin D. In the Seguimiento Universidad de Navarra (SUN) cohort in Spain, Alonso et al (2005) reported a 54% reduction in HTN in participants with the highest consumption of low-fat dairy products compared to those with the lowest consumption, and they found no association between whole-fat dairy or total calcium intake and incident HTN. Likewise, the Toledo et al (2009) study in Spain found no significant (NS) relationship between high-fat dairy and BP, but BP was significantly lower among the highest consumers of low-fat dairy products.

In general, studies from the Netherlands did not show as strong a relationship between the intake of milk and milk products and BP. Engberink et al (2009a) followed more than 20,000 participants for five years in the Netherlands and concluded that dairy intake has little effect on population BP. Snijder et al (2008) concluded that dairy consumption was not associated with changes in metabolic variables in their study with a Dutch elderly population. Engberink et al (2009b) followed older Dutch participants for six years and they concluded that low-fat dairy may be related to HTN prevention, but high-fat dairy and cheese did not show the same effect.

Five cross-sectional studies (Azadbakht, 2005; Beydoun, 2008; Djousse, 2006;

Houston, 2008; Ruidavets, 2006) conducted in Iran, France and the US also were reviewed and all showed some positive impact of milk and milk product consumption on BP, although the results were not consistent for all population groups. Using data from National Health and Nutrition Examination Surveys (NHANES) 1999 to 2004, Beydoun et al (2008) found that among all study participants, and among men in particular, fluid milk was inversely related to BP (systolic and diastolic BP), and yogurt was associated with better systolic blood pressure (SBP). In contrast, cheese was positively associated with SBP. Using data on the intake of cheese from NHANES III, Houston et al (2008) found that SBP was not different across categories of cheese consumption, but diastolic blood pressure (DBP) was higher among men in the highest category of cheese consumption compared to non-consumers. In a cross-sectional analysis of almost 5,000 participants from the National Heart, Lung and Blood Institute (NHLBI) Family Heart Study, there was an inverse association between dairy intake and the prevalence of HTN that was independent of calcium intake and seen mainly among participants consuming less saturated fat. A cross-sectional analysis of 1,500 participants in Iran (Azadbakht, 2005) showed an inverse relationship between dairy consumption and HTN. Finally, the French study by Ruidavets et al (2006) concluded that the consumption of dairy products may be associated with reduced BP.

Evaluating the research on this topic is complicated by the types of milk products consumed in the various studies, potential confounding with calcium intakes from other food sources, and the known relationship of BP to weight loss.

Evidence summary paragraphs

Systematic Review

Alvarez-Leon et al, 2006 (positive quality) systematically reviewed papers on the associations between consumption of dairy products and health outcomes, including cancer, bone health and cardiovascular disease (CVD). Relevant articles were obtained through searching the MEDLINE database (from 1966 to January 2005) using the search terms: ‘dairy products,’ defined as ‘raw and processed or manufactured milk and milk-derived products’ including butter, cheese, ice cream, margarine and milk and cultured milk products (yoghurt). This search revealed 85,000 articles. After excluding studies, and including only meta-analysis and systematic reviews, the final sample consisted of 14 meta-analyses and systematic reviews. This final sample consisted of six papers on dairy products and cancer, six papers on dairy products and cardiovascular disease and two papers on dairy products and bone health. Four articles specifically addressed HTN. Evidence from these papers was summarized and evaluated. The authors concluded that there is an inverse association between the intake of dairy products and HTN.

Primary Research

Trials

Bowen et al, 2005 (positive quality) conducted a randomized controlled trial (RCT) to compare the effects on weight, body composition, metabolic parameters and risk markers of two isocaloric, energy-restricted high protein diets that differ in dietary calcium and protein source on weight loss and body composition in healthy, overweight adults (N=50, 30 women and 20 men, ages 25 to 64 years). The study was conducted in Australia. The intervention diets were a high dairy protein and high-

calcium (DP, 2,400mg Ca per day) diet and a high mixed protein and moderate calcium (MP, 500mg Ca per day) diet followed for a 12-week energy restriction phase, followed by a four-week energy balance phase. After 16 weeks, subjects showed significant reductions in total weight (-9.7±3.8kg), fat mass (-8.3±0.4kg) and lean mass (-1.6±0.3kg), but there were no significant (NS) differences between the two diet groups. Systolic and diastolic blood pressure were significantly lower at week 16 compared to baseline independent of dietary group and gender. Overall, SBP decreased by 9.4±1.4mmHg from baseline to week 16 (P<0.001). The largest decrease occurred between week zero and four (-7.6±1.3mmHg; P<0.001) and remained relatively stable between week four and 16. Similarly, DBP decreased by 2.5±0.9mmHg from baseline to week 16 (P<0.001). The largest decrease occurred between baseline and week four (-4.4±0.9mmHg; P<0.001) and remained stable from week four to 12. Diastolic blood pressure increased by 2.1±0.8mmHg from week 12 to 16 (P<0.01). There was no relationship between baseline BP and weight loss or dietary group. The authors concluded that weight loss following energy-restricted, high protein diets is not affected by dietary calcium or protein source. In addition, BP improved with weight loss independent of dietary protein source or calcium intake.

Prospective Cohort Studies

Alonso et al, 2005 (positive quality) conducted a prospective cohort study to assess whether total, low-fat and whole-fat dairy product consumption was associated with risk of HTN in a group of Spanish adults [Seguimiento Universidad de Navarra (SUN) cohort]. Subjects included 6,686 adults (mean age = 37 years) at baseline. Dairy consumption was assessed at baseline using a semiquantitative 136-item food-frequency questionnaire (FFQ), and subjects self-reported whether they were diagnosed with HTN and their most recent systolic and diastolic BP values at baseline and at the two-year follow-up. Subjects were divided into quintiles based on dairy intake: Q1: 155.6±75.3g per day (N=1,177); Q2: 292.4±27.6g per day (N=1,174); Q3: 383.9±29.7g per day (N=1,177); Q4: 530.0±53.0g per day (N=1,176); Q5: 798.8±215.4g per day (N=1,176). At follow-up, 180 new cases of HTN were identified. Results showed a 54% reduction in HTN incidence in participants with the highest consumption of low-fat dairy products compared to those with the lowest consumption (0.46; 95% CI: 0.26, 0.84; P<0.05) after adjustment for main known risk factors for HTN and dietary factors. No significant association between whole-fat dairy or total calcium intake and incident HTN was seen.

Engberink, Geleijnse et al, 2009a (positive quality), a prospective cohort study conducted in the Netherlands, investigated whether dairy consumption, including specific dairy food groups, was associated with BP and risk of HTN in a population-based cohort of participants from the Monitoring Project on Risk Factors for Chronic Diseases. A total of 21,553 participants aged 20 to 65 years who did not use anti-hypertensive medication were included in the baseline analysis; risk of HTN was examined in 3,454 of these participants after a five-year follow-up. Intake of total dairy, specific dairy groups (i.e., low-fat, high-fat, fermented) and dairy products (i.e., cheese, yogurt) were assessed at baseline using a semiquantitative 178-item FFQ. Participants had a median intake of 344g per day of total dairy (approximately 2.3 servings) and 174g per day of low-fat dairy (approximately 1.2 servings); however, the intake of total dairy, specific dairy groups and dairy products were not consistently related to BP. Of the participants who were followed, the risk of HTN tended to be inversely related to

low-fat dairy intake (P=0.24). The authors concluded that dairy intake has little effect on population BP.

Engberink, Hendriksen et al, 2009b (positive quality), a prospective cohort study conducted in the Netherlands, assessed whether hypertension is associated with dairy consumption in older adults (over age 55 years). Dietary intake was assessed at baseline through home checklist, interview with dietitian and 170-item semiquantitative FFQ. Blood pressure was measured at baseline, and re-examined in 1993 to 1995 (after two years) and 1997 to 1999 (after six years). A total of 7,983 subjects were available at baseline, with 2,245 having complete dietary and BP data. Risk of HTN after two years of follow-up (664 incident cases) was inversely associated with dairy product intake; after adjustment for confounders, hazard ratios were 1.00, 0.82 (95% CI: 0.67, 1.02), 0.67 (95% CI: 0.54, 0.84), and 0.76 (95% CI: 0.61, 0.95) for consecutive quartiles of total dairy product intake (P=0.008) and were 1.00, 0.75 (95% CI: 0.60, 0.92), 0.77 (95% CI: 0.63, 0.96) and 0.69 (95% CI: 0.56, 0.86), for consecutive quartiles of low-fat dairy product intake (P=0.003). Analysis of specific types of dairy products showed an inverse association with milk and milk products (P=0.07), but no association with high fat dairy or cheese. After six years of follow-up (984 incident cases), the associations with HTN were attenuated to risk reductions of approximately 20% for both total and low-fat dairy products between the first and last quartiles of intake (P=0.07 and 0.09, respectively). The authors concluded that low-fat dairy intake may be related to prevention of HTN as people age.

Snijder et al, 2008 (positive quality), a prospective cohort study conducted in the Netherlands, investigated the association between dairy consumption and changes in weight and metabolic disturbances, based on data from the Hoorn study, a population-based cohort of white men and women aged 50 to 75 years. Average food intake was measured at baseline using a 92-item semiquantitative FFQ. At baseline and follow-up, participants underwent an extensive physical examination and a blood sample was drawn for biochemical analyses of fasting glucose, post-load glucose, high-density lipoprotein (HDL-C) and low-density lipoprotein (LDL-C) cholesterol and triglycerides (TG). During the physical examination, weight, waist circumference (WC) and BP were measured. A total of 1,124 participants were included in the analysis. Baseline dairy consumption was not associated with 6.4-year changes in systolic or diastolic BP. The authors concluded that dairy consumption was not associated with changes in metabolic variables in a Dutch elderly population.

Toledo et al, 2009 (positive quality) used data from a prospective cohort study to assess the relationship between low-fat dairy product intake and BP levels and change in BP after 12 months in a group of older adults at high risk of CVD participating in a trial on the effects of the Mediterranean diet on cardiovascular outcomes (PREDIMED trial, Spain). Adults (N=2,290, 458 per quintile; ages 55 to 80 years) were divided into quintiles based on low-fat dairy consumption (Q1: 3.1±17.1g per day; Q2: 141.1±53.3g per day; Q3: 236.7±26.8g per day; Q4: 406.1±80.1g per day; Q5: 631.6±139.4g per day). Dietary intake was assessed at baseline and 12 months using a 137-item FFQ, and BP measures were taken at baseline and 12 months by trained personnel. Results showed that adjusted systolic and diastolic BP were significantly lower in the highest quintile of low-fat dairy product intake (-4.2; 95% CI: -6.9, -1.4 and -1.8; 95% CI: -3.2, -.04mmHg, respectively). No significant trends were observed when examining the relationship between high-fat dairy intake and BP. There were also NS interactions

between low-fat or high-fat dairy consumption and obesity or diabetes mellitus (DM).

Wang et al, 2008 (positive quality), a prospective cohort study conducted in the US, examined the associations between intake of dairy products, as well as the major nutrient components in dairy products, with the risk of HTN in participants from the Women's Health Study. Out of 39,876 female health professionals in the Women's Health Study, 28,886 women (mean age 54 years) remained in the analysis after application of exclusion criteria. Intake of dairy products, calcium and vitamin D at baseline were assessed from semi-quantitative FFQs, and incident cases of self-reported hypertension were identified over ten years of follow-up. After adjustment for confounding variables, the relative risks of incident HTN across increasing quintiles of low-fat dairy product intake were 1.00 (reference), 0.98, 0.97, 0.95 and 0.89 (P=0.001). The risk of HTN decreased in the higher quintiles of dietary calcium (multivariate RR = 0.87) and dietary vitamin D (multivariate RR = 0.95) but did not change with calcium or vitamin D supplementation. The authors concluded that intakes of low-fat dairy products, calcium and vitamin D were each inversely associated with risk of HTN in middle-aged and older women.

Cross-Sectional Studies:

Azadbakht et al, 2005 (positive quality), a cross-sectional study conducted in Tehran, Iran, ascertained the relation between dairy consumption and metabolic syndrome in a population-based sample of adults. A representative sample of 1,476 participants were randomly selected from the Tehran Lipid and Glucose Study, including 861 subjects aged 18 to 74 years. After application of exclusion criteria, 827 subjects (357 men, 470 women) were included in the analysis. Dairy consumption was assessed through a 168-item semi-quantitative FFQ, and subjects were categorized into quartiles of intake (less than 1.7, 1.7 to less than 2.3, 2.3 to less than 3.1 and 3.1 or more servings a day). Measurements relevant to the diagnosis of the metabolic syndrome were taken, such as height, weight, WC, BP and fasting blood samples for glucose and lipid concentrations. Mean consumption of milk, yogurt and cheese was 0.7±0.2, 1.06±0.6 and 0.9±0.3 servings per day, respectively; butter and ice cream were not included in the analysis due to their high fat content. Dairy consumption had an inverse association with HTN; odds ratios (OR) by quartile were 1, 0.88, 0.79, 0.71 (P<0.02). These values became weaker after adjustment for calcium intake.

Beydoun et al, 2008 (positive quality), a cross-sectional analysis of merged NHANES data from 1999 to 2004 in the US, assessed the association between consumption of dairy and related nutrients and obesity, central obesity and the metabolic syndrome. Out of 17,061 subjects over age 18 years (8,970 women and 8,091 men) with complete demographic data, 4,519 subjects had complete data on dietary intake (assessed from 24-hour recall data) and metabolic outcomes, such as weight, height, WC, BP and laboratory values (fasting blood glucose, triacylglycerol (TAG) stores and HDL-C). When dairy consumption and related nutrients were examined in relation to individual metabolic outcomes as continuous variables, they found that among all subjects, and among men in particular, fluid milk (servings) was inversely related to blood pressure (SBP and DBP) and yogurt was associated with better SBP. In contrast, cheese was positively associated with SBP.

Djousse et al, 2006 (positive quality), a multicenter cross-sectional study conducted in the US, examined the relation between dairy consumption and prevalent hypertension

among 4,797 participants of the NHLBI Family Heart Study (45% were men, mean age 52.2±13.7 years, range 25 to 94 years). Dietary intake of dairy products were assessed through staff-administered semi-quantitative FFQ. There was an inverse association between dairy intake and prevalent HTN; OR across quartiles of dairy consumption were 1.0 (reference), 0.82 (95% CI: 0.64, 1.05), 0.68 (95% CI: 0.53, 0.89) and 0.62 (95% CI: 0.45, 0.84), respectively, P=0.002; this association was independent of calcium intake, and mainly observed among subjects consuming less saturated fat. Dairy consumption was inversely associated with SBP (P=0.003) but not DBP.

Houston et al, 2008 (positive quality), a cross-sectional study conducted in the US, examined the association between the frequency of cheese consumption and several cardiovascular risk factors, including measures of body fat, blood lipids, BP and blood glucose, using data from NHANES III. 10,872 participants, aged 25 to 75 years, had complete data and were included in the analysis. Cheese consumption (combined full and low-fat) was assessed through an FFQ asking one question about cheese and two questions about the consumption of foods containing large amounts of cheese. Categories of cheese consumption were 0, 1 to 4, 5 to 12, 13 to 29 and 30-plus servings per month. Systolic blood pressure was not significantly different across categories of cheese consumption in men or women. Diastolic blood pressure was significantly higher among men, but not among women, in the highest category of cheese consumption compared to non-consumers (P<0.05).

Ruidavets et al, 2006 (neutral quality), a cross-sectional study conducted in France, investigated the relationships between BP and dairy products, dietary calcium and a mixed dieting behavior characterized by a combination of different levels of intake of calcium and dairy products. Participants were recruited from the population as part of the French MONICA Study (Monitoring of Trends and Determinations in Cardiovascular Disease). Anthropometric data were taken, including WC, waist-to-hip ratio (WHR) and body mass index (BMI); BP was measured twice. Intake of dairy products was measured through food records with follow-up interviews by a dietitian. Four combinations of dairy products were established: 1) Milk, 2) milk plus fresh cheese, 3) milk plus fresh cheese plus cheese, and 4) milk plus fresh cheese plus cheese plus butter. After those without complete data were excluded, 912 men aged 45 to 64 years remained in the analysis. Systolic and diastolic blood pressures significantly decreased from the lowest (145.4±1.55 and 89.0±0.94mmHg, respectively) to the highest quintile (135.6±1.26 and 85.3±0.84mmHg, respectively) of dairy product intakes in bivariate analysis. After multivariate adjustment, the difference in SBP between the two extreme quintiles of calcium intake was 4.1mmHg, for milk intake was 3.8mmHg, for milk and fresh cheese combination was 4.4mmHg, and for total dairy intake was 7.0mmHg. The authors concluded that the consumption of dairy products may be associated with reduced levels of BP.

Overview table

Author, Year, Study Design, Class, Rating	Participants	Description of Study Design	Outcomes
Alonso A, Beunza JJ et al, 2005 Study Design: Prospective Cohort Study Class: B Positive quality	N=6,686 adults at baseline. Mean age: 37 years. Seguimiento Universidad de Navarra [SUN] cohort. Subjects divided into quintiles based on dairy intake (per day): Q1: 155.6±75.3g (N=1,177) Q2: 292.4±27.6g (N=1,174) Q3: 383.9±29.7g (N=1,177) Q4: 530.0±53.0g (N=1,176) Q5: 798.8±215.4g (N=1,176). Location: Spain.	Dairy consumption assessed at baseline using a semiquantitative 136-item FFQ. Subjects self-reported whether they were diagnosed with HTN and most recent SBP and DBP values at baseline and at two-year follow-up.	At follow-up, 180 new cases of HTN identified. 54% ↓ in HTN incidence in participants with highest consumption of low-fat dairy products compared to those with lowest consumption (0.46; 95% CI: 0.26, 0.84; P<0.05) after adjustment for the main known risk factors for HTN and dietary factors. NS association between whole-fat dairy or total Ca intake and incident HTN.
Alvarez-León EE, Roman-Vinas B et al, 2006 Study Design: Meta-analysis or Systematic Review Class: M Positive quality	N=14 meta-analyses and systematic reviews. Six papers on dairy products and cancer. Six papers on dairy products and CVD. Two papers on dairy products and bone health.	Relevant articles obtained through searching MEDLINE database (from 1966 to January 2005) using search terms: 'dairy products,' defined as 'raw and processed or manufactured milk, and milk-derived products' including butter, cheese, ice cream, margarine, and milk and cultured milk products (yoghurt).	Four articles specifically addressed HTN. Authors concluded that there is an inverse association between intake of dairy products and HTN.

Azadbakht L, Mirmiran P et al, 2005 Study Design: Cross-Sectional Study Class: D Positive quality	A representative sample of 1,476 participants were randomly selected from the Tehran Lipid and Glucose Study, including 861 subjects aged 18 to 74 years. N=827 subjects (357 men, 470 women) included in the analysis, after application of exclusion criteria. Location: Tehran, Iran.	Ascertained relation between dairy consumption and metabolic syndrome in a population-based sample of adults. Dairy consumption assessed through a 168-item semi-quantitative FFQ and subjects categorized into quartiles of intake (<1.7, 1.7 to <2.3, 2.3 to <3.1 and ≥3.1 servings a day). Measurements relevant to diagnosis of metabolic syndrome taken, such as height, weight, WC, BP and fasting blood samples for glucose and lipid concentrations.	Mean consumption of milk, yogurt and cheese was 0.7±0.2, 1.06±0.6 and 0.9±0.3 servings per day, respectively; butter and ice cream not included in analysis, due to high fat content. Dairy consumption had an inverse association with HTN; OR by quartile were 1, 0.88, 0.79, 0.71 (P<0.02). These values became weaker after adjustment for Ca intake.
Beydoun et al 2008 Study Design: Cross-sectional Study Class: D Positive quality	N=4,519 subjects had complete data on dietary intake and metabolic outcomes (out of 17,061 subjects >age 18 years (8,970 women, 8,091 men) with complete demographic data). Location: United States.	Analyzed merged NHANES data from 1999 to 2004 in the US, assessed the association between consumption of dairy and related nutrients and obesity, central obesity and metabolic syndrome. Included subjects had complete data on dietary intake (assessed from 24-hour recall data) and metabolic outcomes, such as weight, height, WC, BP and laboratory values (FBG, TG stores and HDL-C).	When dairy consumption and related nutrients were examined in relation to individual metabolic outcomes as continuous variables, among all subjects and among men in particular, fluid milk (servings) inversely related to BP (SBP and DBP) and yogurt associated with better SBP. In contrast, cheese positively associated with SBP.

Bowen J, Noakes M et al, 2005 Study Design: Randomized Controlled Trial Class: A Positive quality	N=50 (30 women, 20 men) Age: 25 to 64 years. Location: Australia.	Compared effects of two isocaloric, energy-restricted high PRO diets that differ in dietary Ca and PRO source on weight ↓ and body composition. Intervention diets were 1) high dairy PRO and high-Ca (DP, 2,400mg Ca per day) diet and 2) high mixed PRO and moderate Ca (MP, 500mg Ca per day) diet followed for a 12-week energy restriction phase, followed by a four-week energy balance phase.	After 16 weeks, subjects showed significant ↓ in total weight (-9.7±3.8kg), fat mass (-8.3±0.4kg) and lean mass (-1.6±0.3kg), but NS differences between the two diet groups. SBP and DBP significantly ↓ at week 16 compared to baseline independent of dietary group and gender. Overall, SBP ↓ by 9.4±1.4mmHg from baseline to week 16 (P<0.001). Largest ↓ occurred between week 0 and four (-7.6±1.3mmHg; P<0.001) and remained relatively stable between week four and 16. Similarly, DBP ↓ by 2.5±0.9mmHg from baseline to week 16 (P<0.001). Largest ↓ occurred between baseline and week four (-4.4±0.9mmHg; P<0.001) and remained stable from week four to 12. DBP ↑ by 2.1±0.8mmHg from week 12 to 16 (P<0.01). No relationship between baseline BP and weight loss or dietary group.
Djousse et al 2006 Study Design: Cross-sectional Study Class: D Positive quality	N=4,797 participants of the NHLBI Family Heart Study (45% men). Mean age: 52.2±13.7 years (range 25 to 94 years). Location: United States.	Examined relation between dairy consumption and prevalent HTN. Dietary intake of dairy products assessed through staff-administered semi-quantitative FFQ.	Inverse association between dairy intake and prevalent HTN: OR across quartiles of dairy consumption were 1.0 (reference), 0.82 (95% CI: 0.64, 1.05), 0.68 (95% CI: 0.53, 0.89) and 0.62 (95% CI: 0.45, 0.84), respectively, P=0.002; this association was independent of Ca intake and mainly observed among subjects consuming ↓ SFA. Dairy consumption inversely associated with SBP (P=0.003), but not DBP.

Engberink MF, Geleijnse JM et al 2009 Study Design: Prospective Cohort Study Class: B Positive quality	N=21,553 participants who did not use anti-hypertensive medication were included in baseline analysis. Risk of HTN examined in 3,454 of these participants after a five-year follow-up. Age: 20 to 65 years. Location: The Netherlands.	Investigated whether dairy consumption, including specific dairy food groups, was associated with BP and risk of HTN in a population-based cohort of participants from the Monitoring Project on Risk Factors for Chronic Diseases. Intake of total dairy, specific dairy groups (i.e., low-fat, high-fat, fermented) and dairy products (i.e., cheese, yogurt) assessed at baseline using a semiquantitative 178-item FFQ.	Participants had median intake of 344g per day of total dairy (~2.3 servings) and 174g per day of low-fat dairy (~1.2 servings); however, intake of total dairy, specific dairy groups and dairy products not consistently related to BP. Of the participants who were followed, risk of HTN tended to be inversely related to low-fat dairy intake (P=0.24). Authors concluded that dairy intake has little effect on population BP.
Engberink MF, Hendriksen MA et al 2009 Study Design: Prospective Cohort Study Class: B Positive quality	N=7,983 older adults (age >55 years) available at baseline, with 2,245 having complete dietary and BP data. Location: The Netherlands.	Assessed whether HTN is associated with dairy consumption in older adults. Dietary intake assessed at baseline through home checklist, interview with dietitian and 170-item semiquantitative FFQ. BP measured at baseline and re-examined in 1993 to 1995 (after two years) and 1997 to 1999 (after six years).	Risk of HTN after two years of follow-up (664 incident cases) inversely associated with dairy product intake; after adjustment for confounders, HRs were 1.00, 0.82 (95% CI: 0.67, 1.02), 0.67 (95% CI: 0.54, 0.84), and 0.76 (95% CI: 0.61, 0.95) for consecutive quartiles of total dairy product intake (P=0.008) and 1.00, 0.75 (95% CI: 0.60, 0.92), 0.77 (95% CI: 0.63, 0.96) and 0.69 (95% CI: 0.56, 0.86), for consecutive quartiles of low-fat dairy product intake (P=0.003). Analysis of specific types of dairy products showed an inverse association with milk/milk products (P=0.07), but no association with ↑fat dairy or cheese. After six years of follow-up (984 incident cases), associations with HTN were attenuated to risk ↓ of ~20% for both total and low-fat dairy products between first and last quartiles of intake (P=0.07 and 0.09, respectively). Authors concluded that low-fat dairy intake may be related to prevention of HTN as people age.

Houston et al 2008 Study Design: Cross-sectional Study Class: D Positive quality	N=10,872 NHANES III participants had complete data and included in analysis. Age: 25 to 75 years. Location: United States.	Examined association between frequency of cheese consumption and several cardiovascular risk factors, including measures of body fat, blood lipids, BP and BG, using data from NHANES III. Cheese consumption (combined full and low-fat) assessed through FFQ asking one question about cheese and two questions about consumption of foods containing large amounts of cheese. Categories of cheese consumption: 0, 1 to 4, 5 to 12, 13 to 29 and 30-plus servings per month.	SBP was NS different across categories of cheese consumption in men or women. DBP significantly ↑ among men, but not among women, in highest category of cheese consumption compared to non-consumers (P<0.05).
Ruidavets et al 2006 Study Design: Cross-sectional Study Class: D Neutral quality	N=912 men in analysis, after those without complete data were excluded. Age: 45 to 64 years. Location: France.	Investigated relationships between BP and dairy products, dietary Ca and a mixed dieting behavior characterized by a combination of different levels of intake of Ca and dairy products. Participants recruited from the population as part of the French MONICA Study (Monitoring of Trends and Determinations in Cardiovascular Disease). Anthropometric data taken, including WC, WHR and BMI; BP was measured twice. Intake of dairy products measured through food records with follow-up interviews by a dietitian. Four combinations of dairy products established: 1) Milk 2) Milk and fresh cheese 3) Milk and fresh cheese and cheese 4) Milk and fresh cheese and cheese and butter.	SBP and DBP significantly ↓ from lowest (145.4±1.55 and 89.0±0.94mmHg, respectively) to the highest quintile (135.6±1.26 and 85.3±0.8mmHg, respectively) of dairy product intakes in bivariate analysis. After multivariate adjustment, difference in SBP between two extreme quintiles of Ca intake was 4.1mmHg, for milk intake 3.8mmHg, for milk and fresh cheese combination 4.4mmHg and for total dairy intake 7.0mmHg. Authors concluded that consumption of dairy products may be associated with ↓ levels of BP.

Snijder et al 2008 Study Design: Prospective Cohort Study Class: B Positive quality	Participants in the Hoorn study, a population-based cohort of white men and women. Age: 50 to 75 years. N=1,124 participants included in the analysis. Location: The Netherlands.	Investigated association between dairy consumption and Δ in weight and metabolic disturbances. Average food intake measured at baseline using a 92-item semiquantitative FFQ. At baseline and follow-up, participants underwent extensive physical exam and blood sample drawn for biochemical analyses of fasting glucose, post-load glucose, HDL-C and LDL-C and TG. During the physical exam, weight, WC and BP measured.	Baseline dairy consumption not associated with 6.4-year Δ in SBP and DBP. Authors concluded that dairy consumption was not associated with Δ in metabolic variables in a Dutch elderly population.
Toledo E, Delgado-Rodríguez M, et al 2009 Study Design: Prospective Cohort Study Class: B Positive quality	N=2,290, 458 per quintile. Age: 55 to 80 years. Q1: 3.1±17.1g per day. Q2: 141.1±53.3g per day. Q3: 236.7±26.8g per day. Q4: 406.1±80.1g per day. Q5: 631.6±139.4g per day. Location: Spain.	Assessed relationship between low-fat dairy product intake and BP levels and BPΔ after 12 months in a group of older adults at high risk of CVD. Dietary intake assessed at baseline and 12 months using a 137-item FFQ. BP measures taken at baseline and 12 months by trained personnel.	Adjusted SBP and DBP significantly ↓ in highest quintile of low-fat dairy product intake (-4.2; 95% CI: -6.9, -1.4 and -1.8; 95% CI: -3.2, -0.04mmHg, respectively). NS trends observed when examining relationship between high-fat dairy intake and BP. NS interactions between low-fat or high-fat dairy consumption and obesity or DM.
Wang L et al 2008 Study Design: Prospective Cohort Study Class: B Positive quality	N=28,886 women in analysis after application of exclusion criteria (out of 39,876 female health professionals in the Women's Health Study). Mean age: 54 years. Location: United States.	Examined associations between intake of dairy products, as well as major nutrient components in dairy products, with risk of HTN in participants from the Women's Health Study. Intake of dairy products, Ca and vitamin D at baseline were assessed from semi-quantitative FFQs and incident cases of self-reported HTN identified over ten years of follow-up.	After adjustment for confounding variables, the RR of incident HTN across increasing quintiles of low-fat dairy product intake were 1.00 (reference), 0.98, 0.97, 0.95 and 0.89 (P=0.001). Risk of HTN ↓ in higher quintiles of dietary Ca (multivariate RR=0.87) and dietary vitamin D (multivariate RR=0.95), but no Δ with Ca or vitamin D supplementation. Authors concluded that intakes of low-fat dairy products, Ca and vitamin D were each inversely associated with risk of HTN in middle-aged and older women.

Search plan and results

Inclusion criteria

- June 2004 to July 2009
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children, two to 18 years; adults, 19 years and older
- *Populations:* Healthy and those with elevated chronic disease risk.

Exclusion criteria

- Studies that only consider cancer outcomes
- Studies that considered milk and milk products as part of a larger dietary pattern
- Milk and milk products in forms not commonly consumed (e.g., enriched with additional calcium)
- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Animal studies
- In vitro studies
- Articles not peer reviewed (web sites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: ("Dairy Products"[mh]) AND ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mesh: NoExp] OR “heart diseases”[mh] OR “chronic disease”[mh] OR "Neoplasms"[majr] OR osteoporosis[mh] OR "Bone Density"[Mesh] OR "Fractures, Bone"[Mesh])

Date searched: 07/29/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 223
- Total articles identified to review from electronic databases: 95
- Articles identified via handsearch or other means: 3
- Number of Primary Articles Identified: 20
- Number of Review Articles Identified: 4
- Total Number of Articles Identified: 24
- Number of Articles Reviewed but Excluded: 74

Included articles (References)

What is the relationship between the intake of milk and milk products and bone health?

Systematic Reviews/Meta-analyses

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: A review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.
2. Huncharek M, Muscat J, Kupelnick B. Impact of dairy products and dietary calcium on bone-mineral content in children: Results of a meta-analysis. *Bone.* 2008 Aug; 43(2): 312-321. Epub 2008 Mar 15. PMID: 18539555.
3. Kanis JA, Johansson H, Oden A, De Laet C, Johnell O, Eisman JA, Mc Closkey E, Mellstrom D, Pols H, Reeve J, Silman A, Tenenhouse A. A meta-analysis of milk intake and fracture risk: low utility for case finding. *Osteoporos Int.* 2005 Jul; 16(7): 799-804. Epub 2004 Oct 21. PMID: 15502959.

Primary Research

Trials

1. Budek AZ, Hoppe C, Michaelsen KF, Mølgaard C. High intake of milk, but not meat, decreases bone turnover in prepubertal boys after 7 days. *Eur J Clin Nutr.* 2007 Aug; 61(8): 957-962. Epub 2007 Jan 17. PMID: 17228345.
2. Kristensen M, Jensen M, Kudsk J, Henriksen M, Mølgaard C. Short-term effects on bone turnover of replacing milk with cola beverages: A 10-day interventional study in young men. *Osteoporos Int.* 2005 Dec; 16(12): 1, 803-1, 808. Epub 2005 May 11. PMID: 15886860.
3. McCabe LD, Martin BR, McCabe GP, Johnston CC, Weaver CM, Peacock M. Dairy intakes affect bone density in the elderly. *Am J Clin Nutr.* 2004 Oct; 80(4): 1, 066-1, 074. PMID: 15447921.

Longitudinal Study

1. Rockell JE, Williams SM, Taylor RW, Grant AM, Jones IE, Goulding A. Two-year changes in bone and body composition in young children with a history of prolonged milk avoidance. *Osteoporos Int.* 2005 Sep; 16(9): 1, 016-1, 023. Epub 2004 Nov 23. PMID: 15565350.

Case-Control Study

1. Konstantynowicz J, Nguyen TV, Kaczmarski M, Jamiolkowski J, Piotrowska-Jastrzebska J, Seeman E. Fractures during growth: Potential role of a milk-free diet. *Osteoporos Int.* 2007 Dec; 18(12): 1, 601-1, 607. Epub 2007 May 22. PMID: 17516020.

Cross-Sectional Study

1. Al-Zahrani MS. Increased intake of dairy products is related to lower periodontitis prevalence. *J Periodontol.* 2006 Feb; 77(2): 289-294. PMID: 16460256. (Hand search)

What is the relationship between the intake of milk and milk products and cardiovascular disease?

Systematic Reviews/Meta-Analyses

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: A review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.
2. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The

survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

Primary Research

Case-Control Study

1. Kontogianni MD, Panagiotakos DB, Chrysohoou C, Pitsavos C, Stefanadis C. Modelling dairy intake on the development of acute coronary syndromes: The CARDIO2000 study. *Eur J Cardiovasc Prev Rehabil.* 2006 Oct; 13(5): 791-797. PMID: 17001220.

What is the relationship between the intake of milk and milk products and blood pressure?

Systematic Review

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: a review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.

Primary Research

Trial

1. Bowen J, Noakes M, Clifton PM.Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. *Int J Obes (Lond).* 2005 Aug; 29(8): 957-965. PMID: 15711601. (Hand search)

Prospective Cohort Studies

1. Alonso A, Beunza JJ, Delgado-Rodríguez M, Martínez JA, Martínez-González MA. Low-fat dairy consumption and reduced risk of hypertension: The Seguimiento Universidad de Navarra (SUN) cohort. *Am J Clin Nutr.* 2005 Nov; 82(5): 972-979. PMID: 16280427.
2. Engberink MF, Hendriksen MA, Schouten EG, van Rooij FJ, Hofman A, Witteman JC, Geleijnse JM. Inverse association between dairy intake and hypertension: The Rotterdam Study. *Am J Clin Nutr.* 2009 Jun; 89(6): 1, 877-1, 883. Epub 2009 Apr 15. PMID: 19369377.
3. Engberink MF, Geleijnse JM, de Jong N, Smit HA, Kok FJ, Verschuren WM. Dairy intake, blood pressure, and incident hypertension in a general Dutch population. *J Nutr.* 2009 Mar; 139(3): 582-587. Epub 2009 Jan 21. PMID: 19158223.
4. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.
5. Toledo E, Delgado-Rodríguez M, Estruch R, Salas-Salvadó J, Corella D, Gomez-Gracia E, Fiol M, Lamuela-Raventós RM, Schröder H, Arós F, Ros E, Ruíz-Gutiérrez V, Lapetra J, Conde-Herrera M, Sáez G, Vinyoles E, Martínez-González MA. Low-fat dairy products and blood pressure: Follow-up of 2290 older persons at high cardiovascular risk participating in the PREDIMED study. *Br J Nutr.* 2009 Jan; 101(1): 59-67. Epub 2008 May 20. PMID: 18492300.

6. Wang L, Manson JE, Buring JE, Lee IM, Sesso HD. Dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women. *Hypertension.* 2008 Apr; 51(4): 1, 073-1, 079. Epub 2008 Feb 7. PMID: 18259007.

Cross-Sectional Studies

1. Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Tehranian adults. *Am J Clin Nutr.* 2005 Sep; 82(3): 523-530. PMID: 16155263.
2. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. *Am J Clin Nutr.* 2008 Jun; 87(6): 1, 914-1, 925. PMID: 18541585; PMCID: PMC2585752. (Hand search)
3. Djoussé L, Pankow JS, Hunt SC, Heiss G, Province MA, Kabagambe EK, Ellison RC. Influence of saturated fat and linolenic acid on the association between intake of dairy products and blood pressure. *Hypertension.* 2006 Aug; 48(2): 335-341. Epub 2006 Jun 26. PMID: 16801477.
4. Houston DK, Driver KE, Bush AJ, Kritchevsky SB. The association between cheese consumption and cardiovascular risk factors among adults. *J Hum Nutr Diet.* 2008 Apr; 21(2): 129-140. PMID: 18339053.
5. Ruidavets JB, Bongard V, Simon C, Dallongeville J, Ducimetière P, Arveiler D, Amouyel P, Bingham A, Ferrières J. Independent contribution of dairy products and calcium intake to blood pressure variations at a population level. *J Hypertens.* 2006 Apr; 24(4): 671-681. PMID: 16531795.

What is the relationship between the intake of milk and milk products and type 2 diabetes?

Meta-Analysis

1. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

What is the relationship between the intake of milk and milk products and metabolic syndrome?

Primary Research

Meta-Analysis

1. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

Prospective Cohort Study

1. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.

Cross-Sectional Studies

1. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. *Am J Clin Nutr.* 2008 Jun; 87(6): 1, 914-1, 925. PMID: 18541585; PMCID: PMC2585752. (Hand search)
2. Ruidavets JB, Bongard V, Dallongeville J, Arveiler D, Ducimetière P, Perret B, Simon C, Amouyel P, Ferrières J. High consumptions of grain, fish, dairy products and combinations of these are associated with a low prevalence of metabolic syndrome. *J Epidemiol Community Health.* 2007 Sep; 61(9): 810-817. PMID: 17699537.

What is the relationship between the intake of milk and milk products and serum cholesterol?

Primary Research

Trial

1. Bowen J, Noakes M, Clifton PM.Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. *Int J Obes (Lond).* 2005 Aug; 29(8): 957-965. PMID: 15711601. (Hand search)

Prospective Cohort Study

1. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.

Cross-Sectional Study

1. Houston DK, Driver KE, Bush AJ, Kritchevsky SB. The association between cheese consumption and cardiovascular risk factors among adults. *J Hum Nutr Diet.* 2008 Apr; 21(2): 129-140. PMID: 18339053.

Excluded articles

Article	Reason for Exclusion
Ahn J, Albanes D, Peters U, Schatzkin A, Lim U, Freedman M, Chatterjee N, Andriole GL, Leitzmann MF, Hayes RB; Prostate, Lung, Colorectal, and Ovarian Trial Project Team. Dairy products, calcium intake, and risk of prostate cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev.* 2007 Dec; 16(12): 2, 623-2, 630. PMID: 18086766.	Cancer outcomes excluded from NEL review.
Al Sarakbi W, Salhab M, Mokbel K. Dairy products and breast cancer risk: A review of the literature. *Int J Fertil Womens Med.* 2005 Nov-Dec; 50(6): 244-249. Review. PMID: 16526414.	Cancer outcomes excluded from NEL review.

Allen NE, Key TJ, Appleby PN, Travis RC, Roddam AW, Tjønneland A, Johnsen NF, Overvad K, Linseisen J, Rohrmann S, Boeing H, Pischon T, Bueno-de-Mesquita HB, Kiemeney L, Tagliabue G, Palli D, Vineis P, Tumino R, Trichopoulou A, Kassapa C, Trichopoulos D, Ardanaz E, Larrañaga N, Tormo MJ, González CA, Quirós JR, Sánchez MJ, Bingham S, Khaw KT, Manjer J, Berglund G, Stattin P, Hallmans G, Slimani N, Ferrari P, Rinaldi S, Riboli E. Animal foods, protein, calcium and prostate cancer risk: the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer.* 2008 May 6; 98(9): 1, 574-1, 581. Epub 2008 Apr 1. PMID: 18382426.	Does not answer question: examined relationship between milk protein intake and health.
Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Tehranian adults. *Am J Clin Nutr.* 2005 Sep; 82(3): 523-530. PMID: 16155263.	Included in blood pressure review, but excluded from metabolic syndrome review because included in Elwood, 2008.
Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: A systematic literature review and meta-analysis. *Cancer Causes Control.* 2007 Nov; 18(9): 967-988. Epub 2007 Jul 19. Review. PMID: 17638104; PMCID: PMC2592095.	Cancer outcomes excluded from NEL review.
Benito P, Caballero J, Moreno J, Gutiérrez-Alcántara C, Muñoz C, Rojo G, Garcia S, Soriguer FC. Effects of milk enriched with omega-3 fatty acid, oleic acid and folic acid in patients with metabolic syndrome. *Clin Nutr.* 2006 Aug; 25(4): 581-587. Epub 2006 May 15. PMID: 16701922.	Participants diagnosed with metabolic syndrome.
Biong AS, Rebnord HM, Fimreite RL, Trygg KU, Ringstad J, Thelle DS, Pedersen JI. Intake of dairy fat and dairy products, and risk of myocardial infarction: A case-control study. *Int J Food Sci Nutr.* 2008 Mar; 59(2): 155-165. PMID: 17886080.	Included in Elwood, 2008.
Biong AS, Veierød MB, Ringstad J, Thelle DS, Pedersen JI. Intake of milk fat, reflected in adipose tissue fatty acids and risk of myocardial infarction: A case-control study. *Eur J Clin Nutr.* 2006 Feb; 60(2): 236-244. PMID: 16267503.	Does not answer question: examined relationship between fatty acids in adipose tissue and myocardial infarction.
Chan JM, Wang F, Holly EA. Pancreatic cancer, animal protein and dietary fat in a population-based study, San Francisco Bay Area, California. *Cancer Causes Control.* 2007 Dec; 18(10): 1, 153-1, 167. Epub 2007 Sep 1. PMID: 17805983.	Cancer outcomes excluded from NEL review.
Cheng S, Lyytikäinen A, Kröger H, Lamberg-Allardt C, Alén M, Koistinen A, Wang QJ, Suuriniemi M, Suominen H, Mahonen A, Nicholson PH, Ivaska KK, Korpela R, Ohlsson C, Väänänen KH, Tylavsky F. Effects of calcium, dairy product, and vitamin D supplementation on bone mass accrual and body composition in 10- to 12-year-old girls: A two-year randomized trial. *Am J Clin Nutr.* 2005 Nov; 82(5): 1, 115-1, 126; quiz 1, 147-1, 148. PMID: 16280447.	Included in Huncharek, 2008.

Cho E, Smith-Warner SA, Spiegelman D, Beeson WL, van den Brandt PA, Colditz GA, Folsom AR, Fraser GE, Freudenheim JL, Giovannucci E, Goldbohm RA, Graham S, Miller AB, Pietinen P, Potter JD, Rohan TE, Terry P, Toniolo P, Virtanen MJ, Willett WC, Wolk A, Wu K, Yaun SS, Zeleniuch-Jacquotte A, Hunter DJ. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. *J Natl Cancer Inst.* 2004 Jul 7; 96(13): 1, 015-1.022. Erratum in: *J Natl Cancer Inst.* 2004 Nov 17; 96(22): 1, 724. PMID: 15240785.	Cancer outcomes excluded from NEL review.
Choi HK, Willett WC, Stampfer MJ, Rimm E, Hu FB. Dairy consumption and risk of type 2 diabetes mellitus in men: a prospective study. *Arch Intern Med.* 2005 May 9; 165(9): 997-1, 003. PMID: 15883237.	Included in Elwood, 2008.
Daly RM, Bass S, Nowson C. Long-term effects of calcium-vitamin-D3-fortified milk on bone geometry and strength in older men. *Bone.* 2006 Oct; 39(4): 946-953. Epub 2006 May 24. PMID: 16725396.	Milk enriched with additional calcium and vitamin D_3.
Daly RM, Brown M, Bass S, Kukuljan S, Nowson C. Calcium- and vitamin D3-fortified milk reduces bone loss at clinically relevant skeletal sites in older men: a 2-year randomized controlled trial. *J Bone Miner Res.* 2006 Mar; 21(3): 397-405. Epub 2005 Dec 19. PMID: 16491287.	Milk enriched with additional calcium and vitamin D_3.
Dixon LB, Pellizzon MA, Jawad AF, Tershakovec AM. Calcium and dairy intake and measures of obesity in hyper- and normocholesterolemic children. *Obes Res.* 2005 Oct; 13(10): 1, 727-1, 738. PMID: 16286520.	The relationship between milk product intake and adiposity in children is reviewed in the Energy Balance section.
Doornbos AM, Meynen EM, Duchateau GS, van der Knaap HC, Trautwein EA. Intake occasion affects the serum cholesterol lowering of a plant sterol-enriched single-dose yoghurt drink in mildly hypercholesterolaemic subjects. *Eur J Clin Nutr.* 2006 Mar; 60(3): 325-333. PMID: 16234829.	Participants diagnosed with hypercholesterolemia.
Du X, Zhu K, Trube A, Zhang Q, Ma G, Hu X, Fraser DR, Greenfield H. School-milk intervention trial enhances growth and bone mineral accretion in Chinese girls aged 10 to 12 years in Beijing. *Br J Nutr.* 2004 Jul; 92(1): 159-168. Erratum in: *Br J Nutr.* 2005 Apr; 93(4): 571-572. PMID: 15230999.	Milk enriched with additional calcium.
Elwood PC, Pickering JE, Fehily AM. Milk and dairy consumption, diabetes and the metabolic syndrome: The Caerphilly prospective study. *J Epidemiol Community Health.* 2007 Aug; 61(8): 695-698. PMID: 17630368.	Included in Elwood, 2008.
Elwood PC, Pickering JE, Fehily AM, Hughes J, Ness AR. Milk drinking, ischaemic heart disease and ischaemic stroke I. Evidence from the Caerphilly cohort. *Eur J Clin Nutr.* 2004 May; 58(5): 711-717. PMID: 15116073.	Included in Elwood, 2008.

Elwood PC, Pickering JE, Hughes J, Fehily AM, Ness AR. Milk drinking, ischaemic heart disease and ischaemic stroke II. Evidence from cohort studies. *Eur J Clin Nutr.* 2004 May; 58(5): 718-724. Review. PMID: 15116074.	The most recent meta-analyses from these authors on these outcomes was included (Elwood, 2008).
Elwood PC, Strain JJ, Robson PJ, Fehily AM, Hughes J, Pickering J, Ness A. Milk consumption, stroke, and heart attack risk: Evidence from the Caerphilly cohort of older men. *J Epidemiol Community Health.* 2005 Jun; 59(6): 502-505. PMID: 15911647; PMCID: PMC1757052.	Included in Elwood, 2008.
Fiorito LM, Mitchell DC, Smiciklas-Wright H, Birch LL. Dairy and dairy-related nutrient intake during middle childhood. *J Am Diet Assoc.* 2006 Apr; 106(4): 534-542. PMID: 16567149; PMCID: PMC2531148.	Does not answer question: did not examine relationship between milk product intake and health.
Gallus S, Bravi F, Talamini R, Negri E, Montella M, Ramazzotti V, Franceschi S, Giacosa A, La Vecchia C. Milk, dairy products and cancer risk (Italy). *Cancer Causes Control.* 2006 May; 17(4): 429-437. PMID: 16596295.	Cancer outcomes excluded from NEL review.
Gao X, LaValley MP, Tucker KL. Prospective studies of dairy product and calcium intakes and prostate cancer risk: a meta-analysis. *J Natl Cancer Inst.* 2005 Dec 7; 97(23): 1, 768-1, 777. Erratum in: *J Natl Cancer Inst.* 2006 Mar 1; 98(5): 366. PMID: 16333032.	Cancer outcomes excluded from NEL review.
Gardner CD, Messina M, Kiazand A, Morris JL, Franke AA. Effect of two types of soy milk and dairy milk on plasma lipids in hypercholesterolemic adults: A randomized trial. *J Am Coll Nutr.* 2007 Dec; 26(6): 669-677. PMID: 18187432.	Participants diagnosed with hypercholesterolemia.
Genkinger JM, Hunter DJ, Spiegelman D, Anderson KE, Arslan A, Beeson WL, Buring JE, Fraser GE, Freudenheim JL, Goldbohm RA, Hankinson SE, Jacobs DR Jr, Koushik A, Lacey JV Jr, Larsson SC, Leitzmann M, McCullough ML, Miller AB, Rodriguez C, Rohan TE, Schouten LJ, Shore R, Smit E, Wolk A, Zhang SM, Smith-Warner SA. Dairy products and ovarian cancer: A pooled analysis of 12 cohort studies. *Cancer Epidemiol Biomarkers Prev.* 2006 Feb; 15(2): 364-372. PMID: 16492930.	Cancer outcomes excluded from NEL review.
Gibbons MJ, Gilchrist NL, Frampton C, Maguire P, Reilly PH, March RL, Wall CR. The effects of a high calcium dairy food on bone health in pre-pubertal children in New Zealand. *Asia Pac J Clin Nutr.* 2004; 13(4): 341-347. PMID: 15563438.	Drink was a high calcium supplement, not milk as defined by the Subcommittee.
Hubner RA, Muir KR, Liu JF, Logan RF, Grainge MJ, Houlston RS; Members of UKCAP Consortium. Dairy products, polymorphisms in the vitamin D receptor gene and colorectal adenoma recurrence. *Int J Cancer.* 2008 Aug 1; 123(3): 586-593. PMID: 18470879.	Cancer outcomes excluded from NEL review.

Huncharek M, Muscat J, Kupelnick B. Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: A meta-analysis of 26, 335 cases from 60 observational studies. *Nutr Cancer.* 2009; 61(1): 47-69. PMID: 19116875.	Cancer outcomes excluded from NEL review.
Huncharek M, Muscat J, Kupelnick B. Dairy products, dietary calcium and vitamin D intake as risk factors for prostate cancer: A meta-analysis of 26, 769 cases from 45 observational studies. *Nutr Cancer.* 2008; 60(4): 421-441. PMID: 18584476.	Cancer outcomes excluded from NEL review.
Kesse E, Bertrais S, Astorg P, Jaouen A, Arnault N, Galan P, Hercberg S. Dairy products, calcium and phosphorus intake, and the risk of prostate cancer: Results of the French prospective SU.VI.MAX (Supplémentation en Vitamines et Minéraux Antioxydants) study. *Br J Nutr.* 2006 Mar; 95(3): 539-545. PMID: 16512941.	Cancer outcomes excluded from NEL review.
Kesse E, Boutron-Ruault MC, Norat T, Riboli E, Clavel-Chapelon F; E3N Group. Dietary calcium, phosphorus, vitamin D, dairy products and the risk of colorectal adenoma and cancer among French women of the E3N-EPIC prospective study. *Int J Cancer.* 2005 Oct 20; 117(1): 137-144. PMID: 15880532.	Cancer outcomes excluded from NEL review.
Kesse-Guyot E, Bertrais S, Duperray B, Arnault N, Bar-Hen A, Galan P, Hercberg S. Dairy products, calcium and the risk of breast cancer: Results of the French SU.VI.MAX prospective study. *Ann Nutr Metab.* 2007; 51(2): 139-145. Epub 2007 May 29. PMID: 17536191.	Cancer outcomes excluded from NEL review.
Koh KA, Sesso HD, Paffenbarger RS Jr, Lee IM. Dairy products, calcium and prostate cancer risk. *Br J Cancer.* 2006 Dec 4; 95(11): 1, 582-1, 585. Epub 2006 Nov 14. PMID: 17106437.	Cancer outcomes excluded from NEL review.
Koralek DO, Bertone-Johnson ER, Leitzmann MF, Sturgeon SR, Lacey JV Jr, Schairer C, Schatzkin A. Relationship between calcium, lactose, vitamin D, and dairy products and ovarian cancer. *Nutr Cancer.* 2006; 56(1): 22-30. PMID: 17176214.	Cancer outcomes excluded from NEL review.
Korpela R, Tuomilehto J, Högström P, Seppo L, Piironen V, Salo-Väänänen P, Toivo J, Lamberg-Allardt C, Kärkkäinen M, Outila T, Sundvall J, Vilkkilä S, Tikkanen MJ. Safety aspects and cholesterol-lowering efficacy of low fat dairy products containing plant sterols. *Eur J Clin Nutr.* 2006 May; 60(5): 633-642. PMID: 16404415.	Dairy products contained plant sterols.
Kurahashi N, Inoue M, Iwasaki M, Sasazuki S, Tsugane AS; Japan Public Health Center-Based Prospective Study Group. Dairy product, saturated fatty acid, and calcium intake and prostate cancer in a prospective cohort of Japanese men. *Cancer Epidemiol Biomarkers Prev.* 2008 Apr; 17(4): 930-937. PMID: 18398033.	Cancer outcomes excluded from NEL review.

Kuriki K, Hirose K, Matsuo K, Wakai K, Ito H, Kanemitsu Y, Hirai T, Kato T, Hamajima N, Takezaki T, Suzuki T, Saito T, Tanaka R, Tajima K. Meat, milk, saturated fatty acids, the Pro12Ala and C161T polymorphisms of the PPARgamma gene and colorectal cancer risk in Japanese. *Cancer Sci.* 2006 Nov; 97(11): 1, 226-1, 235. Epub 2006 Sep 5. PMID: 16965392.	Does not answer question: examined risk related to genetic polymorphisms.
Lancaster KJ. Characteristics influencing daily consumption of fruits and vegetables and low-fat dairy products in older adults with hypertension. *J Nutr Elder.* 2004; 23(4): 21-33. PMID: 15233120.	Does not answer question; did not examine relationship between milk product intake and health; participants diagnosed with hypertension.
Larson NI, Neumark-Sztainer D, Harnack L, Wall M, Story M, Eisenberg ME. Calcium and dairy intake: Longitudinal trends during the transition to young adulthood and correlates of calcium intake. *J Nutr Educ Behav.* 2009 Jul-Aug; 41(4): 254-260. PMID: 19508930.	Does not answer question; did not examine relationship between milk product intake and health.
Larsson SC, Andersson SO, Johansson JE, Wolk A. Cultured milk, yogurt, and dairy intake in relation to bladder cancer risk in a prospective study of Swedish women and men. *Am J Clin Nutr.* 2008 Oct; 88(4): 1, 083-1, 087. PMID: 18842797.	Cancer outcomes excluded from NEL review.
Larsson SC, Bergkvist L, Rutegård J, Giovannucci E, Wolk A. Calcium and dairy food intakes are inversely associated with colorectal cancer risk in the Cohort of Swedish Men. *Am J Clin Nutr.* 2006 Mar; 83(3): 667-673; quiz 728-729. PMID: 16522915.	Cancer outcomes excluded from NEL review.
Larsson SC, Bergkvist L, Wolk A. High-fat dairy food and conjugated linoleic acid intakes in relation to colorectal cancer incidence in the Swedish Mammography Cohort. *Am J Clin Nutr.* 2005 Oct; 82(4): 894-900. PMID: 16210722.	Cancer outcomes excluded from NEL review.
Larsson SC, Bergkvist L, Wolk A. Milk and lactose intakes and ovarian cancer risk in the Swedish Mammography Cohort. *Am J Clin Nutr.* 2004 Nov; 80(5): 1, 353-1, 357. PMID: 15531686.	Cancer outcomes excluded from NEL review.
Larsson SC, Orsini N, Wolk A. Milk, milk products and lactose intake and ovarian cancer risk: A meta-analysis of epidemiological studies. *Int J Cancer.* 2006 Jan 15; 118(2): 431-441. PMID: 16052536.	Cancer outcomes excluded from NEL review.
Lawlor DA, Ebrahim S, Timpson N, Davey Smith G. Avoiding milk is associated with a reduced risk of insulin resistance and the metabolic syndrome: Findings from the British Women's Heart and Health Study. *Diabet Med.* 2005 Jun; 22(6): 808-811. PMID: 15910636.	Included in Elwood, 2008.
Liu S, Choi HK, Ford E, Song Y, Klevak A, Buring JE, Manson JE. A prospective study of dairy intake and the risk of type 2 diabetes in women. *Diabetes Care.* 2006 Jul; 29(7): 1, 579-1, 584. PMID: 16801582.	Included in Elwood, 2008.

Lorenz M, Jochmann N, von Krosigk A, Martus P, Baumann G, Stangl K, Stangl V. Addition of milk prevents vascular protective effects of tea. *Eur Heart J.* 2007 Jan; 28(2): 219-223. Epub 2007 Jan 9. PMID: 17213230.	Does not answer question; did not examine relationship between milk product intake and health.
Ma D, Jones G. Soft drink and milk consumption, physical activity, bone mass, and upper limb fractures in children: a population-based case-control study. *Calcif Tissue Int.* 2004 Oct; 75(4): 286-291. Epub 2004 Jul 30. PMID: 15549642.	Does not answer question; examines relationship between soft drink intake and fracture risk.
Matsumoto M, Ishikawa S, Nakamura Y, Kayaba K, Kajii E. Consumption of dairy products and cancer risks. *J Epidemiol.* 2007 Mar; 17(2): 38-44. PMID: 17420611.	Cancer outcomes excluded from NEL review.
McCullough ML, Rodriguez C, Diver WR, Feigelson HS, Stevens VL, Thun MJ, Calle EE. Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev.* 2005 Dec; 14(12): 2, 898-2, 904. PMID: 16365007.	Cancer outcomes excluded from NEL review.
McGlynn KA, Sakoda LC, Rubertone MV, Sesterhenn IA, Lyu C, Graubard BI, Erickson RL. Body size, dairy consumption, puberty, and risk of testicular germ cell tumors. *Am J Epidemiol.* 2007 Feb 15; 165(4): 355-363. Epub 2006 Nov 16. PMID: 17110638.	Cancer outcomes excluded from NEL review.
Mitrou PN, Albanes D, Weinstein SJ, Pietinen P, Taylor PR, Virtamo J, Leitzmann MF. A prospective study of dietary calcium, dairy products and prostate cancer risk (Finland). *Int J Cancer.* 2007 Jun 1; 120(11): 2, 466-2, 473. PMID: 17278090.	Cancer outcomes excluded from NEL review.
Mizoue T, Kimura Y, Toyomura K, Nagano J, Kono S, Mibu R, Tanaka M, Kakeji Y, Maehara Y, Okamura T, Ikejiri K, Futami K, Yasunami Y, Maekawa T, Takenaka K, Ichimiya H, Imaizumi N. Calcium, dairy foods, vitamin D, and colorectal cancer risk: The Fukuoka Colorectal Cancer Study. *Cancer Epidemiol Biomarkers Prev.* 2008 Oct; 17(10): 2, 800-2, 807. PMID: 18843026.	Cancer outcomes excluded from NEL review.
Mommers M, Schouten LJ, Goldbohm RA, van den Brandt PA. Dairy consumption and ovarian cancer risk in the Netherlands Cohort Study on Diet and Cancer. *Br J Cancer.* 2006 Jan 16; 94(1): 165-170. PMID: 16306872.	Cancer outcomes excluded from NEL review.
Nestel PJ, Chronopulos A, Cehun M. Dairy fat in cheese raises LDL cholesterol less than that in butter in mildly hypercholesterolaemic subjects. *Eur J Clin Nutr.* 2005 Sep; 59(9): 1, 059-1, 063. PMID: 16015270.	Participants diagnosed with hypercholesterolemia.
Park SY, Murphy SP, Wilkens LR, Stram DO, Henderson BE, Kolonel LN. Calcium, vitamin D, and dairy product intake and prostate cancer risk: The Multiethnic Cohort Study. *Am J Epidemiol.* 2007 Dec 1; 166(11): 1, 259-1, 269. Epub 2007 Oct 8. PMID: 17925283.	Cancer outcomes excluded from NEL review.

Park Y, Leitzmann MF, Subar AF, Hollenbeck A, Schatzkin A. Dairy food, calcium, and risk of cancer in the NIH-AARP Diet and Health Study. *Arch Intern Med.* 2009 Feb 23; 169(4): 391-401. PMID: 19237724.	Cancer outcomes excluded from NEL review.
Park Y, Mitrou PN, Kipnis V, Hollenbeck A, Schatzkin A, Leitzmann MF. Calcium, dairy foods, and risk of incident and fatal prostate cancer: the NIH-AARP Diet and Health Study. *Am J Epidemiol.* 2007 Dec 1; 166(11): 1, 270-1, 279. Epub 2007 Oct 12. PMID: 18000020.	Cancer outcomes excluded from NEL review.
Parodi PW. Dairy product consumption and the risk of breast cancer. *J Am Coll Nutr.* 2005 Dec; 24(6 Suppl): 556S-568S. Review. PMID: 16373955.	Cancer outcomes excluded from NEL review.
Qin LQ, Xu JY, Wang PY, Hashi A, Hoshi K, Sato A. Milk/dairy products consumption, galactose metabolism and ovarian cancer: Meta-analysis of epidemiological studies. *Eur J Cancer Prev.* 2005 Feb; 14(1): 13-19. PMID: 15677891.	Cancer outcomes excluded from NEL review.
Qin LQ, Xu JY, Wang PY, Tong J, Hoshi K. Milk consumption is a risk factor for prostate cancer in Western countries: Evidence from cohort studies. *Asia Pac J Clin Nutr.* 2007; 16(3): 467-476. PMID: 17704029.	Cancer outcomes excluded from NEL review.
Qin LQ, Xu JY, Wang PY, Kaneko T, Hoshi K, Sato A. Milk consumption is a risk factor for prostate cancer: Meta-analysis of case-control studies. *Nutr Cancer.* 2004; 48(1): 22-27. PMID: 15203374.	Cancer outcomes excluded from NEL review.
Rohrmann S, Platz EA, Kavanaugh CJ, Thuita L, Hoffman SC, Helzlsouer KJ. Meat and dairy consumption and subsequent risk of prostate cancer in a US cohort study. *Cancer Causes Control.* 2007 Feb; 18(1): 41-50. PMID: 17315319.	Cancer outcomes excluded from NEL review.
Snijder MB, van der Heijden AA, van Dam RM, Stehouwer CD, Hiddink GJ, Nijpels G, Heine RJ, Bouter LM, Dekker JM. Is higher dairy consumption associated with lower body weight and fewer metabolic disturbances? The Hoorn Study. *Am J Clin Nutr.* 2007 Apr; 85(4): 989-995. PMID: 17413097.	Same data set as Snijder, 2008.
Sun Q, Ma J, Campos H, Hu FB. Plasma and erythrocyte biomarkers of dairy fat intake and risk of ischemic heart disease. *Am J Clin Nutr.* 2007 Oct; 86(4): 929-937. PMID: 17921367.	Does not answer question; examined relationship between fatty acids and disease risk.
Taguchi H, Chen H, Yano R, Shoumura S. Comparative effects of milk and soymilk on bone loss in adult ovariectomized osteoporosis rat. *Okajimas Folia Anat Jpn.* 2006 Aug; 83(2): 53-59. PMID: 16944838.	Study tested animals.

Tricon S, Burdge GC, Jones EL, Russell JJ, El-Khazen S, Moretti E, Hall WL, Gerry AB, Leake DS, Grimble RF, Williams CM, Calder PC, Yaqoob P. Effects of dairy products naturally enriched with cis-9, trans-11 conjugated linoleic acid on the blood lipid profile in healthy middle-aged men. *Am J Clin Nutr.* 2006 Apr; 83(4): 744-753. PMID: 16600923.	Milk products enriched with cis-9, trans-11 conjugated linoleic acid.
Tseng M, Breslow RA, Graubard BI, Ziegler RG. Dairy, calcium, and vitamin D intakes and prostate cancer risk in the National Health and Nutrition Examination Epidemiologic Follow-up Study cohort. *Am J Clin Nutr.* 2005 May; 81(5): 1, 147-1, 154. PMID: 15883441.	Cancer outcomes excluded from NEL review.
van der Pols JC, Bain C, Gunnell D, Smith GD, Frobisher C, Martin RM. Childhood dairy intake and adult cancer risk: 65-year follow-up of the Boyd Orr cohort. *Am J Clin Nutr.* 2007 Dec; 86(6): 1, 722-1, 729. PMID: 18065592.	Cancer outcomes excluded from NEL review.
Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: A systematic review and meta-analysis. *Am J Public Health.* 2007 Apr; 97(4): 667-675. Epub 2007 Feb 28. Review. PMID: 17329656; PMCID: PMC1829363.	Does not answer question; did not examine relationship between milk product intake and health.
Warensjö E, Jansson JH, Berglund L, Boman K, Ahrén B, Weinehall L, Lindahl B, Hallmans G, Vessby B. Estimated intake of milk fat is negatively associated with cardiovascular risk factors and does not increase the risk of a first acute myocardial infarction. A prospective case-control study. *Br J Nutr.* 2004 Apr; 91(4): 635-642. PMID: 15035691.	Does not include milk product intake in analyses.
Xu JY, Qin LQ, Wang PY, Li W, Chang C. Effect of milk tripeptides on blood pressure: a meta-analysis of randomized controlled trials. *Nutrition.* 2008 Oct; 24(10): 933-940. Epub 2008 Jun 17. PMID: 18562172.	Does not answer question; did not examine relationship between milk product intake and health.
Zhang J, Kesteloot H. Milk consumption in relation to incidence of prostate, breast, colon, and rectal cancers: Is there an independent effect? Nu*tr Cancer.* 2005; 53(1): 65-72. PMID: 16351508.	Cancer outcomes excluded from NEL review.
Zhu K, Zhang Q, Foo LH, Trube A, Ma G, Hu X, Du X, Cowell CT, Fraser DR, Greenfield H. Growth, bone mass, and vitamin D status of Chinese adolescent girls three years after withdrawal of milk supplementation. *Am J Clin Nutr.* 2006 Mar; 83(3): 714-721. PMID: 16522922.	Milk enriched with additional calcium.

CHAPTER 18. MILK AND MILK PRODUCTS – METABOLIC SYNDROME

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF MILK AND MILK PRODUCTS AND METABOLIC SYNDROME?

Conclusion statement

Limited evidence is available showing intake of milk and milk products are associated with reduced risk of metabolic syndrome.

Grade

Limited

Evidence summary overview

Intake of milk and milk products is associated with reduced risk of metabolic syndrome and may even be protective in certain population groups. The conclusion reached for this question is based on one systematic review with meta-analysis (Elwood, 2008), one prospective cohort study (Snijder, 2008) and two cross-sectional studies (Beydoun, 2008; Ruidavets, 2007).

Elwood et al, (2008) performed a systematic review and meta-analysis and the data showed a reduction in risk associated with the highest level of milk consumption for metabolic syndrome (RR=0.74; 95% CI: 0.64, 0.84) compared to the risk in those with low consumption.

Snijder et al, (2008) conducted a prospective cohort study investigating the association between dairy consumption and changes in weight and metabolic disturbances. The authors concluded that dairy consumption was not associated with changes in metabolic variables in a Dutch elderly population. Two cross-sectional studies (Beydoun, 2008; Ruidavets, 2007) looked at milk and milk product consumption and metabolic syndrome. The French study by Ruidavets et al, (2007) determined that the intake of dairy products was associated with a lower probability of insulin resistance syndrome. No significant (NS) associations between whole milk (per 100g), low-fat milk (per 100g) or skim milk (per 100g) and metabolic syndrome were observed in a study of National Health and Nutrition Examination Surveys (NHANES) 1999-2004 data (Beydoun, 2008).

Evidence summary paragraphs

Systematic Review/Meta-Analysis

Elwood et al, 2008 (positive quality) performed a systematic review and meta-analysis to investigate the literature on milk and dairy consumption and risk of vascular disease and diabetes, examine the evidence related to consumption of whole vs. reduced fat milk and disease risk and consider the likely effect of milk and dairy consumption on survival. The authors also reviewed a 2007 report by the World Cancer Research Fund to determine the impact of milk and dairy consumption on cancer risk. Using Cochrane systematic review methods, MEDLINE was searched up to June 2008 using key words milk/milk protein/dairy/dairy calcium and heart disease/coronary artery disease (CAD)/myocardial infarction (MI)/ischaemic heart disease (IHD), stroke and diabetes/metabolic syndrome. This search revealed 180 papers on milk and heart

disease, 33 papers on milk and stroke, and 111 papers on milk and diabetes. Only studies that were done in human adults using population-based and prospective designs and reported baseline data on milk or dairy consumption, vascular disease outcome or incident diabetes were included in the final review. The final sample included 15 prospective studies on IHD and stroke, four prospective studies on diabetes, four case-control studies on metabolic syndrome and four case-control studies on MI. The data showed a reduction in risk associated with the highest level of milk consumption for metabolic syndrome (RR=0.74; 95% CI: 0.64, 0.84).

Prospective Cohort Study

Snijder et al, 2008 (positive quality), a prospective cohort study conducted in the Netherlands, investigated the association between dairy consumption and changes in weight and metabolic disturbances, based on data from the Hoorn study, a population-based cohort of white men and women aged 50-75 years. Average food intake was measured at baseline using a 92-item semi-quantitative food-frequency questionnaire (FFQ). At baseline and follow-up, participants underwent an extensive physical examination and a blood sample was drawn for biochemical analyses of fasting glucose, post-load glucose, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG). During the physical examination, weight, waist circumference (WC) and blood pressure (BP) were measured. 1,124 participants were included in the analysis. Baseline dairy consumption was not associated with changes in fasting and post-load glucose concentrations, serum lipid levels or BP, nor with the risk of developing metabolic syndrome in 6.4 years (OR=0.86, 95% CI: 0.52, 1.42, comparing highest with lowest quartile of dairy consumption). The authors concluded that dairy consumption was not associated with changes in metabolic variables in a Dutch elderly population.

Cross-Sectional Studies

Beydoun et al, 2008 (positive quality), a cross-sectional analysis of merged NHANES data from 1999-2004 in the US, assessed the association between consumption of dairy and related nutrients and obesity, central obesity and the metabolic syndrome. Out of 17,061 subjects over age 18 years (8,970 women and 8,091 men) with complete demographic data, 4,519 subjects had complete data on dietary intake (assessed from 24-hour recall data) and metabolic outcomes, such as weight, height, WC, BP and laboratory values (fasting blood glucose, triacylglycerol stores and HDL-C). On average, adults consumed 1.54 servings of dairy (0.90 in fluid milk and 0.60 in cheese) per day. Each serving of dairy products increased the risk of MetS by 8% among men. Odds ratios (OR) for one more daily serving of yogurt for metabolic syndrome was 0.40 (95% CI: 0.18, 0.89; P<0.05) and ORs for one more daily serving of cheese for metabolic syndrome was 1.16 (95% CI: 1.04, 1.29; P<0.05). No significant associations between whole milk (per 100g), low-fat milk (per 100g) or skim milk (per 100g) and metabolic syndrome were observed.

Ruidavets et al, 2007 (neutral quality), a cross-sectional study conducted in France, analyzed the relation between various food groups and the frequency of insulin resistance syndrome. Participants were recruited from the population as part of the French MONICA Study (Monitoring of Trends and Determinations in Cardiovascular Disease). Anthropometric data were taken, including WC, waist-to-hip ratio (WHR) and body mass index (BMI); BP was measured twice and fasting blood samples were

analyzed for lipid and glucose measurements. Intakes of dairy products, fish or cereal grains were measured through food records with follow-up interviews by a dietitian. After those without complete data were excluded, 912 men aged 45-64 years remained in the analysis. The prevalence of insulin resistance syndrome was 23.5%, and it reached 29.0%, 28.1% and 28.1% when the intake was below the median for fish, dairy products and cereal grains, respectively. After adjustment for confounding variables, the ORs for insulin resistance syndrome (above median values vs. below) were 0.51 (95% CI: 0.36, 0.71) for fish, 0.67 (95% CI: 0.47, 0.94) for dairy products and 0.69 (95% CI: 0.47, 1.01) for cereal grains. When intakes of all three food groups were high, the odds ratio was 0.22 (95% CI: 0.10, 0.44), leading the authors to conclude that a high consumption of dairy products, fish or cereal grains is associated with a lower probability of insulin resistance syndrome, especially when intakes of all three food groups is high.

Overview table

Author, Year, Study Design, Class, Rating	Participants	Description of Study Design	Outcomes
Beydoun et al 2008 Study Design: Cross-sectional Study Class: D Positive quality	N=4,519 subjects with complete data on dietary intake and metabolic outcomes (Out of 17,061 subjects over age 18 years (8,970 women and 8,091 men) with complete demographic data). Location: United States.	Cross-sectional analysis of merged NHANES data from 1999-2004 in the US, assessed the association between consumption of dairy and related nutrients and obesity, central obesity and metabolic syndrome. Included subjects had complete data on dietary intake (assessed from 24-hour recall data) and metabolic outcomes, such as weight, height, WC, BP and laboratory values (FBG, TG stores and HDL-C).	On average, adults consumed 1.54 servings of dairy (0.90 in fluid milk and 0.60 in cheese) per day. Each serving of dairy products ↑ the risk of MetS by 8% among men. OR for one more daily serving of yogurt for metabolic syndrome was 0.40 (95% CI: 0.18, 0.89; P<0.05) and OR for one more daily serving of cheese for metabolic syndrome was 1.16 (95% CI: 1.04, 1.29; P<0.05). NS associations between whole milk (per 100g), low-fat milk (per 100g) or skim milk (per 100g) and metabolic syndrome were observed.

Elwood PC, Givens DI et al, 2008 Study Design: Systematic review and meta-analysis Class: M Positive quality	Final N=15 prospective studies on IHD and stroke: Four prospective studies on diabetes Four case-control studies on metabolic syndrome Four case-control studies on MI.	MEDLINE was searched up to June 2008 using key words: Milk/milk protein/dairy/dairy calcium and heart disease/coronary artery disease/ myocardial infarction/ ischaemic heart disease, stroke and diabetes/ metabolic syndrome.	Data showed a ↓ in risk associated with the highest level of milk consumption for metabolic syndrome (RR=0.74; 95% CI: 0.64, 0.84).
Ruidavets et al 2007 Study Design: Cross-sectional Study Class: D Neutral quality	N=912 men after those without complete data were excluded. Age: 45-64 years. Location: France.	Cross-sectional study analyzing the relation between various food groups and the frequency of insulin resistance syndrome. Participants were recruited from the population as part of the French MONICA Study (Monitoring of Trends and Determinations in Cardiovascular Disease). Anthropometric data were taken, including WC, WHR and BMI; BP was measured twice and fasting blood samples were analyzed for lipid and glucose measurements. Intakes of dairy products, fish or cereal grains were measured through food records with follow-up interviews by a dietitian.	Prevalence of insulin resistance syndrome was 23.5% and it reached 29.0%, 28.1% and 28.1% when intake was below the median for fish, dairy products and cereal grains, respectively. After adjustment for confounding variables, the OR for insulin resistance syndrome (above median values vs. below) were 0.51 (95% CI: 0.36, 0.71) for fish, 0.67 (95% CI: 0.47, 0.94) for dairy products and 0.69 (95% CI: 0.47, 1.01) for cereal grains. When intakes of all three food groups were ↑, the OR was 0.22 (95% CI: 0.10, 0.44), leading authors to conclude that a ↑ consumption of dairy products, fish or cereal grains is associated with a ↓ probability of insulin resistance syndrome, especially when intakes of all three food groups is ↑.

Snijder et al 2008 Study Design: Prospective Cohort Study Class: B Positive quality	N=1,124 participants in the Hoorn study, a population-based cohort of white men and women. Age: 50-75 years. Location: Netherlands.	Prospective cohort study investigating the association between dairy consumption and Δ in weight and metabolic disturbances. Average food intake measured at baseline using a 92-item semi-quantitative FFQ. At baseline and follow-up, participants underwent extensive physical exam and blood sample drawn for biochemical analyses of FBG, post-load glucose, HDL-C and LDL-C and TG. During physical exam, weight, WC and BP were measured.	Baseline dairy consumption was not associated with Δ in fasting and post-load glucose concentrations, serum lipid levels or BP, nor with risk of developing metabolic syndrome in 6.4 years (OR=0.86, 95% CI: 0.52, 1.42, comparing highest with lowest quartile of dairy consumption). Authors concluded that dairy consumption was not associated with Δ in metabolic variables in a Dutch elderly population.

Search plan and results

Inclusion criteria

- June 2004 to July 2009
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children, two to 18 years; adults, 19 years and older
- *Populations:* Healthy and those with elevated chronic disease risk.

Exclusion criteria

- Studies that only consider cancer outcomes
- Studies that considered milk and milk products as part of a larger dietary pattern
- Milk and milk products in forms not commonly consumed (e.g., enriched with additional calcium)
- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Animal studies
- In vitro studies
- Articles not peer reviewed (web sites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: ("Dairy Products"[mh]) AND ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mesh: NoExp] OR “heart diseases”[mh] OR

"chronic disease"[mh] OR "Neoplasms"[majr] OR osteoporosis[mh] OR "Bone Density"[Mesh] OR "Fractures, Bone"[Mesh])

Date searched: 07/29/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 223
- Total articles identified to review from electronic databases: 95
- Articles identified via handsearch or other means: 3
- Number of Primary Articles Identified: 20
- Number of Review Articles Identified: 4
- Total Number of Articles Identified: 24
- Number of Articles Reviewed but Excluded: 74

Included articles (References)

What is the relationship between the intake of milk and milk products and bone health?

Systematic Reviews/Meta-analyses

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: A review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.
2. Huncharek M, Muscat J, Kupelnick B. Impact of dairy products and dietary calcium on bone-mineral content in children: Results of a meta-analysis. *Bone.* 2008 Aug; 43(2): 312-321. Epub 2008 Mar 15. PMID: 18539555.
3. Kanis JA, Johansson H, Oden A, De Laet C, Johnell O, Eisman JA, Mc Closkey E, Mellstrom D, Pols H, Reeve J, Silman A, Tenenhouse A. A meta-analysis of milk intake and fracture risk: low utility for case finding. *Osteoporos Int.* 2005 Jul; 16(7): 799-804. Epub 2004 Oct 21. PMID: 15502959.

Primary Research

Trials

1. Budek AZ, Hoppe C, Michaelsen KF, Mølgaard C. High intake of milk, but not meat, decreases bone turnover in prepubertal boys after 7 days. *Eur J Clin Nutr.* 2007 Aug; 61(8): 957-962. Epub 2007 Jan 17. PMID: 17228345.
2. Kristensen M, Jensen M, Kudsk J, Henriksen M, Mølgaard C. Short-term effects on bone turnover of replacing milk with cola beverages: A 10-day interventional study in young men. *Osteoporos Int.* 2005 Dec; 16(12): 1, 803-1, 808. Epub 2005 May 11. PMID: 15886860.
3. McCabe LD, Martin BR, McCabe GP, Johnston CC, Weaver CM, Peacock M. Dairy intakes affect bone density in the elderly. *Am J Clin Nutr.* 2004 Oct; 80(4): 1, 066-1, 074. PMID: 15447921.

Longitudinal Study

1. Rockell JE, Williams SM, Taylor RW, Grant AM, Jones IE, Goulding A. Two-year changes in bone and body composition in young children with a history of prolonged milk avoidance. *Osteoporos Int.* 2005 Sep; 16(9): 1, 016-1, 023. Epub 2004 Nov 23. PMID: 15565350.

Case-Control Study

1. Konstantynowicz J, Nguyen TV, Kaczmarski M, Jamiolkowski J, Piotrowska-Jastrzebska J, Seeman E. Fractures during growth: Potential role of a milk-free diet. *Osteoporos Int.* 2007 Dec; 18(12): 1, 601-1, 607. Epub 2007 May 22. PMID: 17516020.

Cross-Sectional Study

1. Al-Zahrani MS. Increased intake of dairy products is related to lower periodontitis prevalence. *J Periodontol.* 2006 Feb; 77(2): 289-294. PMID: 16460256. (Hand search)

What is the relationship between the intake of milk and milk products and cardiovascular disease?

Systematic Reviews/Meta-Analyses

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: A review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.
2. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

Primary Research

Case-Control Study

1. Kontogianni MD, Panagiotakos DB, Chrysohoou C, Pitsavos C, Stefanadis C. Modelling dairy intake on the development of acute coronary syndromes: The CARDIO2000 study. *Eur J Cardiovasc Prev Rehabil.* 2006 Oct; 13(5): 791-797. PMID: 17001220.

What is the relationship between the intake of milk and milk products and blood pressure?

Systematic Review

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: a review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.

Primary Research

Trial

1. Bowen J, Noakes M, Clifton PM.Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. *Int J Obes (Lond).* 2005 Aug; 29(8): 957-965. PMID: 15711601. (Hand search)

Prospective Cohort Studies

1. Alonso A, Beunza JJ, Delgado-Rodríguez M, Martínez JA, Martínez-González MA. Low-fat dairy consumption and reduced risk of hypertension: The Seguimiento Universidad de Navarra (SUN) cohort. *Am J Clin Nutr.* 2005 Nov;

82(5): 972-979. PMID: 16280427.
2. Engberink MF, Hendriksen MA, Schouten EG, van Rooij FJ, Hofman A, Witteman JC, Geleijnse JM. Inverse association between dairy intake and hypertension: The Rotterdam Study. *Am J Clin Nutr.* 2009 Jun; 89(6): 1, 877-1, 883. Epub 2009 Apr 15. PMID: 19369377.
3. Engberink MF, Geleijnse JM, de Jong N, Smit HA, Kok FJ, Verschuren WM. Dairy intake, blood pressure, and incident hypertension in a general Dutch population. *J Nutr.* 2009 Mar; 139(3): 582-587. Epub 2009 Jan 21. PMID: 19158223.
4. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.
5. Toledo E, Delgado-Rodríguez M, Estruch R, Salas-Salvadó J, Corella D, Gomez-Gracia E, Fiol M, Lamuela-Raventós RM, Schröder H, Arós F, Ros E, Ruíz-Gutiérrez V, Lapetra J, Conde-Herrera M, Sáez G, Vinyoles E, Martínez-González MA. Low-fat dairy products and blood pressure: Follow-up of 2290 older persons at high cardiovascular risk participating in the PREDIMED study. *Br J Nutr.* 2009 Jan; 101(1): 59-67. Epub 2008 May 20. PMID: 18492300.
6. Wang L, Manson JE, Buring JE, Lee IM, Sesso HD. Dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women. *Hypertension.* 2008 Apr; 51(4): 1, 073-1, 079. Epub 2008 Feb 7. PMID: 18259007.

Cross-Sectional Studies

1. Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Tehranian adults. *Am J Clin Nutr.* 2005 Sep; 82(3): 523-530. PMID: 16155263.
2. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. *Am J Clin Nutr.* 2008 Jun; 87(6): 1, 914-1, 925. PMID: 18541585; PMCID: PMC2585752. (Hand search)
3. Djoussé L, Pankow JS, Hunt SC, Heiss G, Province MA, Kabagambe EK, Ellison RC. Influence of saturated fat and linolenic acid on the association between intake of dairy products and blood pressure. *Hypertension.* 2006 Aug; 48(2): 335-341. Epub 2006 Jun 26. PMID: 16801477.
4. Houston DK, Driver KE, Bush AJ, Kritchevsky SB. The association between cheese consumption and cardiovascular risk factors among adults. *J Hum Nutr Diet.* 2008 Apr; 21(2): 129-140. PMID: 18339053.
5. Ruidavets JB, Bongard V, Simon C, Dallongeville J, Ducimetière P, Arveiler D, Amouyel P, Bingham A, Ferrières J. Independent contribution of dairy products and calcium intake to blood pressure variations at a population level. *J Hypertens.* 2006 Apr; 24(4): 671-681. PMID: 16531795.

What is the relationship between the intake of milk and milk products and type 2 diabetes?

Meta-Analysis

1. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

What is the relationship between the intake of milk and milk products and metabolic syndrome?

Primary Research

Meta-Analysis

1. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

Prospective Cohort Study

1. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.

Cross-Sectional Studies

1. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. *Am J Clin Nutr.* 2008 Jun; 87(6): 1, 914-1, 925. PMID: 18541585; PMCID: PMC2585752. (Hand search)
2. Ruidavets JB, Bongard V, Dallongeville J, Arveiler D, Ducimetière P, Perret B, Simon C, Amouyel P, Ferrières J. High consumptions of grain, fish, dairy products and combinations of these are associated with a low prevalence of metabolic syndrome. *J Epidemiol Community Health.* 2007 Sep; 61(9): 810-817. PMID: 17699537.

What is the relationship between the intake of milk and milk products and serum cholesterol?

Primary Research

Trial

1. Bowen J, Noakes M, Clifton PM.Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. *Int J Obes (Lond).* 2005 Aug; 29(8): 957-965. PMID: 15711601. (Hand search)

Prospective Cohort Study

1. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.

Cross-Sectional Study

1. Houston DK, Driver KE, Bush AJ, Kritchevsky SB. The association between cheese consumption and cardiovascular risk factors among adults. *J Hum Nutr Diet.* 2008 Apr; 21(2): 129-140. PMID: 18339053.

Excluded articles

Article	Reason for Exclusion
Ahn J, Albanes D, Peters U, Schatzkin A, Lim U, Freedman M, Chatterjee N, Andriole GL, Leitzmann MF, Hayes RB; Prostate, Lung, Colorectal, and Ovarian Trial Project Team. Dairy products, calcium intake, and risk of prostate cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev.* 2007 Dec; 16(12): 2, 623-2, 630. PMID: 18086766.	Cancer outcomes excluded from NEL review.
Al Sarakbi W, Salhab M, Mokbel K. Dairy products and breast cancer risk: A review of the literature. *Int J Fertil Womens Med.* 2005 Nov-Dec; 50(6): 244-249. Review. PMID: 16526414.	Cancer outcomes excluded from NEL review.
Allen NE, Key TJ, Appleby PN, Travis RC, Roddam AW, Tjønneland A, Johnsen NF, Overvad K, Linseisen J, Rohrmann S, Boeing H, Pischon T, Bueno-de-Mesquita HB, Kiemeney L, Tagliabue G, Palli D, Vineis P, Tumino R, Trichopoulou A, Kassapa C, Trichopoulos D, Ardanaz E, Larrañaga N, Tormo MJ, González CA, Quirós JR, Sánchez MJ, Bingham S, Khaw KT, Manjer J, Berglund G, Stattin P, Hallmans G, Slimani N, Ferrari P, Rinaldi S, Riboli E. Animal foods, protein, calcium and prostate cancer risk: the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer.* 2008 May 6; 98(9): 1, 574-1, 581. Epub 2008 Apr 1. PMID: 18382426.	Does not answer question: examined relationship between milk protein intake and health.
Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Tehranian adults. *Am J Clin Nutr.* 2005 Sep; 82(3): 523-530. PMID: 16155263.	Included in blood pressure review, but excluded from metabolic syndrome review because included in Elwood, 2008.
Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: A systematic literature review and meta-analysis. *Cancer Causes Control.* 2007 Nov; 18(9): 967-988. Epub 2007 Jul 19. Review. PMID: 17638104; PMCID: PMC2592095.	Cancer outcomes excluded from NEL review.
Benito P, Caballero J, Moreno J, Gutiérrez-Alcántara C, Muñoz C, Rojo G, Garcia S, Soriguer FC. Effects of milk enriched with omega-3 fatty acid, oleic acid and folic acid in patients with metabolic syndrome. *Clin Nutr.* 2006 Aug; 25(4): 581-587. Epub 2006 May 15. PMID: 16701922.	Participants diagnosed with metabolic syndrome.
Biong AS, Rebnord HM, Fimreite RL, Trygg KU, Ringstad J, Thelle DS, Pedersen JI. Intake of dairy fat and dairy products, and risk of myocardial infarction: A case-control study. *Int J Food Sci Nutr.* 2008 Mar; 59(2): 155-165. PMID: 17886080.	Included in Elwood, 2008.

Biong AS, Veierød MB, Ringstad J, Thelle DS, Pedersen JI. Intake of milk fat, reflected in adipose tissue fatty acids and risk of myocardial infarction: A case-control study. *Eur J Clin Nutr.* 2006 Feb; 60(2): 236-244. PMID: 16267503.	Does not answer question: examined relationship between fatty acids in adipose tissue and myocardial infarction.
Chan JM, Wang F, Holly EA. Pancreatic cancer, animal protein and dietary fat in a population-based study, San Francisco Bay Area, California. *Cancer Causes Control.* 2007 Dec; 18(10): 1, 153-1, 167. Epub 2007 Sep 1. PMID: 17805983.	Cancer outcomes excluded from NEL review.
Cheng S, Lyytikäinen A, Kröger H, Lamberg-Allardt C, Alén M, Koistinen A, Wang QJ, Suuriniemi M, Suominen H, Mahonen A, Nicholson PH, Ivaska KK, Korpela R, Ohlsson C, Väänänen KH, Tylavsky F. Effects of calcium, dairy product, and vitamin D supplementation on bone mass accrual and body composition in 10- to 12-year-old girls: A two-year randomized trial. *Am J Clin Nutr.* 2005 Nov; 82(5): 1, 115-1, 126; quiz 1, 147-1, 148. PMID: 16280447.	Included in Huncharek, 2008.
Cho E, Smith-Warner SA, Spiegelman D, Beeson WL, van den Brandt PA, Colditz GA, Folsom AR, Fraser GE, Freudenheim JL, Giovannucci E, Goldbohm RA, Graham S, Miller AB, Pietinen P, Potter JD, Rohan TE, Terry P, Toniolo P, Virtanen MJ, Willett WC, Wolk A, Wu K, Yaun SS, Zeleniuch-Jacquotte A, Hunter DJ. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. *J Natl Cancer Inst.* 2004 Jul 7; 96(13): 1, 015-1.022. Erratum in: *J Natl Cancer Inst.* 2004 Nov 17; 96(22): 1, 724. PMID: 15240785.	Cancer outcomes excluded from NEL review.
Choi HK, Willett WC, Stampfer MJ, Rimm E, Hu FB. Dairy consumption and risk of type 2 diabetes mellitus in men: a prospective study. *Arch Intern Med.* 2005 May 9; 165(9): 997-1, 003. PMID: 15883237.	Included in Elwood, 2008.
Daly RM, Bass S, Nowson C. Long-term effects of calcium-vitamin-D3-fortified milk on bone geometry and strength in older men. *Bone.* 2006 Oct; 39(4): 946-953. Epub 2006 May 24. PMID: 16725396.	Milk enriched with additional calcium and vitamin D_3.
Daly RM, Brown M, Bass S, Kukuljan S, Nowson C. Calcium- and vitamin D3-fortified milk reduces bone loss at clinically relevant skeletal sites in older men: a 2-year randomized controlled trial. *J Bone Miner Res.* 2006 Mar; 21(3): 397-405. Epub 2005 Dec 19. PMID: 16491287.	Milk enriched with additional calcium and vitamin D_3.
Dixon LB, Pellizzon MA, Jawad AF, Tershakovec AM. Calcium and dairy intake and measures of obesity in hyper- and normocholesterolemic children. *Obes Res.* 2005 Oct; 13(10): 1, 727-1, 738. PMID: 16286520.	The relationship between milk product intake and adiposity in children is reviewed in the Energy Balance section.

Doornbos AM, Meynen EM, Duchateau GS, van der Knaap HC, Trautwein EA. Intake occasion affects the serum cholesterol lowering of a plant sterol-enriched single-dose yoghurt drink in mildly hypercholesterolaemic subjects. *Eur J Clin Nutr.* 2006 Mar; 60(3): 325-333. PMID: 16234829.	Participants diagnosed with hypercholesterolemia.
Du X, Zhu K, Trube A, Zhang Q, Ma G, Hu X, Fraser DR, Greenfield H. School-milk intervention trial enhances growth and bone mineral accretion in Chinese girls aged 10 to 12 years in Beijing. *Br J Nutr.* 2004 Jul; 92(1): 159-168. Erratum in: *Br J Nutr.* 2005 Apr; 93(4): 571-572. PMID: 15230999.	Milk enriched with additional calcium.
Elwood PC, Pickering JE, Fehily AM. Milk and dairy consumption, diabetes and the metabolic syndrome: The Caerphilly prospective study. *J Epidemiol Community Health.* 2007 Aug; 61(8): 695-698. PMID: 17630368.	Included in Elwood, 2008.
Elwood PC, Pickering JE, Fehily AM, Hughes J, Ness AR. Milk drinking, ischaemic heart disease and ischaemic stroke I. Evidence from the Caerphilly cohort. *Eur J Clin Nutr.* 2004 May; 58(5): 711-717. PMID: 15116073.	Included in Elwood, 2008.
Elwood PC, Pickering JE, Hughes J, Fehily AM, Ness AR. Milk drinking, ischaemic heart disease and ischaemic stroke II. Evidence from cohort studies. *Eur J Clin Nutr.* 2004 May; 58(5): 718-724. Review. PMID: 15116074.	The most recent meta-analyses from these authors on these outcomes was included (Elwood, 2008).
Elwood PC, Strain JJ, Robson PJ, Fehily AM, Hughes J, Pickering J, Ness A. Milk consumption, stroke, and heart attack risk: Evidence from the Caerphilly cohort of older men. *J Epidemiol Community Health.* 2005 Jun; 59(6): 502-505. PMID: 15911647; PMCID: PMC1757052.	Included in Elwood, 2008.
Fiorito LM, Mitchell DC, Smiciklas-Wright H, Birch LL. Dairy and dairy-related nutrient intake during middle childhood. *J Am Diet Assoc.* 2006 Apr; 106(4): 534-542. PMID: 16567149; PMCID: PMC2531148.	Does not answer question: did not examine relationship between milk product intake and health.
Gallus S, Bravi F, Talamini R, Negri E, Montella M, Ramazzotti V, Franceschi S, Giacosa A, La Vecchia C. Milk, dairy products and cancer risk (Italy). *Cancer Causes Control.* 2006 May; 17(4): 429-437. PMID: 16596295.	Cancer outcomes excluded from NEL review.
Gao X, LaValley MP, Tucker KL. Prospective studies of dairy product and calcium intakes and prostate cancer risk: a meta-analysis. *J Natl Cancer Inst.* 2005 Dec 7; 97(23): 1, 768-1, 777. Erratum in: *J Natl Cancer Inst.* 2006 Mar 1; 98(5): 366. PMID: 16333032.	Cancer outcomes excluded from NEL review.
Gardner CD, Messina M, Kiazand A, Morris JL, Franke AA. Effect of two types of soy milk and dairy milk on plasma lipids in hypercholesterolemic adults: A randomized trial. *J Am Coll Nutr.* 2007 Dec; 26(6): 669-677. PMID: 18187432.	Participants diagnosed with hypercholesterolemia.

Genkinger JM, Hunter DJ, Spiegelman D, Anderson KE, Arslan A, Beeson WL, Buring JE, Fraser GE, Freudenheim JL, Goldbohm RA, Hankinson SE, Jacobs DR Jr, Koushik A, Lacey JV Jr, Larsson SC, Leitzmann M, McCullough ML, Miller AB, Rodriguez C, Rohan TE, Schouten LJ, Shore R, Smit E, Wolk A, Zhang SM, Smith-Warner SA. Dairy products and ovarian cancer: A pooled analysis of 12 cohort studies. *Cancer Epidemiol Biomarkers Prev.* 2006 Feb; 15(2): 364-372. PMID: 16492930.	Cancer outcomes excluded from NEL review.
Gibbons MJ, Gilchrist NL, Frampton C, Maguire P, Reilly PH, March RL, Wall CR. The effects of a high calcium dairy food on bone health in pre-pubertal children in New Zealand. *Asia Pac J Clin Nutr.* 2004; 13(4): 341-347. PMID: 15563438.	Drink was a high calcium supplement, not milk as defined by the Subcommittee.
Hubner RA, Muir KR, Liu JF, Logan RF, Grainge MJ, Houlston RS; Members of UKCAP Consortium. Dairy products, polymorphisms in the vitamin D receptor gene and colorectal adenoma recurrence. *Int J Cancer.* 2008 Aug 1; 123(3): 586-593. PMID: 18470879.	Cancer outcomes excluded from NEL review.
Huncharek M, Muscat J, Kupelnick B. Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: A meta-analysis of 26, 335 cases from 60 observational studies. *Nutr Cancer.* 2009; 61(1): 47-69. PMID: 19116875.	Cancer outcomes excluded from NEL review.
Huncharek M, Muscat J, Kupelnick B. Dairy products, dietary calcium and vitamin D intake as risk factors for prostate cancer: A meta-analysis of 26, 769 cases from 45 observational studies. *Nutr Cancer.* 2008; 60(4): 421-441. PMID: 18584476.	Cancer outcomes excluded from NEL review.
Kesse E, Bertrais S, Astorg P, Jaouen A, Arnault N, Galan P, Hercberg S. Dairy products, calcium and phosphorus intake, and the risk of prostate cancer: Results of the French prospective SU.VI.MAX (Supplémentation en Vitamines et Minéraux Antioxydants) study. *Br J Nutr.* 2006 Mar; 95(3): 539-545. PMID: 16512941.	Cancer outcomes excluded from NEL review.
Kesse E, Boutron-Ruault MC, Norat T, Riboli E, Clavel-Chapelon F; E3N Group. Dietary calcium, phosphorus, vitamin D, dairy products and the risk of colorectal adenoma and cancer among French women of the E3N-EPIC prospective study. *Int J Cancer.* 2005 Oct 20; 117(1): 137-144. PMID: 15880532.	Cancer outcomes excluded from NEL review.
Kesse-Guyot E, Bertrais S, Duperray B, Arnault N, Bar-Hen A, Galan P, Hercberg S. Dairy products, calcium and the risk of breast cancer: Results of the French SU.VI.MAX prospective study. *Ann Nutr Metab.* 2007; 51(2): 139-145. Epub 2007 May 29. PMID: 17536191.	Cancer outcomes excluded from NEL review.
Koh KA, Sesso HD, Paffenbarger RS Jr, Lee IM. Dairy products, calcium and prostate cancer risk. *Br J Cancer.* 2006 Dec 4; 95(11): 1, 582-1, 585. Epub 2006 Nov 14. PMID: 17106437.	Cancer outcomes excluded from NEL review.

Koralek DO, Bertone-Johnson ER, Leitzmann MF, Sturgeon SR, Lacey JV Jr, Schairer C, Schatzkin A. Relationship between calcium, lactose, vitamin D, and dairy products and ovarian cancer. *Nutr Cancer.* 2006; 56(1): 22-30. PMID: 17176214.	Cancer outcomes excluded from NEL review.
Korpela R, Tuomilehto J, Högström P, Seppo L, Piironen V, Salo-Väänänen P, Toivo J, Lamberg-Allardt C, Kärkkäinen M, Outila T, Sundvall J, Vilkkilä S, Tikkanen MJ. Safety aspects and cholesterol-lowering efficacy of low fat dairy products containing plant sterols. *Eur J Clin Nutr.* 2006 May; 60(5): 633-642. PMID: 16404415.	Dairy products contained plant sterols.
Kurahashi N, Inoue M, Iwasaki M, Sasazuki S, Tsugane AS; Japan Public Health Center-Based Prospective Study Group. Dairy product, saturated fatty acid, and calcium intake and prostate cancer in a prospective cohort of Japanese men. *Cancer Epidemiol Biomarkers Prev.* 2008 Apr; 17(4): 930-937. PMID: 18398033.	Cancer outcomes excluded from NEL review.
Kuriki K, Hirose K, Matsuo K, Wakai K, Ito H, Kanemitsu Y, Hirai T, Kato T, Hamajima N, Takezaki T, Suzuki T, Saito T, Tanaka R, Tajima K. Meat, milk, saturated fatty acids, the Pro12Ala and C161T polymorphisms of the PPARgamma gene and colorectal cancer risk in Japanese. *Cancer Sci.* 2006 Nov; 97(11): 1, 226-1, 235. Epub 2006 Sep 5. PMID: 16965392.	Does not answer question: examined risk related to genetic polymorphisms.
Lancaster KJ. Characteristics influencing daily consumption of fruits and vegetables and low-fat dairy products in older adults with hypertension. *J Nutr Elder.* 2004; 23(4): 21-33. PMID: 15233120.	Does not answer question; did not examine relationship between milk product intake and health; participants diagnosed with hypertension.
Larson NI, Neumark-Sztainer D, Harnack L, Wall M, Story M, Eisenberg ME. Calcium and dairy intake: Longitudinal trends during the transition to young adulthood and correlates of calcium intake. *J Nutr Educ Behav.* 2009 Jul-Aug; 41(4): 254-260. PMID: 19508930.	Does not answer question; did not examine relationship between milk product intake and health.
Larsson SC, Andersson SO, Johansson JE, Wolk A. Cultured milk, yogurt, and dairy intake in relation to bladder cancer risk in a prospective study of Swedish women and men. *Am J Clin Nutr.* 2008 Oct; 88(4): 1, 083-1, 087. PMID: 18842797.	Cancer outcomes excluded from NEL review.
Larsson SC, Bergkvist L, Rutegård J, Giovannucci E, Wolk A. Calcium and dairy food intakes are inversely associated with colorectal cancer risk in the Cohort of Swedish Men. *Am J Clin Nutr.* 2006 Mar; 83(3): 667-673; quiz 728-729. PMID: 16522915.	Cancer outcomes excluded from NEL review.
Larsson SC, Bergkvist L, Wolk A. High-fat dairy food and conjugated linoleic acid intakes in relation to colorectal cancer incidence in the Swedish Mammography Cohort. *Am J Clin Nutr.* 2005 Oct; 82(4): 894-900. PMID: 16210722.	Cancer outcomes excluded from NEL review.

Larsson SC, Bergkvist L, Wolk A. Milk and lactose intakes and ovarian cancer risk in the Swedish Mammography Cohort. *Am J Clin Nutr.* 2004 Nov; 80(5): 1, 353-1, 357. PMID: 15531686.	Cancer outcomes excluded from NEL review.
Larsson SC, Orsini N, Wolk A. Milk, milk products and lactose intake and ovarian cancer risk: A meta-analysis of epidemiological studies. *Int J Cancer.* 2006 Jan 15; 118(2): 431-441. PMID: 16052536.	Cancer outcomes excluded from NEL review.
Lawlor DA, Ebrahim S, Timpson N, Davey Smith G. Avoiding milk is associated with a reduced risk of insulin resistance and the metabolic syndrome: Findings from the British Women's Heart and Health Study. *Diabet Med.* 2005 Jun; 22(6): 808-811. PMID: 15910636.	Included in Elwood, 2008.
Liu S, Choi HK, Ford E, Song Y, Klevak A, Buring JE, Manson JE. A prospective study of dairy intake and the risk of type 2 diabetes in women. *Diabetes Care.* 2006 Jul; 29(7): 1, 579-1, 584. PMID: 16801582.	Included in Elwood, 2008.
Lorenz M, Jochmann N, von Krosigk A, Martus P, Baumann G, Stangl K, Stangl V. Addition of milk prevents vascular protective effects of tea. *Eur Heart J.* 2007 Jan; 28(2): 219-223. Epub 2007 Jan 9. PMID: 17213230.	Does not answer question; did not examine relationship between milk product intake and health.
Ma D, Jones G. Soft drink and milk consumption, physical activity, bone mass, and upper limb fractures in children: a population-based case-control study. *Calcif Tissue Int.* 2004 Oct; 75(4): 286-291. Epub 2004 Jul 30. PMID: 15549642.	Does not answer question; examines relationship between soft drink intake and fracture risk.
Matsumoto M, Ishikawa S, Nakamura Y, Kayaba K, Kajii E. Consumption of dairy products and cancer risks. *J Epidemiol.* 2007 Mar; 17(2): 38-44. PMID: 17420611.	Cancer outcomes excluded from NEL review.
McCullough ML, Rodriguez C, Diver WR, Feigelson HS, Stevens VL, Thun MJ, Calle EE. Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev.* 2005 Dec; 14(12): 2, 898-2, 904. PMID: 16365007.	Cancer outcomes excluded from NEL review.
McGlynn KA, Sakoda LC, Rubertone MV, Sesterhenn IA, Lyu C, Graubard BI, Erickson RL. Body size, dairy consumption, puberty, and risk of testicular germ cell tumors. *Am J Epidemiol.* 2007 Feb 15; 165(4): 355-363. Epub 2006 Nov 16. PMID: 17110638.	Cancer outcomes excluded from NEL review.
Mitrou PN, Albanes D, Weinstein SJ, Pietinen P, Taylor PR, Virtamo J, Leitzmann MF. A prospective study of dietary calcium, dairy products and prostate cancer risk (Finland). *Int J Cancer.* 2007 Jun 1; 120(11): 2, 466-2, 473. PMID: 17278090.	Cancer outcomes excluded from NEL review.

Mizoue T, Kimura Y, Toyomura K, Nagano J, Kono S, Mibu R, Tanaka M, Kakeji Y, Maehara Y, Okamura T, Ikejiri K, Futami K, Yasunami Y, Maekawa T, Takenaka K, Ichimiya H, Imaizumi N. Calcium, dairy foods, vitamin D, and colorectal cancer risk: The Fukuoka Colorectal Cancer Study. *Cancer Epidemiol Biomarkers Prev.* 2008 Oct; 17(10): 2, 800-2, 807. PMID: 18843026.	Cancer outcomes excluded from NEL review.
Mommers M, Schouten LJ, Goldbohm RA, van den Brandt PA. Dairy consumption and ovarian cancer risk in the Netherlands Cohort Study on Diet and Cancer. *Br J Cancer.* 2006 Jan 16; 94(1): 165-170. PMID: 16306872.	Cancer outcomes excluded from NEL review.
Nestel PJ, Chronopulos A, Cehun M. Dairy fat in cheese raises LDL cholesterol less than that in butter in mildly hypercholesterolaemic subjects. *Eur J Clin Nutr.* 2005 Sep; 59(9): 1, 059-1, 063. PMID: 16015270.	Participants diagnosed with hypercholesterolemia.
Park SY, Murphy SP, Wilkens LR, Stram DO, Henderson BE, Kolonel LN. Calcium, vitamin D, and dairy product intake and prostate cancer risk: The Multiethnic Cohort Study. *Am J Epidemiol.* 2007 Dec 1; 166(11): 1, 259-1, 269. Epub 2007 Oct 8. PMID: 17925283.	Cancer outcomes excluded from NEL review.
Park Y, Leitzmann MF, Subar AF, Hollenbeck A, Schatzkin A. Dairy food, calcium, and risk of cancer in the NIH-AARP Diet and Health Study. *Arch Intern Med.* 2009 Feb 23; 169(4): 391-401. PMID: 19237724.	Cancer outcomes excluded from NEL review.
Park Y, Mitrou PN, Kipnis V, Hollenbeck A, Schatzkin A, Leitzmann MF. Calcium, dairy foods, and risk of incident and fatal prostate cancer: the NIH-AARP Diet and Health Study. *Am J Epidemiol.* 2007 Dec 1; 166(11): 1, 270-1, 279. Epub 2007 Oct 12. PMID: 18000020.	Cancer outcomes excluded from NEL review.
Parodi PW. Dairy product consumption and the risk of breast cancer. *J Am Coll Nutr.* 2005 Dec; 24(6 Suppl): 556S-568S. Review. PMID: 16373955.	Cancer outcomes excluded from NEL review.
Qin LQ, Xu JY, Wang PY, Hashi A, Hoshi K, Sato A. Milk/dairy products consumption, galactose metabolism and ovarian cancer: Meta-analysis of epidemiological studies. *Eur J Cancer Prev.* 2005 Feb; 14(1): 13-19. PMID: 15677891.	Cancer outcomes excluded from NEL review.
Qin LQ, Xu JY, Wang PY, Tong J, Hoshi K. Milk consumption is a risk factor for prostate cancer in Western countries: Evidence from cohort studies. *Asia Pac J Clin Nutr.* 2007; 16(3): 467-476. PMID: 17704029.	Cancer outcomes excluded from NEL review.
Qin LQ, Xu JY, Wang PY, Kaneko T, Hoshi K, Sato A. Milk consumption is a risk factor for prostate cancer: Meta-analysis of case-control studies. *Nutr Cancer.* 2004; 48(1): 22-27. PMID: 15203374.	Cancer outcomes excluded from NEL review.

Rohrmann S, Platz EA, Kavanaugh CJ, Thuita L, Hoffman SC, Helzlsouer KJ. Meat and dairy consumption and subsequent risk of prostate cancer in a US cohort study. *Cancer Causes Control.* 2007 Feb; 18(1): 41-50. PMID: 17315319.	Cancer outcomes excluded from NEL review.
Snijder MB, van der Heijden AA, van Dam RM, Stehouwer CD, Hiddink GJ, Nijpels G, Heine RJ, Bouter LM, Dekker JM. Is higher dairy consumption associated with lower body weight and fewer metabolic disturbances? The Hoorn Study. *Am J Clin Nutr.* 2007 Apr; 85(4): 989-995. PMID: 17413097.	Same data set as Snijder, 2008.
Sun Q, Ma J, Campos H, Hu FB. Plasma and erythrocyte biomarkers of dairy fat intake and risk of ischemic heart disease. *Am J Clin Nutr.* 2007 Oct; 86(4): 929-937. PMID: 17921367.	Does not answer question; examined relationship between fatty acids and disease risk.
Taguchi H, Chen H, Yano R, Shoumura S. Comparative effects of milk and soymilk on bone loss in adult ovariectomized osteoporosis rat. *Okajimas Folia Anat Jpn.* 2006 Aug; 83(2): 53-59. PMID: 16944838.	Study tested animals.
Tricon S, Burdge GC, Jones EL, Russell JJ, El-Khazen S, Moretti E, Hall WL, Gerry AB, Leake DS, Grimble RF, Williams CM, Calder PC, Yaqoob P. Effects of dairy products naturally enriched with cis-9, trans-11 conjugated linoleic acid on the blood lipid profile in healthy middle-aged men. *Am J Clin Nutr.* 2006 Apr; 83(4): 744-753. PMID: 16600923.	Milk products enriched with cis-9, trans-11 conjugated linoleic acid.
Tseng M, Breslow RA, Graubard BI, Ziegler RG. Dairy, calcium, and vitamin D intakes and prostate cancer risk in the National Health and Nutrition Examination Epidemiologic Follow-up Study cohort. *Am J Clin Nutr.* 2005 May; 81(5): 1, 147-1, 154. PMID: 15883441.	Cancer outcomes excluded from NEL review.
van der Pols JC, Bain C, Gunnell D, Smith GD, Frobisher C, Martin RM. Childhood dairy intake and adult cancer risk: 65-year follow-up of the Boyd Orr cohort. *Am J Clin Nutr.* 2007 Dec; 86(6): 1, 722-1, 729. PMID: 18065592.	Cancer outcomes excluded from NEL review.
Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: A systematic review and meta-analysis. *Am J Public Health.* 2007 Apr; 97(4): 667-675. Epub 2007 Feb 28. Review. PMID: 17329656; PMCID: PMC1829363.	Does not answer question; did not examine relationship between milk product intake and health.
Warensjö E, Jansson JH, Berglund L, Boman K, Ahrén B, Weinehall L, Lindahl B, Hallmans G, Vessby B. Estimated intake of milk fat is negatively associated with cardiovascular risk factors and does not increase the risk of a first acute myocardial infarction. A prospective case-control study. *Br J Nutr.* 2004 Apr; 91(4): 635-642. PMID: 15035691.	Does not include milk product intake in analyses.

Xu JY, Qin LQ, Wang PY, Li W, Chang C. Effect of milk tripeptides on blood pressure: a meta-analysis of randomized controlled trials. *Nutrition.* 2008 Oct; 24(10): 933-940. Epub 2008 Jun 17. PMID: 18562172.	Does not answer question; did not examine relationship between milk product intake and health.
Zhang J, Kesteloot H. Milk consumption in relation to incidence of prostate, breast, colon, and rectal cancers: Is there an independent effect? Nu*tr Cancer.* 2005; 53(1): 65-72. PMID: 16351508.	Cancer outcomes excluded from NEL review.
Zhu K, Zhang Q, Foo LH, Trube A, Ma G, Hu X, Du X, Cowell CT, Fraser DR, Greenfield H. Growth, bone mass, and vitamin D status of Chinese adolescent girls three years after withdrawal of milk supplementation. *Am J Clin Nutr.* 2006 Mar; 83(3): 714-721. PMID: 16522922.	Milk enriched with additional calcium.

CHAPTER 19. MILK AND MILK PRODUCTS – SERUM CHOLESTEROL

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF MILK AND MILK PRODUCTS AND SERUM CHOLESTEROL?

Conclusion statement

Insufficient evidence is available to assess the relationship between intake of milk and milk products and serum cholesterol levels.

Grade

Limited

Evidence summary overview

Few studies have been conducted on the relationship between the intake of milk and milk products and blood cholesterol, although the high saturated fat content of milk fat would theoretically support a positive association with whole milk products. Three articles published since 2004 were reviewed on this topic: A randomized trial (Bowen, 2005), a prospective cohort study (Snijder, 2008) and a cross-sectional study (Houston, 2008).

In the dairy product feeding study (Bowen, 2005), intake of milk products was associated with reduced blood cholesterol, although this was associated with weight loss in the study. In a study of Dutch elderly (Snijder, 2008), baseline dairy consumption was not associated with changes in serum lipid levels over 6.4 years. A study of National Health and Nutrition Examination Surveys (NHANES) III data found that in women, more frequent cheese consumption was associated with higher high-density lipoprotein cholesterol (HDL-C) and lower low-density lipoprotein cholesterol (LDL-C) ($P<0.05$), while in men, more frequent cheese consumption was associated with higher body mass index (BMI), waist circumference (WC), HDL-C and LDL-C ($P<0.05$). Thus, intake of milk and milk products in recent studies did not always show expected increases in total blood cholesterol and may be linked to increased HDL-C.

Evidence summary paragraphs

Randomized Controlled Trial

Bowen et al, 2005 (positive quality) conducted a randomized controlled trial (RCT) to compare the effects on weight, body composition, metabolic parameters and risk markers of two isocaloric, energy-restricted high protein diets that differ in dietary calcium (Ca) and protein source on weight loss and body composition in healthy, overweight adults (N=50, 30 women and 20 men, ages 25 to 64 years). The study was conducted in Australia. The intervention diets were a high dairy protein and high-calcium (DP, 2,400mg Ca per day) diet and a high mixed protein and moderate calcium (MP, 500mg Ca per day) diet followed for a 12-week energy restriction phase, followed by a four-week energy balance phase. After 16 weeks, subjects showed significant reductions in total weight (-9.7±3.8kg), fat mass (-8.3±0.4kg) and lean mass (-1.6±0.3kg), but there were no significant (NS) differences between the two diet groups. Also, subjects experienced significant improvements in total cholesterol (TC),

LDL-C and triglycerides (TG) between baseline and 16-week dietary treatment; however, these differences were independent of dietary intervention. The authors concluded that weight loss following energy-restricted, high protein diets is not affected by dietary calcium or protein source. In addition, lipid profile improved with weight loss independent of dietary protein source or calcium intake.

Prospective Cohort Study

Snijder et al, 2008 (positive quality), a prospective cohort study conducted in the Netherlands, investigated the association between dairy consumption and changes in weight and metabolic disturbances, based on data from the Hoorn study, a population-based cohort of white men and women aged 50 to 75 years. Average food intake was measured at baseline using a 92-item semi-quantitative food-frequency questionnaire (FFQ). At baseline and follow-up, participants underwent an extensive physical examination and a blood sample was drawn for biochemical analyses of fasting glucose, post-load glucose, HDL-C and LDL-C and TG. During the physical examination, weight, waist circumference and blood pressure (BP) were measured. 1,124 participants were included in the analysis. Baseline dairy consumption was not associated with 6.4-year changes in serum lipid levels. The authors concluded that dairy consumption was not associated with changes in metabolic variables in a Dutch elderly population.

Cross-Sectional Study

Houston et al, 2008 (positive quality), a cross-sectional study conducted in the US, examined the association between the frequency of cheese consumption and several cardiovascular risk factors, including measures of body fat, blood lipids, BP and blood glucose, using data from NHANES III. A total of 10,872 participants, aged 25 to 75 years, had complete data and were included in the analysis. Cheese consumption (combined full- and low-fat) was assessed through a FFQ asking one question about cheese and two questions about the consumption of foods containing large amounts of cheese. Categories of cheese consumption were 0, 1 to 4, 5 to 12, 13 to 29 and 30-plus servings per month. In women, more frequent cheese consumption was associated with higher HDL-C and lower LDL-C ($P<0.05$), while in men, more frequent cheese consumption was associated with higher BMI, WC, HDL-C and LDL-C ($P<0.05$). Authors concluded that moderate cheese consumption does not appear to be associated with a worse cardiovascular disease (CVD) risk profile in men or women, and that the gender differences observed may be due to types of cheese consumed.

Overview table

Author, Year, Study Design, Class, Rating	Participants	Description of Study Design	Outcomes
Bowen J, Noakes M et al, 2005 Study Design: Randomized Controlled Trial Class: A Positive quality	N=50 (30 women, 20 men). Age: 25 to 64 years. Location: Australia.	Compared effects of two isocaloric, energy-restricted high PRO diets that differ in dietary Ca and PRO source on weight loss and body composition. Intervention diets were a high dairy PRO and high-Ca (DP, 2,400mg Ca per day) diet and a high mixed PRO and moderate Ca (MP, 500mg Ca per day) diet followed for a 12-week energy restriction phase, followed by a four-week energy balance phase.	After 16 weeks, subjects showed significant ↓ in total weight (-9.7±3.8kg), fat mass (-8.3±0.4kg) and lean mass (-1.6±0.3kg), but NS differences between the two diet groups. Also, subjects experienced significant improvements in TC, LDL-C and TG between baseline and 16-week dietary treatment; however, differences were independent of dietary intervention. Authors concluded that weight ↓ following energy-restricted, high PRO diets is not affected by dietary Ca or PRO source. In addition, lipid profile improved with weight ↓ independent of dietary PRO source or Ca intake.
Houston et al 2008 Study Design: Cross-sectional Study Class: D Positive quality	N=10,872 NHANES III participants. Age: 25 to 75 years. Location: United States.	Examined association between the frequency of cheese consumption and several cardiovascular risk factors, including measures of body fat, blood lipids, BP and BG, using data from NHANES III. Cheese consumption (combined full and low-fat) assessed through FFQ asking one question about cheese and two questions about consumption of foods containing large amounts of cheese. Categories of cheese consumption were 0, 1 to 4, 5 to 12, 13 to 29 and 30-plus servings per month.	In women, more frequent cheese consumption was associated with higher HDL-C and lower LDL-C ($P<0.05$), while in men, more frequent cheese consumption was associated with higher BMI, WC, HDL-C and LDL-C ($P<0.05$). Authors concluded that moderate cheese consumption does not appear to be associated with a worse CVD risk profile in men or women, and that gender differences observed may be due to types of cheese consumed.

Snijder et al 2008 Study Design: Prospective Cohort Study Class: B Positive quality	N=1,124 (Hoorn study, a population-based cohort of white men and women) Age: 50 to 75 years. Location: The Netherlands.	Investigated association between dairy consumption and Δ in weight and metabolic disturbances. Average food intake measured at baseline using a 92-item semiquantitative FFQ. At baseline and follow-up, participants underwent an extensive physical exam and blood sample was drawn for biochemical analyses of fasting glucose, post-load glucose, HDL-C and LDL-C and TG. During physical exam, weight, WC and BP were measured.	Baseline dairy consumption not associated with 6.4-year Δ in serum lipid levels. Authors concluded that dairy consumption not associated with Δ in metabolic variables in a Dutch elderly population.

Search plan and results

Inclusion criteria

- June 2004 to July 2009
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children, two to 18 years; adults, 19 years and older
- *Populations:* Healthy and those with elevated chronic disease risk.

Exclusion criteria

- Studies that only consider cancer outcomes
- Studies that considered milk and milk products as part of a larger dietary pattern
- Milk and milk products in forms not commonly consumed (e.g., enriched with additional calcium)
- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Animal studies
- In vitro studies
- Articles not peer reviewed (web sites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: ("Dairy Products"[mh]) AND ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mesh: NoExp] OR “heart diseases”[mh] OR “chronic disease”[mh] OR "Neoplasms"[majr] OR osteoporosis[mh] OR "Bone Density"[Mesh] OR "Fractures, Bone"[Mesh])

Date searched: 07/29/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 223
- Total articles identified to review from electronic databases: 95
- Articles identified via handsearch or other means: 3
- Number of Primary Articles Identified: 20
- Number of Review Articles Identified: 4
- Total Number of Articles Identified: 24
- Number of Articles Reviewed but Excluded: 74

Included articles (References)

What is the relationship between the intake of milk and milk products and bone health?

Systematic Reviews/Meta-analyses

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: A review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.
2. Huncharek M, Muscat J, Kupelnick B. Impact of dairy products and dietary calcium on bone-mineral content in children: Results of a meta-analysis. *Bone.* 2008 Aug; 43(2): 312-321. Epub 2008 Mar 15. PMID: 18539555.
3. Kanis JA, Johansson H, Oden A, De Laet C, Johnell O, Eisman JA, Mc Closkey E, Mellstrom D, Pols H, Reeve J, Silman A, Tenenhouse A. A meta-analysis of milk intake and fracture risk: low utility for case finding. *Osteoporos Int.* 2005 Jul; 16(7): 799-804. Epub 2004 Oct 21. PMID: 15502959.

Primary Research

Trials

1. Budek AZ, Hoppe C, Michaelsen KF, Mølgaard C. High intake of milk, but not meat, decreases bone turnover in prepubertal boys after 7 days. *Eur J Clin Nutr.* 2007 Aug; 61(8): 957-962. Epub 2007 Jan 17. PMID: 17228345.
2. Kristensen M, Jensen M, Kudsk J, Henriksen M, Mølgaard C. Short-term effects on bone turnover of replacing milk with cola beverages: A 10-day interventional study in young men. *Osteoporos Int.* 2005 Dec; 16(12): 1, 803-1, 808. Epub 2005 May 11. PMID: 15886860.
3. McCabe LD, Martin BR, McCabe GP, Johnston CC, Weaver CM, Peacock M. Dairy intakes affect bone density in the elderly. *Am J Clin Nutr.* 2004 Oct; 80(4): 1, 066-1, 074. PMID: 15447921.

Longitudinal Study

1. Rockell JE, Williams SM, Taylor RW, Grant AM, Jones IE, Goulding A. Two-year changes in bone and body composition in young children with a history of prolonged milk avoidance. *Osteoporos Int.* 2005 Sep; 16(9): 1, 016-1, 023. Epub 2004 Nov 23. PMID: 15565350.

Case-Control Study

1. Konstantynowicz J, Nguyen TV, Kaczmarski M, Jamiolkowski J, Piotrowska-

Jastrzebska J, Seeman E. Fractures during growth: Potential role of a milk-free diet. *Osteoporos Int.* 2007 Dec; 18(12): 1, 601-1, 607. Epub 2007 May 22. PMID: 17516020.

Cross-Sectional Study

1. Al-Zahrani MS. Increased intake of dairy products is related to lower periodontitis prevalence. *J Periodontol.* 2006 Feb; 77(2): 289-294. PMID: 16460256. (Hand search)

What is the relationship between the intake of milk and milk products and cardiovascular disease?

Systematic Reviews/Meta-Analyses

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: A review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.
2. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

Primary Research

Case-Control Study

1. Kontogianni MD, Panagiotakos DB, Chrysohoou C, Pitsavos C, Stefanadis C. Modelling dairy intake on the development of acute coronary syndromes: The CARDIO2000 study. *Eur J Cardiovasc Prev Rehabil.* 2006 Oct; 13(5): 791-797. PMID: 17001220.

What is the relationship between the intake of milk and milk products and blood pressure?

Systematic Review

1. Alvarez-León EE, Román-Viñas B, Serra-Majem L. Dairy products and health: a review of the epidemiological evidence. *Br J Nutr.* 2006 Aug; 96 Suppl 1: S94-S99. Review. PMID: 16923261.

Primary Research

Trial

1. Bowen J, Noakes M, Clifton PM.Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. *Int J Obes (Lond).* 2005 Aug; 29(8): 957-965. PMID: 15711601. (Hand search)

Prospective Cohort Studies

1. Alonso A, Beunza JJ, Delgado-Rodríguez M, Martínez JA, Martínez-González MA. Low-fat dairy consumption and reduced risk of hypertension: The Seguimiento Universidad de Navarra (SUN) cohort. *Am J Clin Nutr.* 2005 Nov; 82(5): 972-979. PMID: 16280427.
2. Engberink MF, Hendriksen MA, Schouten EG, van Rooij FJ, Hofman A,

Witteman JC, Geleijnse JM. Inverse association between dairy intake and hypertension: The Rotterdam Study. *Am J Clin Nutr.* 2009 Jun; 89(6): 1, 877-1, 883. Epub 2009 Apr 15. PMID: 19369377.

3. Engberink MF, Geleijnse JM, de Jong N, Smit HA, Kok FJ, Verschuren WM. Dairy intake, blood pressure, and incident hypertension in a general Dutch population. *J Nutr.* 2009 Mar; 139(3): 582-587. Epub 2009 Jan 21. PMID: 19158223.
4. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.
5. Toledo E, Delgado-Rodríguez M, Estruch R, Salas-Salvadó J, Corella D, Gomez-Gracia E, Fiol M, Lamuela-Raventós RM, Schröder H, Arós F, Ros E, Ruíz-Gutiérrez V, Lapetra J, Conde-Herrera M, Sáez G, Vinyoles E, Martínez-González MA. Low-fat dairy products and blood pressure: Follow-up of 2290 older persons at high cardiovascular risk participating in the PREDIMED study. *Br J Nutr.* 2009 Jan; 101(1): 59-67. Epub 2008 May 20. PMID: 18492300.
6. Wang L, Manson JE, Buring JE, Lee IM, Sesso HD. Dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women. *Hypertension.* 2008 Apr; 51(4): 1, 073-1, 079. Epub 2008 Feb 7. PMID: 18259007.

Cross-Sectional Studies

1. Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Tehranian adults. *Am J Clin Nutr.* 2005 Sep; 82(3): 523-530. PMID: 16155263.
2. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. *Am J Clin Nutr.* 2008 Jun; 87(6): 1, 914-1, 925. PMID: 18541585; PMCID: PMC2585752. (Hand search)
3. Djoussé L, Pankow JS, Hunt SC, Heiss G, Province MA, Kabagambe EK, Ellison RC. Influence of saturated fat and linolenic acid on the association between intake of dairy products and blood pressure. *Hypertension.* 2006 Aug; 48(2): 335-341. Epub 2006 Jun 26. PMID: 16801477.
4. Houston DK, Driver KE, Bush AJ, Kritchevsky SB. The association between cheese consumption and cardiovascular risk factors among adults. *J Hum Nutr Diet.* 2008 Apr; 21(2): 129-140. PMID: 18339053.
5. Ruidavets JB, Bongard V, Simon C, Dallongeville J, Ducimetière P, Arveiler D, Amouyel P, Bingham A, Ferrières J. Independent contribution of dairy products and calcium intake to blood pressure variations at a population level. *J Hypertens.* 2006 Apr; 24(4): 671-681. PMID: 16531795.

What is the relationship between the intake of milk and milk products and type 2 diabetes?

Meta-Analysis

1. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: An overview of evidence

from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

What is the relationship between the intake of milk and milk products and metabolic syndrome?

Primary Research

Meta-Analysis

1. Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. The survival advantage of milk and dairy consumption: An overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr.* 2008 Dec; 27(6): 723S-734S. PMID: 19155432.

Prospective Cohort Study

1. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.

Cross-Sectional Studies

1. Beydoun MA, Gary TL, Caballero BH, Lawrence RS, Cheskin LJ, Wang Y. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. *Am J Clin Nutr.* 2008 Jun; 87(6): 1, 914-1, 925. PMID: 18541585; PMCID: PMC2585752. (Hand search)
2. Ruidavets JB, Bongard V, Dallongeville J, Arveiler D, Ducimetière P, Perret B, Simon C, Amouyel P, Ferrières J. High consumptions of grain, fish, dairy products and combinations of these are associated with a low prevalence of metabolic syndrome. *J Epidemiol Community Health.* 2007 Sep; 61(9): 810-817. PMID: 17699537.

What is the relationship between the intake of milk and milk products and serum cholesterol?

Primary Research

Trial

1. Bowen J, Noakes M, Clifton PM.Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. *Int J Obes (Lond).* 2005 Aug; 29(8): 957-965. PMID: 15711601. (Hand search)

Prospective Cohort Study

1. Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: The Hoorn Study. *Obesity (Silver Spring).* 2008 Mar; 16(3): 706-709. Epub 2008 Jan 17. PMID: 18239556.

Cross-Sectional Study

1. Houston DK, Driver KE, Bush AJ, Kritchevsky SB. The association between

cheese consumption and cardiovascular risk factors among adults. *J Hum Nutr Diet.* 2008 Apr; 21(2): 129-140. PMID: 18339053.

Excluded articles

Article	Reason for Exclusion
Ahn J, Albanes D, Peters U, Schatzkin A, Lim U, Freedman M, Chatterjee N, Andriole GL, Leitzmann MF, Hayes RB; Prostate, Lung, Colorectal, and Ovarian Trial Project Team. Dairy products, calcium intake, and risk of prostate cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev.* 2007 Dec; 16(12): 2, 623-2, 630. PMID: 18086766.	Cancer outcomes excluded from NEL review.
Al Sarakbi W, Salhab M, Mokbel K. Dairy products and breast cancer risk: A review of the literature. *Int J Fertil Womens Med.* 2005 Nov-Dec; 50(6): 244-249. Review. PMID: 16526414.	Cancer outcomes excluded from NEL review.
Allen NE, Key TJ, Appleby PN, Travis RC, Roddam AW, Tjønneland A, Johnsen NF, Overvad K, Linseisen J, Rohrmann S, Boeing H, Pischon T, Bueno-de-Mesquita HB, Kiemeney L, Tagliabue G, Palli D, Vineis P, Tumino R, Trichopoulou A, Kassapa C, Trichopoulos D, Ardanaz E, Larrañaga N, Tormo MJ, González CA, Quirós JR, Sánchez MJ, Bingham S, Khaw KT, Manjer J, Berglund G, Stattin P, Hallmans G, Slimani N, Ferrari P, Rinaldi S, Riboli E. Animal foods, protein, calcium and prostate cancer risk: the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer.* 2008 May 6; 98(9): 1, 574-1, 581. Epub 2008 Apr 1. PMID: 18382426.	Does not answer question: examined relationship between milk protein intake and health.
Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Dairy consumption is inversely associated with the prevalence of the metabolic syndrome in Tehranian adults. *Am J Clin Nutr.* 2005 Sep; 82(3): 523-530. PMID: 16155263.	Included in blood pressure review, but excluded from metabolic syndrome review because included in Elwood, 2008.
Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: A systematic literature review and meta-analysis. *Cancer Causes Control.* 2007 Nov; 18(9): 967-988. Epub 2007 Jul 19. Review. PMID: 17638104; PMCID: PMC2592095.	Cancer outcomes excluded from NEL review.
Benito P, Caballero J, Moreno J, Gutiérrez-Alcántara C, Muñoz C, Rojo G, Garcia S, Soriguer FC. Effects of milk enriched with omega-3 fatty acid, oleic acid and folic acid in patients with metabolic syndrome. *Clin Nutr.* 2006 Aug; 25(4): 581-587. Epub 2006 May 15. PMID: 16701922.	Participants diagnosed with metabolic syndrome.
Biong AS, Rebnord HM, Fimreite RL, Trygg KU, Ringstad J, Thelle DS, Pedersen JI. Intake of dairy fat and dairy products, and risk of myocardial infarction: A case-control study. *Int J Food Sci Nutr.* 2008 Mar; 59(2): 155-165. PMID: 17886080.	Included in Elwood, 2008.

Biong AS, Veierød MB, Ringstad J, Thelle DS, Pedersen JI. Intake of milk fat, reflected in adipose tissue fatty acids and risk of myocardial infarction: A case-control study. *Eur J Clin Nutr.* 2006 Feb; 60(2): 236-244. PMID: 16267503.	Does not answer question: examined relationship between fatty acids in adipose tissue and myocardial infarction.
Chan JM, Wang F, Holly EA. Pancreatic cancer, animal protein and dietary fat in a population-based study, San Francisco Bay Area, California. *Cancer Causes Control.* 2007 Dec; 18(10): 1, 153-1, 167. Epub 2007 Sep 1. PMID: 17805983.	Cancer outcomes excluded from NEL review.
Cheng S, Lyytikäinen A, Kröger H, Lamberg-Allardt C, Alén M, Koistinen A, Wang QJ, Suuriniemi M, Suominen H, Mahonen A, Nicholson PH, Ivaska KK, Korpela R, Ohlsson C, Väänänen KH, Tylavsky F. Effects of calcium, dairy product, and vitamin D supplementation on bone mass accrual and body composition in 10- to 12-year-old girls: A two-year randomized trial. *Am J Clin Nutr.* 2005 Nov; 82(5): 1, 115-1, 126; quiz 1, 147-1, 148. PMID: 16280447.	Included in Huncharek, 2008.
Cho E, Smith-Warner SA, Spiegelman D, Beeson WL, van den Brandt PA, Colditz GA, Folsom AR, Fraser GE, Freudenheim JL, Giovannucci E, Goldbohm RA, Graham S, Miller AB, Pietinen P, Potter JD, Rohan TE, Terry P, Toniolo P, Virtanen MJ, Willett WC, Wolk A, Wu K, Yaun SS, Zeleniuch-Jacquotte A, Hunter DJ. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. *J Natl Cancer Inst.* 2004 Jul 7; 96(13): 1, 015-1.022. Erratum in: *J Natl Cancer Inst.* 2004 Nov 17; 96(22): 1, 724. PMID: 15240785.	Cancer outcomes excluded from NEL review.
Choi HK, Willett WC, Stampfer MJ, Rimm E, Hu FB. Dairy consumption and risk of type 2 diabetes mellitus in men: a prospective study. *Arch Intern Med.* 2005 May 9; 165(9): 997-1, 003. PMID: 15883237.	Included in Elwood, 2008.
Daly RM, Bass S, Nowson C. Long-term effects of calcium-vitamin-D3-fortified milk on bone geometry and strength in older men. *Bone.* 2006 Oct; 39(4): 946-953. Epub 2006 May 24. PMID: 16725396.	Milk enriched with additional calcium and vitamin D_3.
Daly RM, Brown M, Bass S, Kukuljan S, Nowson C. Calcium- and vitamin D3-fortified milk reduces bone loss at clinically relevant skeletal sites in older men: a 2-year randomized controlled trial. *J Bone Miner Res.* 2006 Mar; 21(3): 397-405. Epub 2005 Dec 19. PMID: 16491287.	Milk enriched with additional calcium and vitamin D_3.
Dixon LB, Pellizzon MA, Jawad AF, Tershakovec AM. Calcium and dairy intake and measures of obesity in hyper- and normocholesterolemic children. *Obes Res.* 2005 Oct; 13(10): 1, 727-1, 738. PMID: 16286520.	The relationship between milk product intake and adiposity in children is reviewed in the Energy Balance section.

Doornbos AM, Meynen EM, Duchateau GS, van der Knaap HC, Trautwein EA. Intake occasion affects the serum cholesterol lowering of a plant sterol-enriched single-dose yoghurt drink in mildly hypercholesterolaemic subjects. *Eur J Clin Nutr.* 2006 Mar; 60(3): 325-333. PMID: 16234829.	Participants diagnosed with hypercholesterolemia.
Du X, Zhu K, Trube A, Zhang Q, Ma G, Hu X, Fraser DR, Greenfield H. School-milk intervention trial enhances growth and bone mineral accretion in Chinese girls aged 10 to 12 years in Beijing. *Br J Nutr.* 2004 Jul; 92(1): 159-168. Erratum in: *Br J Nutr.* 2005 Apr; 93(4): 571-572. PMID: 15230999.	Milk enriched with additional calcium.
Elwood PC, Pickering JE, Fehily AM. Milk and dairy consumption, diabetes and the metabolic syndrome: The Caerphilly prospective study. *J Epidemiol Community Health.* 2007 Aug; 61(8): 695-698. PMID: 17630368.	Included in Elwood, 2008.
Elwood PC, Pickering JE, Fehily AM, Hughes J, Ness AR. Milk drinking, ischaemic heart disease and ischaemic stroke I. Evidence from the Caerphilly cohort. *Eur J Clin Nutr.* 2004 May; 58(5): 711-717. PMID: 15116073.	Included in Elwood, 2008.
Elwood PC, Pickering JE, Hughes J, Fehily AM, Ness AR. Milk drinking, ischaemic heart disease and ischaemic stroke II. Evidence from cohort studies. *Eur J Clin Nutr.* 2004 May; 58(5): 718-724. Review. PMID: 15116074.	The most recent meta-analyses from these authors on these outcomes was included (Elwood, 2008).
Elwood PC, Strain JJ, Robson PJ, Fehily AM, Hughes J, Pickering J, Ness A. Milk consumption, stroke, and heart attack risk: Evidence from the Caerphilly cohort of older men. *J Epidemiol Community Health.* 2005 Jun; 59(6): 502-505. PMID: 15911647; PMCID: PMC1757052.	Included in Elwood, 2008.
Fiorito LM, Mitchell DC, Smiciklas-Wright H, Birch LL. Dairy and dairy-related nutrient intake during middle childhood. *J Am Diet Assoc.* 2006 Apr; 106(4): 534-542. PMID: 16567149; PMCID: PMC2531148.	Does not answer question: did not examine relationship between milk product intake and health.
Gallus S, Bravi F, Talamini R, Negri E, Montella M, Ramazzotti V, Franceschi S, Giacosa A, La Vecchia C. Milk, dairy products and cancer risk (Italy). *Cancer Causes Control.* 2006 May; 17(4): 429-437. PMID: 16596295.	Cancer outcomes excluded from NEL review.
Gao X, LaValley MP, Tucker KL. Prospective studies of dairy product and calcium intakes and prostate cancer risk: a meta-analysis. *J Natl Cancer Inst.* 2005 Dec 7; 97(23): 1, 768-1, 777. Erratum in: *J Natl Cancer Inst.* 2006 Mar 1; 98(5): 366. PMID: 16333032.	Cancer outcomes excluded from NEL review.
Gardner CD, Messina M, Kiazand A, Morris JL, Franke AA. Effect of two types of soy milk and dairy milk on plasma lipids in hypercholesterolemic adults: A randomized trial. *J Am Coll Nutr.* 2007 Dec; 26(6): 669-677. PMID: 18187432.	Participants diagnosed with hypercholesterolemia.

Genkinger JM, Hunter DJ, Spiegelman D, Anderson KE, Arslan A, Beeson WL, Buring JE, Fraser GE, Freudenheim JL, Goldbohm RA, Hankinson SE, Jacobs DR Jr, Koushik A, Lacey JV Jr, Larsson SC, Leitzmann M, McCullough ML, Miller AB, Rodriguez C, Rohan TE, Schouten LJ, Shore R, Smit E, Wolk A, Zhang SM, Smith-Warner SA. Dairy products and ovarian cancer: A pooled analysis of 12 cohort studies. *Cancer Epidemiol Biomarkers Prev.* 2006 Feb; 15(2): 364-372. PMID: 16492930.	Cancer outcomes excluded from NEL review.
Gibbons MJ, Gilchrist NL, Frampton C, Maguire P, Reilly PH, March RL, Wall CR. The effects of a high calcium dairy food on bone health in pre-pubertal children in New Zealand. *Asia Pac J Clin Nutr.* 2004; 13(4): 341-347. PMID: 15563438.	Drink was a high calcium supplement, not milk as defined by the Subcommittee.
Hubner RA, Muir KR, Liu JF, Logan RF, Grainge MJ, Houlston RS; Members of UKCAP Consortium. Dairy products, polymorphisms in the vitamin D receptor gene and colorectal adenoma recurrence. *Int J Cancer.* 2008 Aug 1; 123(3): 586-593. PMID: 18470879.	Cancer outcomes excluded from NEL review.
Huncharek M, Muscat J, Kupelnick B. Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: A meta-analysis of 26, 335 cases from 60 observational studies. *Nutr Cancer.* 2009; 61(1): 47-69. PMID: 19116875.	Cancer outcomes excluded from NEL review.
Huncharek M, Muscat J, Kupelnick B. Dairy products, dietary calcium and vitamin D intake as risk factors for prostate cancer: A meta-analysis of 26, 769 cases from 45 observational studies. *Nutr Cancer.* 2008; 60(4): 421-441. PMID: 18584476.	Cancer outcomes excluded from NEL review.
Kesse E, Bertrais S, Astorg P, Jaouen A, Arnault N, Galan P, Hercberg S. Dairy products, calcium and phosphorus intake, and the risk of prostate cancer: Results of the French prospective SU.VI.MAX (Supplémentation en Vitamines et Minéraux Antioxydants) study. *Br J Nutr.* 2006 Mar; 95(3): 539-545. PMID: 16512941.	Cancer outcomes excluded from NEL review.
Kesse E, Boutron-Ruault MC, Norat T, Riboli E, Clavel-Chapelon F; E3N Group. Dietary calcium, phosphorus, vitamin D, dairy products and the risk of colorectal adenoma and cancer among French women of the E3N-EPIC prospective study. *Int J Cancer.* 2005 Oct 20; 117(1): 137-144. PMID: 15880532.	Cancer outcomes excluded from NEL review.
Kesse-Guyot E, Bertrais S, Duperray B, Arnault N, Bar-Hen A, Galan P, Hercberg S. Dairy products, calcium and the risk of breast cancer: Results of the French SU.VI.MAX prospective study. *Ann Nutr Metab.* 2007; 51(2): 139-145. Epub 2007 May 29. PMID: 17536191.	Cancer outcomes excluded from NEL review.
Koh KA, Sesso HD, Paffenbarger RS Jr, Lee IM. Dairy products, calcium and prostate cancer risk. *Br J Cancer.* 2006 Dec 4; 95(11): 1, 582-1, 585. Epub 2006 Nov 14. PMID: 17106437.	Cancer outcomes excluded from NEL review.

Koralek DO, Bertone-Johnson ER, Leitzmann MF, Sturgeon SR, Lacey JV Jr, Schairer C, Schatzkin A. Relationship between calcium, lactose, vitamin D, and dairy products and ovarian cancer. *Nutr Cancer.* 2006; 56(1): 22-30. PMID: 17176214.	Cancer outcomes excluded from NEL review.
Korpela R, Tuomilehto J, Högström P, Seppo L, Piironen V, Salo-Väänänen P, Toivo J, Lamberg-Allardt C, Kärkkäinen M, Outila T, Sundvall J, Vilkkilä S, Tikkanen MJ. Safety aspects and cholesterol-lowering efficacy of low fat dairy products containing plant sterols. *Eur J Clin Nutr.* 2006 May; 60(5): 633-642. PMID: 16404415.	Dairy products contained plant sterols.
Kurahashi N, Inoue M, Iwasaki M, Sasazuki S, Tsugane AS; Japan Public Health Center-Based Prospective Study Group. Dairy product, saturated fatty acid, and calcium intake and prostate cancer in a prospective cohort of Japanese men. *Cancer Epidemiol Biomarkers Prev.* 2008 Apr; 17(4): 930-937. PMID: 18398033.	Cancer outcomes excluded from NEL review.
Kuriki K, Hirose K, Matsuo K, Wakai K, Ito H, Kanemitsu Y, Hirai T, Kato T, Hamajima N, Takezaki T, Suzuki T, Saito T, Tanaka R, Tajima K. Meat, milk, saturated fatty acids, the Pro12Ala and C161T polymorphisms of the PPARgamma gene and colorectal cancer risk in Japanese. *Cancer Sci.* 2006 Nov; 97(11): 1, 226-1, 235. Epub 2006 Sep 5. PMID: 16965392.	Does not answer question: examined risk related to genetic polymorphisms.
Lancaster KJ. Characteristics influencing daily consumption of fruits and vegetables and low-fat dairy products in older adults with hypertension. *J Nutr Elder.* 2004; 23(4): 21-33. PMID: 15233120.	Does not answer question; did not examine relationship between milk product intake and health; participants diagnosed with hypertension.
Larson NI, Neumark-Sztainer D, Harnack L, Wall M, Story M, Eisenberg ME. Calcium and dairy intake: Longitudinal trends during the transition to young adulthood and correlates of calcium intake. *J Nutr Educ Behav.* 2009 Jul-Aug; 41(4): 254-260. PMID: 19508930.	Does not answer question; did not examine relationship between milk product intake and health.
Larsson SC, Andersson SO, Johansson JE, Wolk A. Cultured milk, yogurt, and dairy intake in relation to bladder cancer risk in a prospective study of Swedish women and men. *Am J Clin Nutr.* 2008 Oct; 88(4): 1, 083-1, 087. PMID: 18842797.	Cancer outcomes excluded from NEL review.
Larsson SC, Bergkvist L, Rutegård J, Giovannucci E, Wolk A. Calcium and dairy food intakes are inversely associated with colorectal cancer risk in the Cohort of Swedish Men. *Am J Clin Nutr.* 2006 Mar; 83(3): 667-673; quiz 728-729. PMID: 16522915.	Cancer outcomes excluded from NEL review.
Larsson SC, Bergkvist L, Wolk A. High-fat dairy food and conjugated linoleic acid intakes in relation to colorectal cancer incidence in the Swedish Mammography Cohort. *Am J Clin Nutr.* 2005 Oct; 82(4): 894-900. PMID: 16210722.	Cancer outcomes excluded from NEL review.

Larsson SC, Bergkvist L, Wolk A. Milk and lactose intakes and ovarian cancer risk in the Swedish Mammography Cohort. *Am J Clin Nutr.* 2004 Nov; 80(5): 1, 353-1, 357. PMID: 15531686.	Cancer outcomes excluded from NEL review.
Larsson SC, Orsini N, Wolk A. Milk, milk products and lactose intake and ovarian cancer risk: A meta-analysis of epidemiological studies. *Int J Cancer.* 2006 Jan 15; 118(2): 431-441. PMID: 16052536.	Cancer outcomes excluded from NEL review.
Lawlor DA, Ebrahim S, Timpson N, Davey Smith G. Avoiding milk is associated with a reduced risk of insulin resistance and the metabolic syndrome: Findings from the British Women's Heart and Health Study. *Diabet Med.* 2005 Jun; 22(6): 808-811. PMID: 15910636.	Included in Elwood, 2008.
Liu S, Choi HK, Ford E, Song Y, Klevak A, Buring JE, Manson JE. A prospective study of dairy intake and the risk of type 2 diabetes in women. *Diabetes Care.* 2006 Jul; 29(7): 1, 579-1, 584. PMID: 16801582.	Included in Elwood, 2008.
Lorenz M, Jochmann N, von Krosigk A, Martus P, Baumann G, Stangl K, Stangl V. Addition of milk prevents vascular protective effects of tea. *Eur Heart J.* 2007 Jan; 28(2): 219-223. Epub 2007 Jan 9. PMID: 17213230.	Does not answer question; did not examine relationship between milk product intake and health.
Ma D, Jones G. Soft drink and milk consumption, physical activity, bone mass, and upper limb fractures in children: a population-based case-control study. *Calcif Tissue Int.* 2004 Oct; 75(4): 286-291. Epub 2004 Jul 30. PMID: 15549642.	Does not answer question; examines relationship between soft drink intake and fracture risk.
Matsumoto M, Ishikawa S, Nakamura Y, Kayaba K, Kajii E. Consumption of dairy products and cancer risks. *J Epidemiol.* 2007 Mar; 17(2): 38-44. PMID: 17420611.	Cancer outcomes excluded from NEL review.
McCullough ML, Rodriguez C, Diver WR, Feigelson HS, Stevens VL, Thun MJ, Calle EE. Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev.* 2005 Dec; 14(12): 2, 898-2, 904. PMID: 16365007.	Cancer outcomes excluded from NEL review.
McGlynn KA, Sakoda LC, Rubertone MV, Sesterhenn IA, Lyu C, Graubard BI, Erickson RL. Body size, dairy consumption, puberty, and risk of testicular germ cell tumors. *Am J Epidemiol.* 2007 Feb 15; 165(4): 355-363. Epub 2006 Nov 16. PMID: 17110638.	Cancer outcomes excluded from NEL review.
Mitrou PN, Albanes D, Weinstein SJ, Pietinen P, Taylor PR, Virtamo J, Leitzmann MF. A prospective study of dietary calcium, dairy products and prostate cancer risk (Finland). *Int J Cancer.* 2007 Jun 1; 120(11): 2, 466-2, 473. PMID: 17278090.	Cancer outcomes excluded from NEL review.

Mizoue T, Kimura Y, Toyomura K, Nagano J, Kono S, Mibu R, Tanaka M, Kakeji Y, Maehara Y, Okamura T, Ikejiri K, Futami K, Yasunami Y, Maekawa T, Takenaka K, Ichimiya H, Imaizumi N. Calcium, dairy foods, vitamin D, and colorectal cancer risk: The Fukuoka Colorectal Cancer Study. *Cancer Epidemiol Biomarkers Prev.* 2008 Oct; 17(10): 2, 800-2, 807. PMID: 18843026.	Cancer outcomes excluded from NEL review.
Mommers M, Schouten LJ, Goldbohm RA, van den Brandt PA. Dairy consumption and ovarian cancer risk in the Netherlands Cohort Study on Diet and Cancer. *Br J Cancer.* 2006 Jan 16; 94(1): 165-170. PMID: 16306872.	Cancer outcomes excluded from NEL review.
Nestel PJ, Chronopulos A, Cehun M. Dairy fat in cheese raises LDL cholesterol less than that in butter in mildly hypercholesterolaemic subjects. *Eur J Clin Nutr.* 2005 Sep; 59(9): 1, 059-1, 063. PMID: 16015270.	Participants diagnosed with hypercholesterolemia.
Park SY, Murphy SP, Wilkens LR, Stram DO, Henderson BE, Kolonel LN. Calcium, vitamin D, and dairy product intake and prostate cancer risk: The Multiethnic Cohort Study. *Am J Epidemiol.* 2007 Dec 1; 166(11): 1, 259-1, 269. Epub 2007 Oct 8. PMID: 17925283.	Cancer outcomes excluded from NEL review.
Park Y, Leitzmann MF, Subar AF, Hollenbeck A, Schatzkin A. Dairy food, calcium, and risk of cancer in the NIH-AARP Diet and Health Study. *Arch Intern Med.* 2009 Feb 23; 169(4): 391-401. PMID: 19237724.	Cancer outcomes excluded from NEL review.
Park Y, Mitrou PN, Kipnis V, Hollenbeck A, Schatzkin A, Leitzmann MF. Calcium, dairy foods, and risk of incident and fatal prostate cancer: the NIH-AARP Diet and Health Study. *Am J Epidemiol.* 2007 Dec 1; 166(11): 1, 270-1, 279. Epub 2007 Oct 12. PMID: 18000020.	Cancer outcomes excluded from NEL review.
Parodi PW. Dairy product consumption and the risk of breast cancer. *J Am Coll Nutr.* 2005 Dec; 24(6 Suppl): 556S-568S. Review. PMID: 16373955.	Cancer outcomes excluded from NEL review.
Qin LQ, Xu JY, Wang PY, Hashi A, Hoshi K, Sato A. Milk/dairy products consumption, galactose metabolism and ovarian cancer: Meta-analysis of epidemiological studies. *Eur J Cancer Prev.* 2005 Feb; 14(1): 13-19. PMID: 15677891.	Cancer outcomes excluded from NEL review.
Qin LQ, Xu JY, Wang PY, Tong J, Hoshi K. Milk consumption is a risk factor for prostate cancer in Western countries: Evidence from cohort studies. *Asia Pac J Clin Nutr.* 2007; 16(3): 467-476. PMID: 17704029.	Cancer outcomes excluded from NEL review.
Qin LQ, Xu JY, Wang PY, Kaneko T, Hoshi K, Sato A. Milk consumption is a risk factor for prostate cancer: Meta-analysis of case-control studies. *Nutr Cancer.* 2004; 48(1): 22-27. PMID: 15203374.	Cancer outcomes excluded from NEL review.

Rohrmann S, Platz EA, Kavanaugh CJ, Thuita L, Hoffman SC, Helzlsouer KJ. Meat and dairy consumption and subsequent risk of prostate cancer in a US cohort study. *Cancer Causes Control.* 2007 Feb; 18(1): 41-50. PMID: 17315319.	Cancer outcomes excluded from NEL review.
Snijder MB, van der Heijden AA, van Dam RM, Stehouwer CD, Hiddink GJ, Nijpels G, Heine RJ, Bouter LM, Dekker JM. Is higher dairy consumption associated with lower body weight and fewer metabolic disturbances? The Hoorn Study. *Am J Clin Nutr.* 2007 Apr; 85(4): 989-995. PMID: 17413097.	Same data set as Snijder, 2008.
Sun Q, Ma J, Campos H, Hu FB. Plasma and erythrocyte biomarkers of dairy fat intake and risk of ischemic heart disease. *Am J Clin Nutr.* 2007 Oct; 86(4): 929-937. PMID: 17921367.	Does not answer question; examined relationship between fatty acids and disease risk.
Taguchi H, Chen H, Yano R, Shoumura S. Comparative effects of milk and soymilk on bone loss in adult ovariectomized osteoporosis rat. *Okajimas Folia Anat Jpn.* 2006 Aug; 83(2): 53-59. PMID: 16944838.	Study tested animals.
Tricon S, Burdge GC, Jones EL, Russell JJ, El-Khazen S, Moretti E, Hall WL, Gerry AB, Leake DS, Grimble RF, Williams CM, Calder PC, Yaqoob P. Effects of dairy products naturally enriched with cis-9, trans-11 conjugated linoleic acid on the blood lipid profile in healthy middle-aged men. *Am J Clin Nutr.* 2006 Apr; 83(4): 744-753. PMID: 16600923.	Milk products enriched with cis-9, trans-11 conjugated linoleic acid.
Tseng M, Breslow RA, Graubard BI, Ziegler RG. Dairy, calcium, and vitamin D intakes and prostate cancer risk in the National Health and Nutrition Examination Epidemiologic Follow-up Study cohort. *Am J Clin Nutr.* 2005 May; 81(5): 1, 147-1, 154. PMID: 15883441.	Cancer outcomes excluded from NEL review.
van der Pols JC, Bain C, Gunnell D, Smith GD, Frobisher C, Martin RM. Childhood dairy intake and adult cancer risk: 65-year follow-up of the Boyd Orr cohort. *Am J Clin Nutr.* 2007 Dec; 86(6): 1, 722-1, 729. PMID: 18065592.	Cancer outcomes excluded from NEL review.
Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: A systematic review and meta-analysis. *Am J Public Health.* 2007 Apr; 97(4): 667-675. Epub 2007 Feb 28. Review. PMID: 17329656; PMCID: PMC1829363.	Does not answer question; did not examine relationship between milk product intake and health.
Warensjö E, Jansson JH, Berglund L, Boman K, Ahrén B, Weinehall L, Lindahl B, Hallmans G, Vessby B. Estimated intake of milk fat is negatively associated with cardiovascular risk factors and does not increase the risk of a first acute myocardial infarction. A prospective case-control study. *Br J Nutr.* 2004 Apr; 91(4): 635-642. PMID: 15035691.	Does not include milk product intake in analyses.

Xu JY, Qin LQ, Wang PY, Li W, Chang C. Effect of milk tripeptides on blood pressure: a meta-analysis of randomized controlled trials. *Nutrition.* 2008 Oct; 24(10): 933-940. Epub 2008 Jun 17. PMID: 18562172.	Does not answer question; did not examine relationship between milk product intake and health.
Zhang J, Kesteloot H. Milk consumption in relation to incidence of prostate, breast, colon, and rectal cancers: Is there an independent effect? Nu*tr Cancer.* 2005; 53(1): 65-72. PMID: 16351508.	Cancer outcomes excluded from NEL review.
Zhu K, Zhang Q, Foo LH, Trube A, Ma G, Hu X, Du X, Cowell CT, Fraser DR, Greenfield H. Growth, bone mass, and vitamin D status of Chinese adolescent girls three years after withdrawal of milk supplementation. *Am J Clin Nutr.* 2006 Mar; 83(3): 714-721. PMID: 16522922.	Milk enriched with additional calcium.

CHAPTER 20. VEGETABLE AND SOY PROTEIN – CHRONIC DISEASE

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF VEGETABLE PROTEIN, INCLUDING SOY PROTEIN AND CHRONIC DISEASE?

Conclusion statement

Few studies are available and the limited body of evidence suggests that vegetable protein intake does not offer special protection against type 2 diabetes, coronary heart disease and selected cancers.

Grade

Limited

Evidence summary overview

This review included seven studies examining the relationship between vegetable protein or soy protein and coronary heart disease (CHD), type 2 diabetes mellitus (T2D), and cancer published since 2000. Six prospective cohort studies (Halton, 2006; Kelemen, 2005; Halton, 2008; Sluijs, 2010; Song, 2004; Lee, 2009) and one ecological study (Nagata, 2000) were reviewed. Five studies addressed vegetable protein and two studies focused on soy protein. Six of the studies reported on five large (N=37,000 to 85,000) unique prospective cohorts; three of the cohorts were from the US, one from the Netherlands and one from China. The two studies examining soy protein were both conducted outside of the US. Five of the seven studies included only women.

Coronary Heart Disease

Vegetable protein: Two studies (Halton, 2006; Kelemen, 2005) examined the relationship between vegetable protein and CHD. Both studies were prospective cohort studies with women in the US. In the Nurses' Health Study (Halton, 2006), vegetable protein was inversely associated with the risk of CHD in the age- and smoking-adjusted model, but no relationship was observed in multivariate analyses. Using data from the Iowa Women's Health Study, Kelemen et al. (2005) estimated a 30% decrease in CHD mortality from an isoenergetic substitution of vegetable protein for carbohydrate and of vegetable protein for animal protein.

Soy protein: Nagata (2000) conducted an ecological study in Japan and found no relationship between soy protein and heart disease mortality.

Type 2 Diabetes

Vegetable protein: Three prospective cohort studies (Halton, 2008; Sluijs, 2010; Song, 2004) examined the relationship between vegetable protein and T2D. Two studies (Halton, 2008; Song, 2004) were conducted with women in the US, and the third study (Sluijs, 2010) reported on men and women from the Dutch EPIC-cohort in the Netherlands. In the Nurses' Health Study (Halton, 2008), vegetable protein was inversely associated with T2D in the age-adjusted model, but no relationship was observed in multivariate analyses. No relationship between vegetable protein intake and T2D was observed in the Women's Health Study (Song, 2004) or the Dutch cohort of the EPIC study (Sluijs, 2010).

Cancer

Vegetable protein: Substituting vegetable protein for carbohydrate or vegetable protein for animal protein did not significantly affect risk for cancer in the Iowa Women's Health Study (Kelemen, 2005)

Soy protein: In the Shanghai Women's Health Study (Lee, 2009), an inverse relationship between soy protein intake and premenopausal breast cancer was observed, but no association was observed for postmenopausal breast cancer. The median intake for the highest soy protein quintile was 16.02g per day. Nagata (2000) conducted an ecological study in Japan and observed no association between soy protein intake and breast, prostate or lung cancer mortality. However, a positive association between soy protein intake and colorectal cancer mortality and an inverse association between soy protein intake and stomach cancer mortality were observed. The mean (SD) soy protein intake was 6.5 (0.8)g per day.

Evidence summary paragraphs

Halton et al, 2006 (positive quality) examined the association between a low-carbohydrate diet score and risk of CHD in 82,802 women (age 30 to 55 years) from the Nurses' Health Study cohort in the US. Secondary analyses examined the association between vegetable protein intake and CHD risk. Non-fatal myocardial infarction (MI) was self-reported with follow-up confirmation, and fatal coronary events were identified from state vital records and National Death Index or reported by next of kin or the US Postal Service. Diet was assessed using a semi-quantitative food frequency questionnaire (FFQ) in 1980, 1984, 1986, 1990, 1994 and 1998. During 20 years of follow-up, 1,994 cases of CHD were identified. Vegetable protein was inversely associated with the risk of CHD in the age- and smoking-adjusted model (RR between extreme deciles = 0.80; 95% CI: 0.63, 1.00; P for trend = 0.009). However, this association became non-significant in multivariate analyses (RR between extreme deciles = 1.08; 95% CI: 0.82, 1.43; P=0.59). The authors concluded that vegetable protein intake was not significantly associated with the risk of CHD according to multivariate analyses.

Kelemen et al, 2005 (neutral quality) investigated the associations of different protein sources with chronic disease mortality in 29,017 postmenopausal women (age 55 to 69 years) in the Iowa Women's Health Study (US). Mortality was ascertained through linkage with the National Death Index. Diet over the previous year was assessed with a semi-quantitative FFQ at baseline. During 15 years of follow-up, 4,843 new cancers, 739 CHD deaths, 1,676 cancer deaths, and 3,978 total deaths were identified. Among women in the highest intake quintile, CHD mortality decreased by 30% from an isoenergetic substitution of vegetable protein for carbohydrate (multivariate RR=0.70; 95% CI: 0.49, 0.99; P=0.02) and of vegetable for animal protein (multivariate RR=0.70; 95% CI: 0.51, 0.98; P=0.02). Risk ratios for cancer and all-cause mortality were not significant (NS) in fully adjusted models. The authors concluded that dietary proteins from animal and vegetable food sources appear to be differentially associated with mortality from CHD, specifically an inverse association of vegetable protein and a positive association of animal protein, when substituted for carbohydrates in the diet.

Halton et al, 2008 (positive quality) prospectively examined the association between a low-carbohydrate diet score and the risk of T2D among females in the US. Additional analyses examined the relationship between macronutrient intake, including vegetable

protein and T2D. Participants were 85,059 women (age 30 to 55 years, 98% white) from the Nurses' Health Study cohort. Type 2 diabetes was ascertained by self-report on biennial questionnaires. If a participant reported a diagnosis of diabetes, a supplementary questionnaire was mailed regarding symptoms, diagnostic testing and treatment to confirm the diagnosis. Diet over the previous year was assessed by means of a semi-quantitative FFQ in 1980, 1984, 1986, 1990, 1994 and 1998. During 20 years of follow-up, 4,670 cases of T2D were documented. Vegetable protein was inversely associated with the risk of CHD in the age-adjusted model (RR between extreme deciles = 0.90; 95% CI: 0.77, 1.04; P=0.001). However, this association became non-significant in multivariate analyses (RR between extreme deciles = 0.97; 95% CI: 0.81, 1.17; P=0.36). The authors concluded that vegetable protein intakes were not associated with risk of T2D in women.

Sluijs et al, 2010 (positive quality), a prospective cohort study, examined the association among dietary total, vegetable and animal protein intake and T2D incidence among 38,094 participants of the European Prospective Investigation into Cancer and Nutrition (EPIC)-NL study. Participants were from the Dutch EPIC cohort. Incident diabetes was self-reported on questionnaires and verified against medical records. Dietary protein intake was measured with a self-administered validated 178-item FFQ. During 10 years of follow-up, 918 incident cases of diabetes were documented. Vegetable protein intake was not related to diabetes (HR between extreme quartiles = 0.84; 95% CI: 0.70, 1.01; P=0.10). Adjustment for confounders did not materially change these results.

Song et al, 2004 (positive quality) prospectively assessed the associations between red meat consumption and incidence of T2D in US women. Additional analyses examined the relation between vegetable protein intake and T2D. Participants were 37,309 women (age 45 years or more) from the Women's Health Study. Type 2 diabetes was ascertained by self-report on annual questionnaires with confirmation in a subset of the sample. Dietary intake was assessed with a 131-item semi-quantitative FFQ at baseline (1993). Over an average of 8.8 years, 1,558 incident cases of T2D were identified. In the fully adjusted model, multivariate RR comparing extreme quintiles of vegetable protein intake was 0.91 (95% CI: 0.73, 1.14; P=0.83). No association between T2D and vegetable protein intake was observed.

Lee et al, 2009 (positive quality) investigated the association of soy food intake in adolescence and adulthood with breast cancer risk among 73,225 women from the Shanghai Women's Health Study (age 40 and 70 years). Breast cancer was ascertained by a combination of biennial surveys and linkage with the Shanghai Cancer Registry and Shanghai death certificate registry. Diet was assessed with a validated FFQ at baseline and again two to three years later. The FFQ covered "virtually all soy foods consumed in urban Shanghai" including soy milk, tofu, soy products other than tofu, dried soybeans, soybean sprouts and fresh soybeans. Dietary intake during adolescence (between the ages of 13 and 15 years) was estimated using a brief FFQ, including 19 raw food items or groups, and soy food items, including soy milk, tofu and other soy products, dry soybeans, and fresh legumes, including soy beans. Over a mean follow-up of 7.4 years, 594 incident cases of breast cancer were identified. Soy protein intake was inversely associated with the overall risk of breast cancer, although the trend tests were not statistically significant (multivariate RR between extreme quintiles = 0.89; 95% CI: 0.66, 1.15; P=0.158). Soy

protein was inversely associated with the risk of pre-menopausal breast cancer (multivariate RR between extreme quintiles = 0.41; 95% CI: 0.25, 0.70; P<0.001). No significant association with soy protein consumption was found for post-menopausal breast cancer (RR for extreme quintiles = 1.22; 95% CI: 0.87, 1.71; P=0.504). Women in the highest tertile of soy protein intake in both adolescence and adulthood had the greatest decrease in relative risk for pre-menopausal breast cancer compared with women in the lowest tertile of soy protein intake at both of these time points (RR: 0.41; 95% CI: 0.22, 0.75). The authors concluded that this prospective cohort study provided evidence of a protective effect of soy food, including soy protein, intake against pre-menopausal breast cancer.

Nagata, 2000 (neutral quality) examined correlations between soy product intake and mortality rates from several types of cancer and heart disease in an ecological study of approximately 6,000 randomly selected households in Japan. Age-standardized mortality rates for heart disease and stomach, colorectal, lung, breast and prostate cancer were obtained from the National Vital Statistics, 1995. Soy intake was obtained from the National Nutritional Survey Report between 1980 and 1985 by annual three-day diet records. Soy items included in the survey were miso, tofu, fried tofu and soybeans, and the rest of soy products such as soy milk and yuba; estimation of soy protein intake was based on the food table used in the survey. Among men, there was a significant inverse association between soy protein and stomach cancer mortality (R=-0.31; P<0.05) in the adjusted model. Among men and women, there was a significant positive association between soy protein and colorectal cancer mortality (R=0.36; P<0.05; R=0.51; P<0.01, respectively) in adjusted models. No significant associations for lung, breast or prostate cancer were observed in adjusted models. There was NS association between soy protein and heart disease mortality in adjusted models. Nagata reported a modest inverse relationship between soy protein intake and stomach cancer mortality as well as a modest positive relationship between the intake of soy protein and colorectal cancer mortality in this ecological study in Japan.

Overview table

Author, Year, Study Design, Class, Rating	Study Name	Location	Vegetable Protein Association (Pos, Neg, None)	Soy Protein Association (Pos, Neg, None)
Halton et al 2006 Study Design: Prospective Cohort Study Class: B Positive quality	Nurses' Health Study.	US.	Ø Coronary Heart Disease (CHD).	Not examined.

Halton TL, Liu S et al, 2008 Study Design: Prospective cohort Class: B Positive quality	Nurses' Health Study.	US.	Ø Type 2 Diabetes (T2D).	Not examined.
Kelemen et al 2005 Study Design: Prospective cohort study Class: B Neutral quality	Iowa Women's Health Study.	US.	*Substituting veg. protein for CHO:* (-) CHD mortality Ø Cancer Ø All-cause mortality *Substituting veg. protein for animal protein:* (-) CHD mortality Ø Cancer Ø All-cause mortality.	Not examined.
Lee et al 2009 Study Design: Prospective Cohort Study Class: B Positive quality	Shanghai Women's Health Study.	China.	Not examined.	(-) Pre-menopausal breast cancer Ø Post-menopausal breast cancer.
Nagata 2000 Study Design: Longitudinal study Class: C Neutral quality	Ecological study.	Japan.	Not examined.	Ø Heart disease mortality Ø Breast, prostate cancer mortality (+) Colorectal cancer mortality.
Sluijs I, Beulens JW et al, 2010 Study Design: Prospective cohort study Class: B Positive quality	European Prospective Investigation into Cancer and Nutrition (EPIC)-NL	The Netherlands.	Ø T2D.	Not examined.

Song Y, Manson JE et al, 2004 Study Design: Prospective cohort study Class: B Positive quality	Women's Health Study.	US.	Ø T2D.	Not examined.

Search plan and results

Inclusion criteria

- January 2000 to September 2009
- Prospective cohort studies on colorectal, breast and prostate cancers
- All study types for other health outcomes
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children two to 18 years; Adults 19 years and older
- *Populations:* Healthy, those with elevated chronic disease risk.

Exclusion criteria

- Medical treatment or therapy
- Systematic reviews and meta-analyses on colorectal, breast and prostate cancers
- Narrative reviews
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "overweight"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mh:NoExp] OR “heart diseases”[mh] OR "Coronary Disease"[Mesh] OR “blood pressure”[mh] OR “chronic disease”[mh] OR obesity[mh] OR "Body Weights and Measures"[mh]) AND ("Soybean Proteins"[Mesh] OR "Vegetable Proteins"[Mesh]) Limit Eng/humans ("Soybean Proteins"[Mesh] OR "Vegetable Proteins"[Mesh]) AND ("Prostatic Neoplasms"[Mesh] OR "Breast Neoplasms"[Mesh] OR "Colorectal Neoplasms"[mesh]) clinical trials "Cohort Studies"[Mesh]

Date searched: 09/19/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 343
- Total articles identified to review from electronic databases: 86
- Articles identified via handsearch or other means: 8
- Number of Primary Articles Identified: 19
- Number of Review Articles Identified: 5
- Total Number of Articles Identified: 24
- Number of Articles Reviewed but Excluded: 70

Included articles (References)

What is the relationship between the intake of vegetable protein, including soy protein and chronic disease?

1. Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. *Am J Clin Nutr*. 2008 Feb; 87 (2): 339-346. PMID: 18258623. (Hand search)
2. Kelemen LE, Kushi LH, Jacobs DR Jr, Cerhan JR. Associations of dietary protein with disease and mortality in a prospective study of postmenopausal women. *Am J Epidemiol*. 2005 Feb 1; 161 (3): 239-249. PMID: 15671256.
3. Lee SA, Shu XO, Li H, Yang G, Cai H, Wen W, Ji BT, Gao J, Gao YT, Zheng W. Adolescent and adult soy food intake and breast cancer risk: Results from the Shanghai Women's Health Study. *Am J Clin Nutr*. 2009 Jun; 89 (6): 1, 920-1, 926. Epub 2009 Apr 29. PMID: 19403632; PMCID: PMC2683002.
4. Sluijs I, Beulens JW, van der A DL, Spijkerman AM, Grobbee DE, van der Schouw YT. Dietary intake of total, animal, and vegetable protein and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-NL study. *Diabetes Care.* 2010 Jan; 33(1): 43-48. Epub 2009 Oct 13. PMID: 19825820; PMCID: PMC2797984. (Hand search)
5. Song Y, Manson JE, Buring JE, Liu S. A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: The women's health study. *Diabetes Care*. 2004 Sep; 27 (9): 2, 108-2, 115. PMID: 15333470. (Hand search)
6. Nagata C. Ecological study of the association between soy product intake and mortality from cancer and heart disease in Japan. *Int J Epidemiol*. 2000 Oct; 29 (5): 832-836. PMID: 11034965.

What is the relationship between the intake of vegetable protein and blood pressure among adults without hypertension?

1. Stamler J, Liu K, Ruth KJ, Pryer J, Greenland P. Eight-year blood pressure change in middle-aged men: Relationship to multiple nutrients. *Hypertension.* 2002 May; 39 (5): 1, 000-1, 0006. PMID: 12019283. (Hand search)
2. Wang YF, Yancy WS Jr, Yu D, Champagne C, Appel LJ, Lin PH. The relationship between dietary protein intake and blood pressure: results from the PREMIER study. *J Hum Hypertens*. 2008 Nov; 22 (11): 745-754. Epub 2008 Jun 26. PMID: 18580887.
3. Steffen LM, Kroenke CH, Yu X, Pereira MA, Slattery ML, Van Horn L, Gross MD, Jacobs DR Jr. Associations of plant food, dairy product, and meat intakes

with 15-year incidence of elevated blood pressure in young black and white adults: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr.* 2005 Dec; 82 (6): 1, 169-1, 177; quiz 1, 363-1, 364. PMID: 16332648. (Hand search)

4. Elliott P, Stamler J, Dyer AR, Appel L, Dennis B, Kesteloot H, Ueshima H, Okayama A, Chan Q, Garside DB, Zhou B. Association between protein intake and blood pressure: The INTERMAP Study. *Arch Intern Med.* 2006 Jan 9; 166 (1): 79-87. PMID: 16401814.
5. Umesawa M, Sato S, Imano H, Kitamura A, Shimamoto T, Yamagishi K, Tanigawa T, Iso H. Relations between protein intake and blood pressure in Japanese men and women: The Circulatory Risk in Communities Study (CIRCS). *Am J Clin Nutr*. 2009 Aug; 90 (2): 377-384. Epub 2009 Jun 10. PMID: 19515740.

What is the relationship between the intake of soy protein and blood pressure among adults without hypertension?

1. Teede HJ, Dalais FS, Kotsopoulos D, Liang YL, Davis S, McGrath BP. Dietary soy has both beneficial and potentially adverse cardiovascular effects: A placebo-controlled study in men and postmenopausal women. *J Clin Endocrinol Metab.* 2001 Jul; 86 (7): 3, 053-3, 060. PMID: 11443167.
2. Liao FH, Shieh MJ, Yang SC, Lin SH, Chien YW. Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in overweight adults. *Nutrition.* 2007 Jul-Aug; 23 (7-8): 551-556. Epub 2007 Jun 15. PMID: 17574819.
3. Pan A, Franco OH, Ye J, Demark-Wahnefried W, Ye X, Yu Z, Li H, Lin X. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in middle-aged and elderly Chinese. *J Nutr.* 2008 Dec; 138 (12): 2, 413-2, 421. PMID: 19022966.

What is the relationship between the intake of soy protein and body weight?

Systematic Review

1. Cope MB, Erdman JW Jr, Allison DB. The potential role of soy foods in weight and adiposity reduction: An evidence-based review. *Obes Rev.* 2008 May; 9 (3): 219-235. Review. PMID: 18419671. (Hand search)

Primary Citations

1. Liao FH, Shieh MJ, Yang SC, Lin SH, Chien YW. Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in overweight adults. *Nutrition*. 2007 Jul-Aug; 23 (7-8): 551-556. Epub 2007 Jun 15. PMID: 17574819.
2. McVeigh BL, Dillingham BL, Lampe JW, Duncan AM. Effect of soy protein varying in isoflavone content on serum lipids in healthy young men. *Am J Clin Nutr.* 2006 Feb; 83 (2): 244-251. PMID: 16469981.
3. Pan A, Franco OH, Ye J, Demark-Wahnefried W, Ye X, Yu Z, Li H, Lin X. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in middle-aged and elderly Chinese. *J Nutr.* 2008 Dec; 138 (12): 2, 413-2, 421. PMID: 19022966.

Systematic Reviews / Meta-Analyses

1. Yang G, Shu XO, Jin F, Zhang X, Li HL, Li Q, Gao YT, Zheng W. Longitudinal study of soy food intake and blood pressure among middle-aged and elderly Chinese women. *Am J Clin Nutr*. 2005 May; 81 (5): 1, 012-1, 017. PMID: 15883423.
2. Harland JI, Haffner TA. Systematic review, meta-analysis and regression of randomized controlled trials reporting an association between an intake of circa 25g soy protein per day and blood cholesterol. *Atherosclerosis*. 2008 Sep; 200 (1): 13-27. Epub 2008 Apr 15. Review. PMID: 18534601.

What is the relationship between the intake of soy protein and blood lipids among adults without hyperlipidemia?

1. Reynolds K, Chin A, Lees KA, Nguyen A, Bujnowski D, He J. A meta-analysis of the effect of soy protein supplementation on serum lipids. *Am J Cardiol*. 2006 Sep 1; 98 (5): 633-640. Epub 2006 Jul 12. PMID: 16923451. (Hand search)
2. Weggemans RM, Trautwein EA. Relation between soy-associated isoflavones and LDL and HDL cholesterol concentrations in humans: A meta-analysis. *Eur J Clin Nutr.* 2003 Aug; 57 (8): 940-946. PMID: 12879088.
3. Zhan S, Ho SC. Meta-analysis of the effects of soy protein containing isoflavones on the lipid profile. *Am J Clin Nutr.* 2005 Feb; 81 (2): 397-408. PMID: 15699227.

Primary Citations

1. Liao FH, Shieh MJ, Yang SC, Lin SH, Chien YW. Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in overweight adults. *Nutrition. 2007* Jul-Aug; 23 (7-8): 551-556. Epub 2007 Jun 15. PMID: 17574819.
2. Pan A, Franco OH, Ye J, Demark-Wahnefried W, Ye X, Yu Z, Li H, Lin X. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in middle-aged and elderly Chinese. *J Nutr*. 2008 Dec; 138 (12): 2, 413-2, 421. PMID: 19022966.
3. He J, Gu D, Wu X, Chen J, Duan X, Chen J, Whelton PK. Effect of soybean protein on blood pressure: A randomized, controlled trial. *Ann Intern Med.* 2005 Jul 5; 143 (1):1-9. PMID: 15998749.
4. Alonso A, Beunza JJ, Bes-Rastrollo M, Pajares RM, Martínez-González MA. Vegetable protein and fiber from cereal are inversely associated with the risk of hypertension in a Spanish cohort. *Arch Med Res*. 2006 Aug; 37 (6): 778-786. PMID: 16824939.
5. Halton TL, Willett WC, Liu S, Manson JE, Albert CM, Rexrode K, Hu FB. Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med*. 2006 Nov 9; 355 (19): 1, 991-2, 002. PMID: 17093250. (Hand search)

Excluded articles

Article	Reason for Exclusion
Ashton EL, Dalais FS, Ball MJ. Effect of meat replacement by tofu on CHD risk factors including copper induced LDL oxidation. *J Am Coll Nutr.* 2000 Nov-Dec; 19 (6): 761-767. PMID: 11194529.	Included in Zhan, 2005.

Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Hu FB, Willett WC. Dietary soya intake alters plasma antioxidant status and lipid peroxidation in postmenopausal women with the metabolic syndrome. *Br J Nutr.* 2007 Oct; 98 (4): 807-813. Epub 2007 May 17. PMID: 17506931.	Participants diagnosed with metabolic syndrome.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Hu FB, Willett WC. Soy consumption, markers of inflammation, and endothelial function: A cross-over study in postmenopausal women with the metabolic syndrome. *Diabetes Care*. 2007 Apr; 30 (4): 967-973. PMID: 17392557.	Participants diagnosed with metabolic syndrome.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Padyab M, Hu FB, Willett WC. Soy inclusion in the diet improves features of the metabolic syndrome: a randomized crossover study in postmenopausal women. *Am J Clin Nutr.* 2007 Mar; 85 (3): 735-741. PMID: 17344494.	Participants diagnosed with metabolic syndrome.
Azadbakht L, Shakerhosseini R, Atabak S, Jamshidian M, Mehrabi Y, Esmaill-Zadeh A. Beneficiary effect of dietary soy protein on lowering plasma levels of lipid and improving kidney function in type II diabetes with nephropathy. *Eur J Clin Nutr.* 2003 Oct; 57 (10): 1, 292-1, 294. PMID: 14506491.	Participants diagnosed with type 2 diabetes with nephropathy.
Badger TM, Ronis MJ, Simmen RC, Simmen FA. Soy protein isolate and protection against cancer. *J Am Coll Nutr.* 2005 Apr; 24 (2): 146S-149S. PMID: 15798082.	Publication is a summary of a review presented at a professional meeting.
Blum A, Lang N, Vigder F, Israeli P, Gumanovsky M, Lupovitz S, Elgazi A, Peleg A, Ben-Ami M. Effects of soy protein on endothelium-dependent vasodilatation and lipid profile in postmenopausal women with mild hypercholesterolemia. *Clin Invest Med.* 2003 Feb; 26 (1): 20-26. PMID: 12659466.	Participants had mild hypercholesterolemia; included in Harland, 2008.
Brown BD, Thomas W, Hutchins A, Martini MC, Slavin JL. Types of dietary fat and soy minimally affect hormones and biomarkers associated with breast cancer risk in premenopausal women. *Nutr Cancer.* 2002; 43 (1): 22-30. PMID: 12467131.	Does not answer question: examined biomarkers associated with breast cancer, not incidence of breast cancer (not a prospective cohort study).
Chan YH, Lau KK, Yiu KH, Li SW, Chan HT, Tam S, Shu XO, Lau CP, Tse HF. Isoflavone intake in persons at high risk of cardiovascular events: Implications for vascular endothelial function and the carotid atherosclerotic burden. *Am J Clin Nutr.* 2007 Oct; 86 (4): 938-945. PMID: 17921368.	Participants (94%) had CAD or stroke; does not answer question: Outcomes were carotid intima-media thickness and flow-mediated dilation
Chen ST, Ferng SH, Yang CS, Peng SJ, Lee HR, Chen JR. Variable effects of soy protein on plasma lipids in hyperlipidemic and normolipidemic hemodialysis patients. *Am J Kidney Dis.* 2005 Dec; 46 (6): 1, 099-1, 106. PMID: 16310576.	Participants were hemodialysis patients.

Chiechi LM, Secreto G, Vimercati A, Greco P, Venturelli E, Pansini F, Fanelli M, Loizzi P, Selvaggi L. The effects of a soy rich diet on serum lipids: the Menfis randomized trial. *Maturitas*. 2002 Feb 26; 41 (2): 97-104. PMID: 11836040.	Dropout rate higher than inclusion criteria.
Cicero AF, Minardi M, Mirembe S, Pedro E, Gaddi A. Effects of a new low dose soy protein/beta-sitosterol association on plasma lipid levels and oxidation. *Eur J Nutr.* 2004 Oct; 43 (5): 319-322. Epub 2004 Jan 26. PMID: 15309453.	Participants were hypercholesterolemic; does not answer question: Tested a formulation of soy protein with added beta-sitosterol.
Cuevas AM, Irribarra VL, Castillo OA, Yañez MD, Germain AM. Isolated soy protein improves endothelial function in postmenopausal hypercholesterolemic women. *Eur J Clin Nutr.* 2003 Aug; 57 (8): 889-894. PMID: 12879082.	Participants were hypercholesterolemic.
Cupisti A, D'Alessandro C, Ghiadoni L, Morelli E, Panichi V, Barsotti G. Effect of a soy protein diet on serum lipids of renal transplant patients. *J Ren Nutr.* 2004 Jan; 14 (1): 31-35. PMID: 14740328.	Participants had renal transplantation.
Desroches S, Mauger JF, Ausman LM, Lichtenstein AH, Lamarche B. Soy protein favorably affects LDL size independently of isoflavones in hypercholesterolemic men and women. *J Nutr.* 2004 Mar; 134 (3): 574-579. PMID: 14988449.	Participants were hypercholesterolemic.
Dewell A, Weidner G, Sumner MD, Barnard RJ, Marlin RO, Daubenmier JJ, Chi C, Carroll PR, Ornish D. Relationship of dietary protein and soy isoflavones to serum IGF-1 and IGF binding proteins in the Prostate Cancer Lifestyle Trial. *Nutr Cancer.* 2007; 58 (1): 35-42. PMID: 17571965.	Participants were diagnosed with prostate cancer.
Dillingham BL, McVeigh BL, Lampe JW, Duncan AM. Soy protein isolates of varying isoflavone content exert minor effects on serum reproductive hormones in healthy young men. *J Nutr.* 2005 Mar; 135 (3): 584-591. PMID: 15735098.	Does not answer question: Examined soy protein intake on reproductive hormones.
Engelman HM, Alekel DL, Hanson LN, Kanthasamy AG, Reddy MB. Blood lipid and oxidative stress responses to soy protein with isoflavones and phytic acid in postmenopausal women. *Am J Clin Nutr.* 2005 Mar; 81 (3): 590-596. PMID: 15755827.	Does not answer question: Examined impact of soy protein components (isoflavones and phytate) on blood lipids and oxidative stress.
Gardner CD, Messina M, Kiazand A, Morris JL, Franke AA. Effect of two types of soy milk and dairy milk on plasma lipids in hypercholesterolemic adults: A randomized trial. *J Am Coll Nutr.* 2007 Dec; 26 (6): 669-677. PMID: 18187432.	Participants were hypercholesterolemic; included in Harland, 2008.
Gardner CD, Newell KA, Cherin R, Haskell WL. The effect of soy protein with or without isoflavones relative to milk protein on plasma lipids in hypercholesterolemic postmenopausal women. *Am J Clin Nutr*. 2001 Apr; 73 (4): 728-735. PMID: 11273847.	Participants were hypercholesterolemic; included in Weggemans, 2003.

Genovese MI, Lajolo FM. Isoflavones in soy-based foods consumed in Brazil: Levels, distribution, and estimated intake. *J Agric Food Chem*. 2002 Oct 9; 50 (21): 5, 987-5, 993. PMID: 12358470.	Does not include health outcomes in analyses.
Giampietro PG, Bruno G, Furcolo G, Casati A, Brunetti E, Spadoni GL, Galli E. Soy protein formulas in children: No hormonal effects in long-term feeding. *J Pediatr Endocrinol Metab.* 2004 Feb;17 (2): 191-196. PMID: 15055353.	Does not answer question: Examined hormonal and metabolic effects of long-term soy protein formula feeding.
Goldin BR, Brauner E, Adlercreutz H, Ausman LM, Lichtenstein AH. Hormonal response to diets high in soy or animal protein without and with isoflavones in moderately hypercholesterolemic subjects. *Nutr Cancer*. 2005; 51 (1): 1-6. PMID: 15749623.	Participants were hypercholesterolemic; does not answer question: Examined hormonal response to diets high in soy or animal protein.
Grainger EM, Schwartz SJ, Wang S, Unlu NZ, Boileau TW, Ferketich AK, Monk JP, Gong MC, Bahnson RR, DeGroff VL, Clinton SK. A combination of tomato and soy products for men with recurring prostate cancer and rising prostate specific antigen. *Nutr Cancer*. 2008; 60 (2): 145-154. PMID: 18444145.	Participants diagnosed with prostate cancer.
Greany KA, Nettleton JA, Wangen KE, Thomas W, Kurzer MS. Consumption of isoflavone-rich soy protein does not alter homocysteine or markers of inflammation in postmenopausal women. *Eur J Clin Nutr.* 2008 Dec; 62 (12): 1, 419-1, 425. Epub 2007 Sep 5. PMID: 17805230.	Does not answer question: Does not examine outcome of interest (examines homocysteine, C-reactive protein and adhesion molecules).
Greany KA, Nettleton JA, Wangen KE, Thomas W, Kurzer MS. Probiotic consumption does not enhance the cholesterol-lowering effect of soy in postmenopausal women. *J Nutr.* 2004 Dec; 134 (12): 3, 277-3, 283. PubMed PMID: 15570025.	Participants were hypercholesterolemic; included in Harland, 2008.
Hamilton-Reeves JM, Rebello SA, Thomas W, Kurzer MS, Slaton JW. Effects of soy protein isolate consumption on prostate cancer biomarkers in men with HGPIN, ASAP, and low-grade prostate cancer. *Nutr Cancer*. 2008; 60 (1): 7-13. PMID: 18444130.	Not a prospective cohort study examining incidence of prostate cancer. Outcomes were prostate cancer biomarkers.
Hamilton-Reeves JM, Rebello SA, Thomas W, Slaton JW, Kurzer MS. Soy protein isolate increases urinary estrogens and the ratio of 2:16alpha-hydroxyestrone in men at high risk of prostate cancer. *J Nutr.* 2007 Oct; 137 (10): 2, 258-2, 263. PMID: 17885008.	Not a prospective cohort study examining incidence of prostate cancer. Outcomes were prostate cancer biomarkers.
Hamilton-Reeves JM, Rebello SA, Thomas W, Slaton JW, Kurzer MS. Isoflavone-rich soy protein isolate suppresses androgen receptor expression without altering estrogen receptor-beta expression or serum hormonal profiles in men at high risk of prostate cancer. *J Nutr.* 2007 Jul; 137 (7): 1, 769-1, 775. PMID: 17585029.	Not a prospective cohort study examining incidence of prostate cancer. Outcomes were prostate cancer biomarkers.

Harrison RA, Sagara M, Rajpura A, Armitage L, Birt N, Birt CA, Yamori Y. Can foods with added soya-protein or fish-oil reduce risk factors for coronary disease? A factorial randomised controlled trial. *Nutr Metab Cardiovasc Dis*. 2004 Dec; 14 (6): 344-350. PMID: 15853118.	Participants had elevated total cholesterol or blood pressure.
Hartman JW, Tang JE, Wilkinson SB, Tarnopolsky MA, Lawrence RL, Fullerton AV, Phillips SM. Consumption of fat-free fluid milk after resistance exercise promotes greater lean mass accretion than does consumption of soy or carbohydrate in young, novice, male weightlifters. *Am J Clin Nutr.* 2007 Aug; 86 (2): 373-381. PMID: 17684208.	Does not answer question: Does not examine relationship between vegetable protein and health (examined consumption of various isocaloric drinks on lean mass accretion following resistance training).
Hoie LH, Guldstrand M, Sjoholm A, Graubaum HJ, Gruenwald J, Zunft HJ, Lueder W. Cholesterol-lowering effects of a new isolated soy protein with high levels of nondenaturated protein in hypercholesterolemic patients. *Adv Ther.* 2007 Mar-Apr; 24 (2): 439-447. PMID: 17565935.	Participants were hypercholesterolemic; included in Harland, 2008.
Hoie LH, Morgenstern EC, Gruenwald J, Graubaum HJ, Busch R, Lüder W, Zunft HJ. A double-blind placebo-controlled clinical trial compares the cholesterol-lowering effects of two different soy protein preparations in hypercholesterolemic subjects. *Eur J Nutr.* 2005 Mar; 44 (2): 65-71. Epub 2004 Apr 5. PMID: 15309422.	Participants were hypercholesterolemic; included in Harland, 2008.
Hori G, Wang MF, Chan YC, Komatsu T, Wong Y, Chen TH, Yamamoto K, Nagaoka S, Yamamoto S. Soy protein hydrolyzate with bound phospholipids reduces serum cholesterol levels in hypercholesterolemic adult male volunteers. *Biosci Biotechnol Biochem*. 2001 Jan; 65 (1): 72-78. PMID: 11272848.	Participants were hypercholesterolemic.
Jenkins DJ, Kendall CW, Jackson CJ, Connelly PW, Parker T, Faulkner D, Vidgen E, Cunnane SC, Leiter LA, Josse RG. Effects of high- and low-isoflavone soyfoods on blood lipids, oxidized LDL, homocysteine, and blood pressure in hyperlipidemic men and women. *Am J Clin Nutr*. 2002 Aug; 76 (2): 365-372. PMID: 12145008.	Participants were hyperlipidemic; included in Weggemans, 2003.
Jenkins DJ, Kendall CW, D'Costa MA, Jackson CJ, Vidgen E, Singer W, Silverman JA, Koumbridis G, Honey J, Rao AV, Fleshner N, Klotz L. Soy consumption and phytoestrogens: effect on serum prostate specific antigen when blood lipids and oxidized low-density lipoprotein are reduced in hyperlipidemic men. *J Urol.* 2003 Feb; 169 (2): 507-511. PMID: 12544298.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Garsetti M, Rosenberg-Zand RS, Jackson CJ, Agarwal S, Rao AV, Diamandis EP, Parker T, Faulkner D, Vuksan V, Vidgen E. Effect of soy protein foods on low-density lipoprotein oxidation and ex vivo sex hormone receptor activity: A controlled crossover trial. *Metabolism.* 2000 Apr; 49 (4): 537-543. PMID: 10778882.	Participants were hyperlipidemic; included in Harland, 2008.

Jenkins DJ, Wong JM, Kendall CW, Esfahani A, Ng VW, Leong TC, Faulkner DA, Vidgen E, Greaves KA, Paul G, Singer W. The effect of a plant-based low-carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. *Arch Intern Med.* 2009 Jun 8; 169 (11): 1, 046-1, 054. Erratum in: Arch Intern Med. 2009 Sep 14; 169 (16): 1, 490. PMID: 19506174.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Faulkner DA, Kemp T, Marchie A, Nguyen TH, Wong JM, de Souza R, Emam A, Vidgen E, Trautwein EA, Lapsley KG, Josse RG, Leiter LA, Singer W. Long-term effects of a plant-based dietary portfolio of cholesterol-lowering foods on blood pressure. *Eur J Clin Nutr*. 2008 Jun; 62 (6): 781-788. Epub 2007 Apr 25. PMID: 17457340.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Marchie A, Faulkner D, Vidgen E, Lapsley KG, Trautwein EA, Parker TL, Josse RG, Leiter LA, Connelly PW. The effect of combining plant sterols, soy protein, viscous fibers, and almonds in treating hypercholesterolemia. *Metabolism*. 2003 Nov; 52 (11): 1, 478-1, 483. PMID: 14624410.	Participants were hypercholesterolemic; included in Cope, 2008.
Jenkins DJ, Kendall CW, Vidgen E, Mehling CC, Parker T, Seyler H, Faulkner D, Garsetti M, Griffin LC, Agarwal S, Rao AV, Cunnane SC, Ryan MA, Connelly PW, Leiter LA, Vuksan V, Josse R. The effect on serum lipids and oxidized low-density lipoprotein of supplementing self-selected low-fat diets with soluble-fiber, soy and vegetable protein foods. *Metabolism.* 2000 Jan; 49 (1): 67-72. PMID: 10647066.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Faulkner D, Vidgen E, Trautwein EA, Parker TL, Marchie A, Koumbridis G, Lapsley KG, Josse RG, Leiter LA, Connelly PW. A dietary portfolio approach to cholesterol reduction: combined effects of plant sterols, vegetable proteins, and viscous fibers in hypercholesterolemia. *Metabolism*. 2002 Dec; 51 (12): 1, 596-1, 604. PMID: 12489074.	Participants were hypercholesterolemic.
Jones PJ, Raeini-Sarjaz M, Jenkins DJ, Kendall CW, Vidgen E, Trautwein EA, Lapsley KG, Marchie A, Cunnane SC, Connelly PW. Effects of a diet high in plant sterols, vegetable proteins, and viscous fibers (dietary portfolio) on circulating sterol levels and red cell fragility in hypercholesterolemic subjects. *Lipids.* 2005 Feb; 40 (2): 169-174. PMID: 15884765.	Participants were hypercholesterolemic.
Kreijkamp-Kaspers S, Kok L, Bots ML, Grobbee DE, Lampe JW, van der Schouw YT. Randomized controlled trial of the effects of soy protein containing isoflavones on vascular function in postmenopausal women. *Am J Clin Nutr.* 2005 Jan; 81 (1): 189-195. PMID: 15640479.	Dropout rate higher than inclusion criteria.
Lichtenstein AH, Jalbert SM, Adlercreutz H, Goldin BR, Rasmussen H, Schaefer EJ, Ausman LM. Lipoprotein response to diets high in soy or animal protein with and without isoflavones in moderately hypercholesterolemic subjects. *Arterioscler Thromb Vasc Biol.* 2002 Nov 1; 22 (11): 1, 852-1, 858. PMID: 12426215.	Participants were hypercholesterolemic; included in Reynolds, 2006.

Luiking YC, Deutz NE, Jäkel M, Soeters PB. Casein and soy protein meals differentially affect whole-body and splanchnic protein metabolism in healthy humans. *J Nutr.* 2005 May; 135 (5): 1, 080-1, 087. PMID: 15867285.	Does not answer question: study examined protein metabolism, not relationship between protein and selected health outcomes.
Ma Y, Chiriboga D, Olendzki BC, Nicolosi R, Merriam PA, Ockene IS. Effect of soy protein containing isoflavones on blood lipids in moderately hypercholesterolemic adults: A randomized controlled trial. *J Am Coll Nutr.* 2005 Aug; 24 (4): 275-285. PMID: 16093405.	Participants were hypercholesterolemic.
Mackey R, Ekangaki A, Eden JA. The effects of soy protein in women and men with elevated plasma lipids. *Biofactors*. 2000; 12 (1-4): 251-257. PMID: 11216493.	Participants were hyperlipidemic.
Maskarinec G. Soy foods for breast cancer survivors and women at high risk for breast cancer? *J Am Diet Assoc.* 2005 Oct; 105 (10): 1, 524-1, 528. PMID: 16183350.	Publication is Commentary.
Matthan NR, Jalbert SM, Ausman LM, Kuvin JT, Karas RH, Lichtenstein AH. Effect of soy protein from differently processed products on cardiovascular disease risk factors and vascular endothelial function in hypercholesterolemic subjects. *Am J Clin Nutr.* 2007 Apr; 85 (4): 960-966. Erratum in: *Am J Clin Nutr.* 2007 Aug; 86 (2): 525. PMID: 17413093.	Participants were hypercholesterolemic; included in Harland, 2008.
McVeigh BL, Dillingham BL, Lampe JW, Duncan AM. Effect of soy protein varying in isoflavone content on serum lipids in healthy young men. *Am J Clin Nutr.* 2006 Feb; 83 (2): 244-251. PMID: 16469981.	**Included in body weight review, but excluded from cholesterol review because included in Harland, 2008.
Merritt JC. Metabolic syndrome: soybean foods and serum lipids. *J Natl Med Assoc.* 2004 Aug; 96 (8): 1, 032-1, 041. PubMed PMID: 15303407; Central PMCID: PMC2568482.	Study design is narrative review.
Möllsten AV, Dahlquist GG, Stattin EL, Rudberg S. Higher intakes of fish protein are related to a lower risk of microalbuminuria in young Swedish type 1 diabetic patients. *Diabetes Care*. 2001 May; 24 (5): 805-810. PMID: 11347734.	Participants were diagnosed with type 1 diabetes.
Nagata C, Shimizu H, Takami R, Hayashi M, Takeda N, Yasuda K. Association of blood pressure with intake of soy products and other food groups in Japanese men and women. *Prev Med.* 2003 Jun; 36 (6): 692-697. PMID: 12744912.	Does not answer question: Examined soy food intake, not soy protein.
Puska P, Korpelainen V, Høie LH, Skovlund E, Smerud KT. Isolated soya protein with standardized levels of isoflavones, cotyledon soya fibres and soya phospholipids improves plasma lipids in hypercholesterolaemia: A double-blind, placebo-controlled trial of a yoghurt formulation. *Br J Nutr.* 2004 Mar; 91 (3): 393-401. PMID: 15005825.	Does not answer question: Examined yogurt formulation containing isolated soya protein, isoflavones, cotyledon soya fibers and soya phospholipids.

Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M; American Heart Association Nutrition Committee. Soy protein, isoflavones, and cardiovascular health: An American Heart Association Science Advisory for professionals from the Nutrition Committee. *Circulation.* 2006 Feb 21; 113 (7): 1, 034-1, 044. Epub 2006 Jan 17. PMID: 16418439.	Publication is AHA Science Advisory; reference list was reviewed.
Sagara M, Kanda T, NJelekera M, Teramoto T, Armitage L, Birt N, Birt C, Yamori Y. Effects of dietary intake of soy protein and isoflavones on cardiovascular disease risk factors in high risk, middle-aged men in Scotland. *J Am Coll Nutr.* 2004 Feb; 23 (1): 85-91. PMID: 14963058.	Included in Harland, 2008.
Sanders TA, Dean TS, Grainger D, Miller GJ, Wiseman H. Moderate intakes of intact soy protein rich in isoflavones compared with ethanol-extracted soy protein increase HDL but do not influence transforming growth factor beta(1) concentrations and hemostatic risk factors for coronary heart disease in healthy subjects. *Am J Clin Nutr.* 2002 Aug; 76 (2): 373-377. PMID: 12145009.	Does not answer question; design of the study does not allow for comparison between diets with and without soy protein. The study addresses the impact of isoflavones from soy on CHD risk.
Shahbazian H, Reza A, Javad S, Heshmatollah S, Mahmood L, Ali A, Hosain HM. Beneficial effects of soy protein isoflavones on lipid and blood glucose concentrations in type 2 diabetic subjects. *Saudi Med J.* 2007 Apr; 28 (4): 652-654. PMID: 17457503.	Participants diagnosed with type 2 diabetes.
Sirtori CR, Eberini I, Arnoldi A. Hypocholesterolaemic effects of soya proteins: Results of recent studies are predictable from the Anderson meta-analysis data. *Br J Nutr*. 2007 May; 97 (5): 816-822. Review. PMID: 17408521.	Not a systematic review or original research study (examines previous research using a predictive model).
Spence LA, Lipscomb ER, Cadogan J, Martin B, Wastney ME, Peacock M, Weaver CM. The effect of soy protein and soy isoflavones on calcium metabolism in postmenopausal women: A randomized crossover study. *Am J Clin Nutr*. 2005 Apr; 81 (4): 916-922. PMID: 15817872.	Does not answer question: Outcome was calcium metabolism, not selected health outcome.
St-Onge MP, Claps N, Wolper C, Heymsfield SB. Supplementation with soy-protein-rich foods does not enhance weight loss. *J Am Diet Assoc.* 2007 Mar; 107 (3): 500-505. PMID: 17324670.	Dropout rate higher than inclusion criteria.
Taku K, Umegaki K, Sato Y, Taki Y, Endoh K, Watanabe S. Soy isoflavones lower serum total and LDL cholesterol in humans: A meta-analysis of 11 randomized controlled trials. *Am J Clin Nutr.* 2007 Apr; 85 (4): 1, 148-1, 156. Erratum in: *Am J Clin Nutr*. 2007 Sep; 86 (3): 809. PMID: 17413118.	Does not answer question: Examined soy isoflavones, not soy protein.
Teede HJ, Dalais FS, Kotsopoulos D, Liang YL, Davis S, McGrath BP. Dietary soy has both beneficial and potentially adverse cardiovascular effects: A placebo-controlled study in men and postmenopausal women. *J Clin Endocrinol Metab.* 2001 Jul; 86 (7): 3, 053-3, 060. PMID: 11443167.	** Included in blood pressure review but excluded from cholesterol review because included in Harland, 2008 and Weggemans, 2003.

Teede HJ, Giannopoulos D, Dalais FS, Hodgson J, McGrath BP. Randomized, controlled, cross-over trial of soy protein with isoflavones on blood pressure and arterial function in hypertensive subjects. *J Am Coll Nutr.* 2006 Dec; 25 (6): 533-540. PMID: 17229901.	Participants were hypertensive.
Tonstad S, Smerud K, Høie L. A comparison of the effects of two doses of soy protein or casein on serum lipids, serum lipoproteins and plasma total homocysteine in hypercholesterolemic subjects. *Am J Clin Nutr.* 2002 Jul; 76 (1): 78-84. PMID: 12081819.	Participants were hypercholesterolemic.
Trock BJ, Hilakivi-Clarke L, Clarke R. Meta-analysis of soy intake and breast cancer risk. *J Natl Cancer Inst.* 2006 Apr 5; 98 (7): 459-471. PMID: 16595782.	Studies included in meta-analysis were excluded based on SC criteria; no prospective cohort studies with soy protein included in review.
Wang Y, Jones PJ, Ausman LM, Lichtenstein AH. Soy protein reduces triglyceride levels and triglyceride fatty acid fractional synthesis rate in hypercholesterolemic subjects. Atherosclerosis. 2004 Apr;173 (2): 269-275. PMID: 15064101.	Participants were hypercholesterolemic.
Wangen KE, Duncan AM, Xu X, Kurzer MS. Soy isoflavones improve plasma lipids in normocholesterolemic and mildly hypercholesterolemic postmenopausal women. Am *J Clin Nutr*. 2001 Feb; 73 (2): 225-231. PMID: 11157317.	Included in Zhan, 2005.
Weghuber D, Widhalm K. Effect of three-month treatment of children and adolescents with familial and polygenic hypercholesterolaemia with a soya-substituted diet. *Br J Nutr*. 2008 Feb; 99 (2): 281-286. Epub 2007 Aug 13. PMID: 17697400.	Participants were children and adolescents with familial or polygenic hypercholesterolemia.
Xu X, Duncan AM, Wangen KE, Kurzer MS. Soy consumption alters endogenous estrogen metabolism in postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2000 Aug; 9 (8): 781-786. PMID: 10952094.	Does not answer question: Examines soy consumption and estrogen metabolism.
Yildirir A, Tokgozoglu SL, Oduncu T, Oto A, Haznedaroglu I, Akinci D, Koksal G, Sade E, Kirazli S, Kes S. Soy protein diet significantly improves endothelial function and lipid parameters. *Clin Cardiol.* 2001 Nov; 24 (11): 711-716. PMID: 11714128.	Participants were hypercholesterolemic

CHAPTER 21. VEGETABLE PROTEIN – BLOOD PRESSURE

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF VEGETABLE PROTEIN AND BLOOD PRESSURE AMONG ADULTS WITHOUT HYPERTENSION?

Conclusion statement

Moderate evidence from both cohort and cross-sectional studies show that intake of vegetable protein is generally linked to lower blood pressure.

Grade

Moderate

Evidence summary overview

This review included six studies (Alonso, 2006; Elliott, 2006; Stamler, 2002; Steffen, 2005; Umesawa, 2009; Wang, 2008) examining the relationship between vegetable protein and blood pressure (BP) and hypertension (HTN) among adults without HTN published since 2000. Four of the studies were prospective cohort studies (three from the US and one from Spain) and two studies reported cross-sectional analyses (one from Japan and one with 17 populations from the US, UK, Japan and the People's Republic of China).

Hypertension: Three prospective cohort studies, with follow-up from 18 months to 15 years, examined the relationship between the intake of vegetable protein and HTN. Steffen and colleagues (2005) reported an inverse association between consumption of plant foods and elevated BP among participants from the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Alonso and colleagues (2006) found that participants from the Seguimiento Universidad de Navarra (SUN) Follow-up Study who consumed more vegetable protein had a lower risk of incident HTN. In the PREMIER Trial, increased intake of plant protein was significantly associated with a lower risk of HTN at six months, but not 18 months (Wang, 2008)

Blood Pressure: Over nine years of follow-up of men in the Chicago Western Electric Study, inverse relationships were observed between baseline vegetable protein intake and average annual change in systolic BP (SBP) and diastolic BP (DBP) (Stamler, 2002). Inverse relationships between plant protein and SBP and DBP were also observed at the six-month follow-up of the PREMIER Trial (Wang, 2008). Cross-sectional analyses from the INTERMAP Study (Elliott, 2006) and Circulatory Risk in Communities Study (Umesawa, 2009) confirm these findings.

Evidence summary paragraphs

Alonso et al, 2006 (positive quality) prospectively assessed the role of different nutritional factors, especially protein and fiber from different sources, on the risk of incident HTN in 5,880 adults (61% female; age >20 years) from the Seguimiento Universidad de Navarra (SUN) Follow-up Study in Spain. New cases of medically diagnosed HTN were identified through responses to a mailed questionnaire after at least two years from recruitment. Dietary intake over the previous year was assessed at baseline with a 136-item semi-quantitative FFQ validated in a Spanish population. Over a median follow-up of 28 months, 180 new cases of HTN were ascertained. After

adjustment for potential confounders and several dietary factors, participants in the highest quintile of vegetable protein intake had a lower risk of incident HTN compared with those in the lowest quintile (HR=0.5, 95% CI: 0.2, 0.9; P for trend=0.06).The authors concluded that in this Mediterranean cohort, dietary intake of vegetable protein was associated with a lower risk of HTN when other nutrients were also taken into consideration.

Stamler et al, 2002 (positive quality) examined the relationships of nutrients, alcohol intake, and change in weight to change in BP over eight years in 1,714 men (age 40 to 55 years) from the Chicago Western Electric Study in the US. Annual follow-up data through examination year nine were used to determine change in BP. At first and second annual examinations, two in-depth interviews were performed to assess usual intake of foods and beverages during the preceding 28 days. Averages of nutrients from the two interviews were used. There was an inverse relationship between baseline vegetable protein intake and average annual DBP change (-0.1353mmHg; Z-score= -2.80). Similarly, there was an independent inverse relationship of vegetable protein and annual SBP change (-0.2445; Z-score= -2.91). The authors noted that they did not measure intake of salt, potassium, magnesium or fiber, and it is possible that vegetable protein is a marker for intake of these nutrients and is not related independently to BP change.

Wang et al, 2008 (positive quality) examined the association of dietary protein intake with BP, and particularly, the independent relationship of animal and plant protein with BP over 18 months of follow-up. Participants were 810 adults (62% female; age 25 to 79 years) from the PREMIER Trial (US). Blood pressure measurements were obtained by study personnel at baseline, six and 18 months. Two 24-hour recalls, one on a weekday and the other on a weekend day, were obtained at baseline, six and 18 months. Dietary plant protein was inversely associated with both SBP and DBP in cross-sectional analyses at the six-month follow-up (P=0.0045 and 0.0096, respectively). In longitudinal analyses, a high intake of plant protein at six months was marginally associated with a reduction of both SBP and DBP from baseline to six months only (P=0.0797 and 0.0866, respectively), independent of change in body weight and waist circumference. Furthermore, increased intake of plant protein was significantly associated with a lower risk of HTN at six but not at 18 months. The odds ratio (OR) for the presence of HTN in relation to dietary nutrient and food intake at six months of follow-up was 0.75 (95% CI: 0.60, 0.95; P=0.015). However, when dietary fiber intake was included in the model, the association of plant protein with risk of HTN became insignificant (P=0.079). The authors concluded that plant protein had a beneficial effect on BP and was associated with a lower risk of HTN at six months and suggests that an increased intake of plant protein may be useful as a means to prevent and treat HTN.

Steffen et al, 2005 (positive quality) evaluated associations of dietary intake, including meat intake, with the 15-year incidence of elevated BP among 4,304 adults (883 black men, 1,249 black women, 989 white men and 1,183 white women; age 18 to 30 years) from the Coronary Artery Risk Development in Young Adults (CARDIA) Study in the US. Blood pressure was assessed at six clinic exams at years zero, two, five, seven 10 and 15. Dietary intake was assessed with an interviewer-administered diet history at years zero and seven. The analyses were conducted by using the average of year zero and year seven dietary data. “Plant food” (fruit, vegetables, whole and

refined grains, nuts, and legumes) intake was considered in analyses. Over 15 years, 23.2% of study participants experienced incident EBP, of whom 13.7% had HTN and 9.4% had high-normal BP. Consumption of plant foods was inversely associated with EBP after 15 years of follow-up. The hazard ratio for 15-year EBP incidence between extreme quintiles was 0.77 (95% CI: 0.55, 1.07; P for trend=0.14) in the fully adjusted model. The authors concluded that consumption of plant foods was inversely associated with 15-year cumulative incidence of EBP in black and white men and women.

Elliott et al, 2006 (positive quality) examined the association of vegetable, animal and total protein intake with BP in a cross-sectional epidemiological study involving 17 populations in four countries (US, United Kingdom, Japan and the People's Republic of China) from the INTERMAP Study. Participants were 4,680 adults (50% female; age 40 to 59 years). Systolic and diastolic BP were measured eight times during four visits. Dietary intake was based on 24-hour dietary recalls recorded four times. There was a significant inverse relationship between vegetable protein intake and BP. After adjusting for confounders, BP differences associated with higher vegetable protein intake of 2.8% kilocalories were -2.14mmHg SBP and -1.35mmHg DBP (P<0.001 for both); after further adjustment for height and weight, these differences were -1.11mmHg systolic (P<0.01) and -0.71mmHg diastolic (P<0.05). The authors concluded that vegetable protein intake was inversely related to BP.

Umesawa et al, 2009 (positive quality) examined the association between protein intake, including plant protein and BP in a cross-sectional study of 7,585 Japanese adults (54% female) from the Circulatory Risk in Communities Study (CIRCS). Systolic and diastolic BP was obtained using the first measurement made by trained health professionals. Dietary intake of plant protein was estimated by a single 24-hour dietary recall. Among men and women without anti-hypertensive medication, a 13.1g per day increment in plant protein intake was associated with a decrease in SBP of 0.48mmHg and in DBP of 0.61mmHg (P=0.047 and P<0.001, respectively) after adjustment for cardiovascular disease risk factors.

Overview table

Author, Year, Study Design, Class, Rating	Study Name	Location	Vegetable Protein Association (Pos, Neg, None)
Alonso A, Beunza JJ et al, 2006 Study Design: Prospective cohort study Class: B Positive quality	Seguimiento Universidad de Navarra (SUN) Follow-up Study.	Spain.	(-) HTN.

Elliott P, Stamler J et al, 2006 Study Design: Cross-sectional study Class: D Positive quality	INTERMAP Study.	US, UK, Japan, and the People's Republic of China.	(-) SBP, (-) DBP.
Stamler J, Liu K et al, 2002 Study Design: Prospective cohort study Class: B Positive quality	Stamler Western Electric Study	US.	(-) SBP, (-) DBP.
Steffen LM, Kroenke CH et al, 2005 Study Design: Prospective cohort study Class: B Positive quality	Coronary Artery Risk Development in Young Adults (CARDIA) Study.	US.	"Plant food": (-) Elevated BP.
Umesawa M, Sata S et al, 2009 Study Design: Cross-sectional study Class: D Positive quality	Circulatory Risk in Communities Study (CIRCS).	Japan.	(-) SBP, (-) DBP among those without antihypertensive medication.
Wang YF, Yancy WS et al, 2008 Study Design: Prospective cohort Class: B Positive quality	PREMIER Trial.	US.	(-) SBP, (-) DBP at six months, (-) HTN at six months, but not 18 months.

Search plan and results

Inclusion criteria

- January 2000 to September 2009
- Prospective cohort studies on colorectal, breast and prostate cancers

- All study types for other health outcomes
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children two to 18 years; Adults 19 years and older
- *Populations:* Healthy, those with elevated chronic disease risk.

Exclusion criteria

- Medical treatment or therapy
- Systematic reviews and meta-analyses on colorectal, breast and prostate cancers
- Narrative reviews
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "overweight"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mh:NoExp] OR “heart diseases”[mh] OR "Coronary Disease"[Mesh] OR “blood pressure”[mh] OR “chronic disease”[mh] OR obesity[mh] OR "Body Weights and Measures"[mh]) AND ("Soybean Proteins"[Mesh] OR "Vegetable Proteins"[Mesh]) Limit Eng/humans ("Soybean Proteins"[Mesh] OR "Vegetable Proteins"[Mesh]) AND ("Prostatic Neoplasms"[Mesh] OR "Breast Neoplasms"[Mesh] OR "Colorectal Neoplasms"[mesh]) clinical trials "Cohort Studies"[Mesh]

Date searched: 09/19/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 343
- Total articles identified to review from electronic databases: 86
- Articles identified via handsearch or other means: 8
- Number of Primary Articles Identified: 19
- Number of Review Articles Identified: 5
- Total Number of Articles Identified: 24
- Number of Articles Reviewed but Excluded: 70

Included articles (References)

What is the relationship between the intake of vegetable protein, including soy protein and chronic disease?

1. Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. *Am J Clin Nutr*. 2008 Feb; 87 (2): 339-346. PMID: 18258623. (Hand search)
2. Kelemen LE, Kushi LH, Jacobs DR Jr, Cerhan JR. Associations of dietary protein with disease and mortality in a prospective study of postmenopausal women. *Am J Epidemiol*. 2005 Feb 1; 161 (3): 239-249. PMID: 15671256.
3. Lee SA, Shu XO, Li H, Yang G, Cai H, Wen W, Ji BT, Gao J, Gao YT, Zheng W. Adolescent and adult soy food intake and breast cancer risk: Results from the Shanghai Women's Health Study. *Am J Clin Nutr*. 2009 Jun; 89 (6): 1, 920-1, 926. Epub 2009 Apr 29. PMID: 19403632; PMCID: PMC2683002.
4. Sluijs I, Beulens JW, van der A DL, Spijkerman AM, Grobbee DE, van der Schouw YT. Dietary intake of total, animal, and vegetable protein and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-NL study. *Diabetes Care.* 2010 Jan; 33(1): 43-48. Epub 2009 Oct 13. PMID: 19825820; PMCID: PMC2797984. (Hand search)
5. Song Y, Manson JE, Buring JE, Liu S. A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: The women's health study. *Diabetes Care*. 2004 Sep; 27 (9): 2, 108-2, 115. PMID: 15333470. (Hand search)
6. Nagata C. Ecological study of the association between soy product intake and mortality from cancer and heart disease in Japan. *Int J Epidemiol*. 2000 Oct; 29 (5): 832-836. PMID: 11034965.

What is the relationship between the intake of vegetable protein and blood pressure among adults without hypertension?

1. Stamler J, Liu K, Ruth KJ, Pryer J, Greenland P. Eight-year blood pressure change in middle-aged men: Relationship to multiple nutrients. *Hypertension.* 2002 May; 39 (5): 1, 000-1, 0006. PMID: 12019283. (Hand search)
2. Wang YF, Yancy WS Jr, Yu D, Champagne C, Appel LJ, Lin PH. The relationship between dietary protein intake and blood pressure: results from the PREMIER study. *J Hum Hypertens*. 2008 Nov; 22 (11): 745-754. Epub 2008 Jun 26. PMID: 18580887.
3. Steffen LM, Kroenke CH, Yu X, Pereira MA, Slattery ML, Van Horn L, Gross MD, Jacobs DR Jr. Associations of plant food, dairy product, and meat intakes with 15-year incidence of elevated blood pressure in young black and white adults: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr.* 2005 Dec; 82 (6): 1, 169-1, 177; quiz 1, 363-1, 364. PMID: 16332648. (Hand search)
4. Elliott P, Stamler J, Dyer AR, Appel L, Dennis B, Kesteloot H, Ueshima H, Okayama A, Chan Q, Garside DB, Zhou B. Association between protein intake and blood pressure: The INTERMAP Study. *Arch Intern Med.* 2006 Jan 9; 166 (1): 79-87. PMID: 16401814.
5. Umesawa M, Sato S, Imano H, Kitamura A, Shimamoto T, Yamagishi K, Tanigawa T, Iso H. Relations between protein intake and blood pressure in Japanese men and women: The Circulatory Risk in Communities Study (CIRCS). *Am J Clin Nutr*. 2009 Aug; 90 (2): 377-384. Epub 2009 Jun 10. PMID: 19515740.

What is the relationship between the intake of soy protein and blood pressure

among adults without hypertension?

1. Teede HJ, Dalais FS, Kotsopoulos D, Liang YL, Davis S, McGrath BP. Dietary soy has both beneficial and potentially adverse cardiovascular effects: A placebo-controlled study in men and postmenopausal women. *J Clin Endocrinol Metab.* 2001 Jul; 86 (7): 3, 053-3, 060. PMID: 11443167.
2. Liao FH, Shieh MJ, Yang SC, Lin SH, Chien YW. Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in overweight adults. *Nutrition.* 2007 Jul-Aug; 23 (7-8): 551-556. Epub 2007 Jun 15. PMID: 17574819.
3. Pan A, Franco OH, Ye J, Demark-Wahnefried W, Ye X, Yu Z, Li H, Lin X. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in middle-aged and elderly Chinese. *J Nutr.* 2008 Dec; 138 (12): 2, 413-2, 421. PMID: 19022966.

What is the relationship between the intake of soy protein and body weight?

Systematic Review

1. Cope MB, Erdman JW Jr, Allison DB. The potential role of soy foods in weight and adiposity reduction: An evidence-based review. *Obes Rev.* 2008 May; 9 (3): 219-235. Review. PMID: 18419671. (Hand search)

Primary Citations

1. Liao FH, Shieh MJ, Yang SC, Lin SH, Chien YW. Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in overweight adults. *Nutrition*. 2007 Jul-Aug; 23 (7-8): 551-556. Epub 2007 Jun 15. PMID: 17574819.
2. McVeigh BL, Dillingham BL, Lampe JW, Duncan AM. Effect of soy protein varying in isoflavone content on serum lipids in healthy young men. *Am J Clin Nutr.* 2006 Feb; 83 (2): 244-251. PMID: 16469981.
3. Pan A, Franco OH, Ye J, Demark-Wahnefried W, Ye X, Yu Z, Li H, Lin X. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in middle-aged and elderly Chinese. *J Nutr.* 2008 Dec; 138 (12): 2, 413-2, 421. PMID: 19022966.

Systematic Reviews / Meta-Analyses

1. Yang G, Shu XO, Jin F, Zhang X, Li HL, Li Q, Gao YT, Zheng W. Longitudinal study of soy food intake and blood pressure among middle-aged and elderly Chinese women. *Am J Clin Nutr*. 2005 May; 81 (5): 1, 012-1, 017. PMID: 15883423.
2. Harland JI, Haffner TA. Systematic review, meta-analysis and regression of randomized controlled trials reporting an association between an intake of circa 25g soy protein per day and blood cholesterol. *Atherosclerosis*. 2008 Sep; 200 (1): 13-27. Epub 2008 Apr 15. Review. PMID: 18534601.

What is the relationship between the intake of soy protein and blood lipids among adults without hyperlipidemia?

1. Reynolds K, Chin A, Lees KA, Nguyen A, Bujnowski D, He J. A meta-analysis of the effect of soy protein supplementation on serum lipids. *Am J Cardiol*. 2006 Sep 1; 98 (5): 633-640. Epub 2006 Jul 12. PMID: 16923451. (Hand search)

2. Weggemans RM, Trautwein EA. Relation between soy-associated isoflavones and LDL and HDL cholesterol concentrations in humans: A meta-analysis. *Eur J Clin Nutr.* 2003 Aug; 57 (8): 940-946. PMID: 12879088.
3. Zhan S, Ho SC. Meta-analysis of the effects of soy protein containing isoflavones on the lipid profile. *Am J Clin Nutr.* 2005 Feb; 81 (2): 397-408. PMID: 15699227.

Primary Citations

1. Liao FH, Shieh MJ, Yang SC, Lin SH, Chien YW. Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in overweight adults. *Nutrition. 2007* Jul-Aug; 23 (7-8): 551-556. Epub 2007 Jun 15. PMID: 17574819.
2. Pan A, Franco OH, Ye J, Demark-Wahnefried W, Ye X, Yu Z, Li H, Lin X. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in middle-aged and elderly Chinese. *J Nutr*. 2008 Dec; 138 (12): 2, 413-2, 421. PMID: 19022966.
3. He J, Gu D, Wu X, Chen J, Duan X, Chen J, Whelton PK. Effect of soybean protein on blood pressure: A randomized, controlled trial. *Ann Intern Med.* 2005 Jul 5; 143 (1):1-9. PMID: 15998749.
4. Alonso A, Beunza JJ, Bes-Rastrollo M, Pajares RM, Martínez-González MA. Vegetable protein and fiber from cereal are inversely associated with the risk of hypertension in a Spanish cohort. *Arch Med Res*. 2006 Aug; 37 (6): 778-786. PMID: 16824939.
5. Halton TL, Willett WC, Liu S, Manson JE, Albert CM, Rexrode K, Hu FB. Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med*. 2006 Nov 9; 355 (19): 1, 991-2, 002. PMID: 17093250. (Hand search)

Excluded articles

Article	Reason for Exclusion
Ashton EL, Dalais FS, Ball MJ. Effect of meat replacement by tofu on CHD risk factors including copper induced LDL oxidation. *J Am Coll Nutr.* 2000 Nov-Dec; 19 (6): 761-767. PMID: 11194529.	Included in Zhan, 2005.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Hu FB, Willett WC. Dietary soya intake alters plasma antioxidant status and lipid peroxidation in postmenopausal women with the metabolic syndrome. *Br J Nutr.* 2007 Oct; 98 (4): 807-813. Epub 2007 May 17. PMID: 17506931.	Participants diagnosed with metabolic syndrome.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Hu FB, Willett WC. Soy consumption, markers of inflammation, and endothelial function: A cross-over study in postmenopausal women with the metabolic syndrome. *Diabetes Care*. 2007 Apr; 30 (4): 967-973. PMID: 17392557.	Participants diagnosed with metabolic syndrome.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Padyab M, Hu FB, Willett WC. Soy inclusion in the diet improves features of the metabolic syndrome: a randomized crossover study in postmenopausal women. *Am J Clin Nutr.* 2007 Mar; 85 (3): 735-741. PMID: 17344494.	Participants diagnosed with metabolic syndrome.

Azadbakht L, Shakerhosseini R, Atabak S, Jamshidian M, Mehrabi Y, Esmaill-Zadeh A. Beneficiary effect of dietary soy protein on lowering plasma levels of lipid and improving kidney function in type II diabetes with nephropathy. *Eur J Clin Nutr.* 2003 Oct; 57 (10): 1, 292-1, 294. PMID: 14506491.	Participants diagnosed with type 2 diabetes with nephropathy.
Badger TM, Ronis MJ, Simmen RC, Simmen FA. Soy protein isolate and protection against cancer. *J Am Coll Nutr.* 2005 Apr; 24 (2): 146S-149S. PMID: 15798082.	Publication is a summary of a review presented at a professional meeting.
Blum A, Lang N, Vigder F, Israeli P, Gumanovsky M, Lupovitz S, Elgazi A, Peleg A, Ben-Ami M. Effects of soy protein on endothelium-dependent vasodilatation and lipid profile in postmenopausal women with mild hypercholesterolemia. *Clin Invest Med.* 2003 Feb; 26 (1): 20-26. PMID: 12659466.	Participants had mild hypercholesterolemia; included in Harland, 2008.
Brown BD, Thomas W, Hutchins A, Martini MC, Slavin JL. Types of dietary fat and soy minimally affect hormones and biomarkers associated with breast cancer risk in premenopausal women. *Nutr Cancer.* 2002; 43 (1): 22-30. PMID: 12467131.	Does not answer question: examined biomarkers associated with breast cancer, not incidence of breast cancer (not a prospective cohort study).
Chan YH, Lau KK, Yiu KH, Li SW, Chan HT, Tam S, Shu XO, Lau CP, Tse HF. Isoflavone intake in persons at high risk of cardiovascular events: Implications for vascular endothelial function and the carotid atherosclerotic burden. *Am J Clin Nutr.* 2007 Oct; 86 (4): 938-945. PMID: 17921368.	Participants (94%) had CAD or stroke; does not answer question: Outcomes were carotid intima-media thickness and flow-mediated dilation
Chen ST, Ferng SH, Yang CS, Peng SJ, Lee HR, Chen JR. Variable effects of soy protein on plasma lipids in hyperlipidemic and normolipidemic hemodialysis patients. *Am J Kidney Dis.* 2005 Dec; 46 (6): 1, 099-1, 106. PMID: 16310576.	Participants were hemodialysis patients.
Chiechi LM, Secreto G, Vimercati A, Greco P, Venturelli E, Pansini F, Fanelli M, Loizzi P, Selvaggi L. The effects of a soy rich diet on serum lipids: the Menfis randomized trial. *Maturitas*. 2002 Feb 26; 41 (2): 97-104. PMID: 11836040.	Dropout rate higher than inclusion criteria.
Cicero AF, Minardi M, Mirembe S, Pedro E, Gaddi A. Effects of a new low dose soy protein/beta-sitosterol association on plasma lipid levels and oxidation. *Eur J Nutr.* 2004 Oct; 43 (5): 319-322. Epub 2004 Jan 26. PMID: 15309453.	Participants were hypercholesterolemic; does not answer question: Tested a formulation of soy protein with added beta-sitosterol.
Cuevas AM, Irribarra VL, Castillo OA, Yañez MD, Germain AM. Isolated soy protein improves endothelial function in postmenopausal hypercholesterolemic women. *Eur J Clin Nutr.* 2003 Aug; 57 (8): 889-894. PMID: 12879082.	Participants were hypercholesterolemic.
Cupisti A, D'Alessandro C, Ghiadoni L, Morelli E, Panichi V, Barsotti G. Effect of a soy protein diet on serum lipids of renal transplant patients. *J Ren Nutr.* 2004 Jan; 14 (1): 31-35. PMID: 14740328.	Participants had renal transplantation.

Desroches S, Mauger JF, Ausman LM, Lichtenstein AH, Lamarche B. Soy protein favorably affects LDL size independently of isoflavones in hypercholesterolemic men and women. *J Nutr.* 2004 Mar; 134 (3): 574-579. PMID: 14988449.	Participants were hypercholesterolemic.
Dewell A, Weidner G, Sumner MD, Barnard RJ, Marlin RO, Daubenmier JJ, Chi C, Carroll PR, Ornish D. Relationship of dietary protein and soy isoflavones to serum IGF-1 and IGF binding proteins in the Prostate Cancer Lifestyle Trial. *Nutr Cancer.* 2007; 58 (1): 35-42. PMID: 17571965.	Participants were diagnosed with prostate cancer.
Dillingham BL, McVeigh BL, Lampe JW, Duncan AM. Soy protein isolates of varying isoflavone content exert minor effects on serum reproductive hormones in healthy young men. *J Nutr.* 2005 Mar; 135 (3): 584-591. PMID: 15735098.	Does not answer question: Examined soy protein intake on reproductive hormones.
Engelman HM, Alekel DL, Hanson LN, Kanthasamy AG, Reddy MB. Blood lipid and oxidative stress responses to soy protein with isoflavones and phytic acid in postmenopausal women. *Am J Clin Nutr.* 2005 Mar; 81 (3): 590-596. PMID: 15755827.	Does not answer question: Examined impact of soy protein components (isoflavones and phytate) on blood lipids and oxidative stress.
Gardner CD, Messina M, Kiazand A, Morris JL, Franke AA. Effect of two types of soy milk and dairy milk on plasma lipids in hypercholesterolemic adults: A randomized trial. *J Am Coll Nutr.* 2007 Dec; 26 (6): 669-677. PMID: 18187432.	Participants were hypercholesterolemic; included in Harland, 2008.
Gardner CD, Newell KA, Cherin R, Haskell WL. The effect of soy protein with or without isoflavones relative to milk protein on plasma lipids in hypercholesterolemic postmenopausal women. *Am J Clin Nutr*. 2001 Apr; 73 (4): 728-735. PMID: 11273847.	Participants were hypercholesterolemic; included in Weggemans, 2003.
Genovese MI, Lajolo FM. Isoflavones in soy-based foods consumed in Brazil: Levels, distribution, and estimated intake. *J Agric Food Chem*. 2002 Oct 9; 50 (21): 5, 987-5, 993. PMID: 12358470.	Does not include health outcomes in analyses.
Giampietro PG, Bruno G, Furcolo G, Casati A, Brunetti E, Spadoni GL, Galli E. Soy protein formulas in children: No hormonal effects in long-term feeding. *J Pediatr Endocrinol Metab.* 2004 Feb;17 (2): 191-196. PMID: 15055353.	Does not answer question: Examined hormonal and metabolic effects of long-term soy protein formula feeding.
Goldin BR, Brauner E, Adlercreutz H, Ausman LM, Lichtenstein AH. Hormonal response to diets high in soy or animal protein without and with isoflavones in moderately hypercholesterolemic subjects. *Nutr Cancer*. 2005; 51 (1): 1-6. PMID: 15749623.	Participants were hypercholesterolemic; does not answer question: Examined hormonal response to diets high in soy or animal protein.
Grainger EM, Schwartz SJ, Wang S, Unlu NZ, Boileau TW, Ferketich AK, Monk JP, Gong MC, Bahnson RR, DeGroff VL, Clinton SK. A combination of tomato and soy products for men with recurring prostate cancer and rising prostate specific antigen. *Nutr Cancer*. 2008; 60 (2): 145-154. PMID: 18444145.	Participants diagnosed with prostate cancer.

Greany KA, Nettleton JA, Wangen KE, Thomas W, Kurzer MS. Consumption of isoflavone-rich soy protein does not alter homocysteine or markers of inflammation in postmenopausal women. *Eur J Clin Nutr.* 2008 Dec; 62 (12): 1, 419-1, 425. Epub 2007 Sep 5. PMID: 17805230.	Does not answer question: Does not examine outcome of interest (examines homocysteine, C-reactive protein and adhesion molecules).
Greany KA, Nettleton JA, Wangen KE, Thomas W, Kurzer MS. Probiotic consumption does not enhance the cholesterol-lowering effect of soy in postmenopausal women. *J Nutr.* 2004 Dec; 134 (12): 3, 277-3, 283. PubMed PMID: 15570025.	Participants were hypercholesterolemic; included in Harland, 2008.
Hamilton-Reeves JM, Rebello SA, Thomas W, Kurzer MS, Slaton JW. Effects of soy protein isolate consumption on prostate cancer biomarkers in men with HGPIN, ASAP, and low-grade prostate cancer. *Nutr Cancer*. 2008; 60 (1): 7-13. PMID: 18444130.	Not a prospective cohort study examining incidence of prostate cancer. Outcomes were prostate cancer biomarkers.
Hamilton-Reeves JM, Rebello SA, Thomas W, Slaton JW, Kurzer MS. Soy protein isolate increases urinary estrogens and the ratio of 2:16alpha-hydroxyestrone in men at high risk of prostate cancer. *J Nutr.* 2007 Oct; 137 (10): 2, 258-2, 263. PMID: 17885008.	Not a prospective cohort study examining incidence of prostate cancer. Outcomes were prostate cancer biomarkers.
Hamilton-Reeves JM, Rebello SA, Thomas W, Slaton JW, Kurzer MS. Isoflavone-rich soy protein isolate suppresses androgen receptor expression without altering estrogen receptor-beta expression or serum hormonal profiles in men at high risk of prostate cancer. *J Nutr.* 2007 Jul; 137 (7): 1, 769-1, 775. PMID: 17585029.	Not a prospective cohort study examining incidence of prostate cancer. Outcomes were prostate cancer biomarkers.
Harrison RA, Sagara M, Rajpura A, Armitage L, Birt N, Birt CA, Yamori Y. Can foods with added soya-protein or fish-oil reduce risk factors for coronary disease? A factorial randomised controlled trial. *Nutr Metab Cardiovasc Dis*. 2004 Dec; 14 (6): 344-350. PMID: 15853118.	Participants had elevated total cholesterol or blood pressure.
Hartman JW, Tang JE, Wilkinson SB, Tarnopolsky MA, Lawrence RL, Fullerton AV, Phillips SM. Consumption of fat-free fluid milk after resistance exercise promotes greater lean mass accretion than does consumption of soy or carbohydrate in young, novice, male weightlifters. *Am J Clin Nutr.* 2007 Aug; 86 (2): 373-381. PMID: 17684208.	Does not answer question: Does not examine relationship between vegetable protein and health (examined consumption of various isocaloric drinks on lean mass accretion following resistance training).
Hoie LH, Guldstrand M, Sjoholm A, Graubaum HJ, Gruenwald J, Zunft HJ, Lueder W. Cholesterol-lowering effects of a new isolated soy protein with high levels of nondenaturated protein in hypercholesterolemic patients. *Adv Ther.* 2007 Mar-Apr; 24 (2): 439-447. PMID: 17565935.	Participants were hypercholesterolemic; included in Harland, 2008.
Hoie LH, Morgenstern EC, Gruenwald J, Graubaum HJ, Busch R, Lüder W, Zunft HJ. A double-blind placebo-controlled clinical trial compares the cholesterol-lowering effects of two different soy protein preparations in hypercholesterolemic subjects. *Eur J Nutr.* 2005 Mar; 44 (2): 65-71. Epub 2004 Apr 5. PMID: 15309422.	Participants were hypercholesterolemic; included in Harland, 2008.

Hori G, Wang MF, Chan YC, Komatsu T, Wong Y, Chen TH, Yamamoto K, Nagaoka S, Yamamoto S. Soy protein hydrolyzate with bound phospholipids reduces serum cholesterol levels in hypercholesterolemic adult male volunteers. *Biosci Biotechnol Biochem*. 2001 Jan; 65 (1): 72-78. PMID: 11272848.	Participants were hypercholesterolemic.
Jenkins DJ, Kendall CW, Jackson CJ, Connelly PW, Parker T, Faulkner D, Vidgen E, Cunnane SC, Leiter LA, Josse RG. Effects of high- and low-isoflavone soyfoods on blood lipids, oxidized LDL, homocysteine, and blood pressure in hyperlipidemic men and women. *Am J Clin Nutr*. 2002 Aug; 76 (2): 365-372. PMID: 12145008.	Participants were hyperlipidemic; included in Weggemans, 2003.
Jenkins DJ, Kendall CW, D'Costa MA, Jackson CJ, Vidgen E, Singer W, Silverman JA, Koumbridis G, Honey J, Rao AV, Fleshner N, Klotz L. Soy consumption and phytoestrogens: effect on serum prostate specific antigen when blood lipids and oxidized low-density lipoprotein are reduced in hyperlipidemic men. *J Urol.* 2003 Feb; 169 (2): 507-511. PMID: 12544298.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Garsetti M, Rosenberg-Zand RS, Jackson CJ, Agarwal S, Rao AV, Diamandis EP, Parker T, Faulkner D, Vuksan V, Vidgen E. Effect of soy protein foods on low-density lipoprotein oxidation and ex vivo sex hormone receptor activity: A controlled crossover trial. *Metabolism.* 2000 Apr; 49 (4): 537-543. PMID: 10778882.	Participants were hyperlipidemic; included in Harland, 2008.
Jenkins DJ, Wong JM, Kendall CW, Esfahani A, Ng VW, Leong TC, Faulkner DA, Vidgen E, Greaves KA, Paul G, Singer W. The effect of a plant-based low-carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. *Arch Intern Med.* 2009 Jun 8; 169 (11): 1, 046-1, 054. Erratum in: Arch Intern Med. 2009 Sep 14; 169 (16): 1, 490. PMID: 19506174.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Faulkner DA, Kemp T, Marchie A, Nguyen TH, Wong JM, de Souza R, Emam A, Vidgen E, Trautwein EA, Lapsley KG, Josse RG, Leiter LA, Singer W. Long-term effects of a plant-based dietary portfolio of cholesterol-lowering foods on blood pressure. *Eur J Clin Nutr*. 2008 Jun; 62 (6): 781-788. Epub 2007 Apr 25. PMID: 17457340.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Marchie A, Faulkner D, Vidgen E, Lapsley KG, Trautwein EA, Parker TL, Josse RG, Leiter LA, Connelly PW. The effect of combining plant sterols, soy protein, viscous fibers, and almonds in treating hypercholesterolemia. *Metabolism*. 2003 Nov; 52 (11): 1, 478-1, 483. PMID: 14624410.	Participants were hypercholesterolemic; included in Cope, 2008.
Jenkins DJ, Kendall CW, Vidgen E, Mehling CC, Parker T, Seyler H, Faulkner D, Garsetti M, Griffin LC, Agarwal S, Rao AV, Cunnane SC, Ryan MA, Connelly PW, Leiter LA, Vuksan V, Josse R. The effect on serum lipids and oxidized low-density lipoprotein of supplementing self-selected low-fat diets with soluble-fiber, soy and vegetable protein foods. *Metabolism.* 2000 Jan; 49 (1): 67-72. PMID: 10647066.	Participants were hyperlipidemic.

Jenkins DJ, Kendall CW, Faulkner D, Vidgen E, Trautwein EA, Parker TL, Marchie A, Koumbridis G, Lapsley KG, Josse RG, Leiter LA, Connelly PW. A dietary portfolio approach to cholesterol reduction: combined effects of plant sterols, vegetable proteins, and viscous fibers in hypercholesterolemia. *Metabolism*. 2002 Dec; 51 (12): 1, 596-1, 604. PMID: 12489074.	Participants were hypercholesterolemic.
Jones PJ, Raeini-Sarjaz M, Jenkins DJ, Kendall CW, Vidgen E, Trautwein EA, Lapsley KG, Marchie A, Cunnane SC, Connelly PW. Effects of a diet high in plant sterols, vegetable proteins, and viscous fibers (dietary portfolio) on circulating sterol levels and red cell fragility in hypercholesterolemic subjects. *Lipids.* 2005 Feb; 40 (2): 169-174. PMID: 15884765.	Participants were hypercholesterolemic.
Kreijkamp-Kaspers S, Kok L, Bots ML, Grobbee DE, Lampe JW, van der Schouw YT. Randomized controlled trial of the effects of soy protein containing isoflavones on vascular function in postmenopausal women. *Am J Clin Nutr.* 2005 Jan; 81 (1): 189-195. PMID: 15640479.	Dropout rate higher than inclusion criteria.
Lichtenstein AH, Jalbert SM, Adlercreutz H, Goldin BR, Rasmussen H, Schaefer EJ, Ausman LM. Lipoprotein response to diets high in soy or animal protein with and without isoflavones in moderately hypercholesterolemic subjects. *Arterioscler Thromb Vasc Biol.* 2002 Nov 1; 22 (11): 1, 852-1, 858. PMID: 12426215.	Participants were hypercholesterolemic; included in Reynolds, 2006.
Luiking YC, Deutz NE, Jäkel M, Soeters PB. Casein and soy protein meals differentially affect whole-body and splanchnic protein metabolism in healthy humans. *J Nutr.* 2005 May; 135 (5): 1, 080-1, 087. PMID: 15867285.	Does not answer question: study examined protein metabolism, not relationship between protein and selected health outcomes.
Ma Y, Chiriboga D, Olendzki BC, Nicolosi R, Merriam PA, Ockene IS. Effect of soy protein containing isoflavones on blood lipids in moderately hypercholesterolemic adults: A randomized controlled trial. *J Am Coll Nutr.* 2005 Aug; 24 (4): 275-285. PMID: 16093405.	Participants were hypercholesterolemic.
Mackey R, Ekangaki A, Eden JA. The effects of soy protein in women and men with elevated plasma lipids. *Biofactors*. 2000; 12 (1-4): 251-257. PMID: 11216493.	Participants were hyperlipidemic.
Maskarinec G. Soy foods for breast cancer survivors and women at high risk for breast cancer? *J Am Diet Assoc.* 2005 Oct; 105 (10): 1, 524-1, 528. PMID: 16183350.	Publication is Commentary.
Matthan NR, Jalbert SM, Ausman LM, Kuvin JT, Karas RH, Lichtenstein AH. Effect of soy protein from differently processed products on cardiovascular disease risk factors and vascular endothelial function in hypercholesterolemic subjects. *Am J Clin Nutr.* 2007 Apr; 85 (4): 960-966. Erratum in: *Am J Clin Nutr.* 2007 Aug; 86 (2): 525. PMID: 17413093.	Participants were hypercholesterolemic; included in Harland, 2008.

McVeigh BL, Dillingham BL, Lampe JW, Duncan AM. Effect of soy protein varying in isoflavone content on serum lipids in healthy young men. *Am J Clin Nutr.* 2006 Feb; 83 (2): 244-251. PMID: 16469981.	**Included in body weight review, but excluded from cholesterol review because included in Harland, 2008.
Merritt JC. Metabolic syndrome: soybean foods and serum lipids. *J Natl Med Assoc.* 2004 Aug; 96 (8): 1, 032-1, 041. PubMed PMID: 15303407; Central PMCID: PMC2568482.	Study design is narrative review.
Möllsten AV, Dahlquist GG, Stattin EL, Rudberg S. Higher intakes of fish protein are related to a lower risk of microalbuminuria in young Swedish type 1 diabetic patients. *Diabetes Care*. 2001 May; 24 (5): 805-810. PMID: 11347734.	Participants were diagnosed with type 1 diabetes.
Nagata C, Shimizu H, Takami R, Hayashi M, Takeda N, Yasuda K. Association of blood pressure with intake of soy products and other food groups in Japanese men and women. *Prev Med.* 2003 Jun; 36 (6): 692-697. PMID: 12744912.	Does not answer question: Examined soy food intake, not soy protein.
Puska P, Korpelainen V, Høie LH, Skovlund E, Smerud KT. Isolated soya protein with standardized levels of isoflavones, cotyledon soya fibres and soya phospholipids improves plasma lipids in hypercholesterolaemia: A double-blind, placebo-controlled trial of a yoghurt formulation. *Br J Nutr.* 2004 Mar; 91 (3): 393-401. PMID: 15005825.	Does not answer question: Examined yogurt formulation containing isolated soya protein, isoflavones, cotyledon soya fibers and soya phospholipids.
Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M; American Heart Association Nutrition Committee. Soy protein, isoflavones, and cardiovascular health: An American Heart Association Science Advisory for professionals from the Nutrition Committee. *Circulation.* 2006 Feb 21; 113 (7): 1, 034-1, 044. Epub 2006 Jan 17. PMID: 16418439.	Publication is AHA Science Advisory; reference list was reviewed.
Sagara M, Kanda T, NJelekera M, Teramoto T, Armitage L, Birt N, Birt C, Yamori Y. Effects of dietary intake of soy protein and isoflavones on cardiovascular disease risk factors in high risk, middle-aged men in Scotland. *J Am Coll Nutr.* 2004 Feb; 23 (1): 85-91. PMID: 14963058.	Included in Harland, 2008.
Sanders TA, Dean TS, Grainger D, Miller GJ, Wiseman H. Moderate intakes of intact soy protein rich in isoflavones compared with ethanol-extracted soy protein increase HDL but do not influence transforming growth factor beta(1) concentrations and hemostatic risk factors for coronary heart disease in healthy subjects. *Am J Clin Nutr.* 2002 Aug; 76 (2): 373-377. PMID: 12145009.	Does not answer question; design of the study does not allow for comparison between diets with and without soy protein. The study addresses the impact of isoflavones from soy on CHD risk.
Shahbazian H, Reza A, Javad S, Heshmatollah S, Mahmood L, Ali A, Hosain HM. Beneficial effects of soy protein isoflavones on lipid and blood glucose concentrations in type 2 diabetic subjects. *Saudi Med J.* 2007 Apr; 28 (4): 652-654. PMID: 17457503.	Participants diagnosed with type 2 diabetes.

Sirtori CR, Eberini I, Arnoldi A. Hypocholesterolaemic effects of soya proteins: Results of recent studies are predictable from the Anderson meta-analysis data. *Br J Nutr*. 2007 May; 97 (5): 816-822. Review. PMID: 17408521.	Not a systematic review or original research study (examines previous research using a predictive model).
Spence LA, Lipscomb ER, Cadogan J, Martin B, Wastney ME, Peacock M, Weaver CM. The effect of soy protein and soy isoflavones on calcium metabolism in postmenopausal women: A randomized crossover study. *Am J Clin Nutr*. 2005 Apr; 81 (4): 916-922. PMID: 15817872.	Does not answer question: Outcome was calcium metabolism, not selected health outcome.
St-Onge MP, Claps N, Wolper C, Heymsfield SB. Supplementation with soy-protein-rich foods does not enhance weight loss. *J Am Diet Assoc.* 2007 Mar; 107 (3): 500-505. PMID: 17324670.	Dropout rate higher than inclusion criteria.
Taku K, Umegaki K, Sato Y, Taki Y, Endoh K, Watanabe S. Soy isoflavones lower serum total and LDL cholesterol in humans: A meta-analysis of 11 randomized controlled trials. *Am J Clin Nutr.* 2007 Apr; 85 (4): 1, 148-1, 156. Erratum in: *Am J Clin Nutr*. 2007 Sep; 86 (3): 809. PMID: 17413118.	Does not answer question: Examined soy isoflavones, not soy protein.
Teede HJ, Dalais FS, Kotsopoulos D, Liang YL, Davis S, McGrath BP. Dietary soy has both beneficial and potentially adverse cardiovascular effects: A placebo-controlled study in men and postmenopausal women. *J Clin Endocrinol Metab.* 2001 Jul; 86 (7): 3, 053-3, 060. PMID: 11443167.	** Included in blood pressure review but excluded from cholesterol review because included in Harland, 2008 and Weggemans, 2003.
Teede HJ, Giannopoulos D, Dalais FS, Hodgson J, McGrath BP. Randomized, controlled, cross-over trial of soy protein with isoflavones on blood pressure and arterial function in hypertensive subjects. *J Am Coll Nutr.* 2006 Dec; 25 (6): 533-540. PMID: 17229901.	Participants were hypertensive.
Tonstad S, Smerud K, Høie L. A comparison of the effects of two doses of soy protein or casein on serum lipids, serum lipoproteins and plasma total homocysteine in hypercholesterolemic subjects. *Am J Clin Nutr.* 2002 Jul; 76 (1): 78-84. PMID: 12081819.	Participants were hypercholesterolemic.
Trock BJ, Hilakivi-Clarke L, Clarke R. Meta-analysis of soy intake and breast cancer risk. *J Natl Cancer Inst.* 2006 Apr 5; 98 (7): 459-471. PMID: 16595782.	Studies included in meta-analysis were excluded based on SC criteria; no prospective cohort studies with soy protein included in review.
Wang Y, Jones PJ, Ausman LM, Lichtenstein AH. Soy protein reduces triglyceride levels and triglyceride fatty acid fractional synthesis rate in hypercholesterolemic subjects. Atherosclerosis. 2004 Apr;173 (2): 269-275. PMID: 15064101.	Participants were hypercholesterolemic.
Wangen KE, Duncan AM, Xu X, Kurzer MS. Soy isoflavones improve plasma lipids in normocholesterolemic and mildly hypercholesterolemic postmenopausal women. Am *J Clin Nutr*. 2001 Feb; 73 (2): 225-231. PMID: 11157317.	Included in Zhan, 2005.

Weghuber D, Widhalm K. Effect of three-month treatment of children and adolescents with familial and polygenic hypercholesterolaemia with a soya-substituted diet. *Br J Nutr*. 2008 Feb; 99 (2): 281-286. Epub 2007 Aug 13. PMID: 17697400.	Participants were children and adolescents with familial or polygenic hypercholesterolemia.
Xu X, Duncan AM, Wangen KE, Kurzer MS. Soy consumption alters endogenous estrogen metabolism in postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2000 Aug; 9 (8): 781-786. PMID: 10952094.	Does not answer question: Examines soy consumption and estrogen metabolism.
Yildirir A, Tokgozoglu SL, Oduncu T, Oto A, Haznedaroglu I, Akinci D, Koksal G, Sade E, Kirazli S, Kes S. Soy protein diet significantly improves endothelial function and lipid parameters. *Clin Cardiol.* 2001 Nov; 24 (11): 711-716. PMID: 11714128.	Participants were hypercholesterolemic

CHAPTER 22. SOY PROTEIN – BLOOD LIPIDS

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF SOY PROTEIN AND BLOOD LIPIDS AMONG ADULTS WITHOUT HYPERLIPIDEMIA?

Conclusion statement

Moderate evidence suggests soy protein intake may have small effects on total and low-density lipoprotein cholesterol in adults with normal or elevated blood lipids, although results from systematic reviews are inconsistent.

Grade

Moderate

Evidence summary overview

This review included four meta-analyses (Harland, 2008; Reynolds, 2006; Weggemans, 2003; Zhan, 2005) and consideration of an additional randomized controlled trial (RCT) (Liao, 2007) and a cross-sectional study (Pan, 2008) that examined the relationship between intake of soy protein and blood lipids among adults without hyperlipidemia published since 2000.

Harland and colleagues (2008) conducted a meta-analysis of 30 RCTs to determine the effect of a daily intake of circa 25g (range 10-40g) soy protein on blood lipids in adults with normal or mildly elevated cholesterolemia. They concluded that inclusion of soy protein (circa 25g) resulted in small, significant reductions in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG); no relationship between soy protein and high-density lipoprotein cholesterol (HDL-C) was observed. Reynolds et al, (2006) conducted a meta-analysis of 27 RCTs that examined the effect of isolated soy protein supplementation (20 to >61 grams per day) on serum lipids. Soy protein supplementation reduced TC, LDL-C and TG and increased HDL-C among adults with and without hypercholesterolemia. Zhan et al, (2005) conducted a meta-analysis with 23 RCTs to identify the effects of soy protein containing isoflavones on lipid profile. They concluded that soy protein containing isoflavones significantly reduced serum TC, LDL-C and TG and significantly increased HDL-C; however, greater reductions of TC where seen among participants with hypercholesterolemia than those without, and no significant effect on HDL-C was observed among participants with normal initial lipid levels. Weggemans and colleagues (2003) examined the effect of soy protein (19-60g per day) with isoflavones on cholesterol concentrations in trials substituting soy protein with dairy or other animal protein sources. The authors concluded that changes in soy protein amount are not related to decreases in LDL-C or increases in HDL-C

There was considerable overlap among the studies considered in the four reviews. The number of articles unique to each review were 17 of 30 for Harland et al, (2008), 11 of 27 for Reynolds et al, (2006), nine of 23 for Zhan et al, (2005), and one of 10 for Weggemans et al, (2003). Four studies were included in all four of the meta-analyses. Differences in articles included in these reviews can be partially explained by inclusion criteria; for example, Weggemans et al, (2003) only included trials that substituted soy protein with dairy or other animal protein sources, while the other reviews also

considered control groups consuming other protein sources (e.g., casein or whey)

Two additional primary citations were identified in the Nutrition Evidence Library (NEL) review that were not captured in any of the meta-analyses. Liao and colleagues (2007) conducted an RCT with isocaloric diets providing 1,200kcal per day from either soy protein or animal and plant protein for eight weeks. They reported greater decreases in TC and LDL-C among participants receiving soy protein than the control group but no changes in TG or HDL-C were observed in either group. In a cross-sectional study, Pan et al, (2008) reported that there were no significant (NS) relationships between soy protein and hypertriglyceridemia or low HDL-C. The median level of soy protein intake was 7.82g per day.

Evidence summary paragraphs

Systematic Reviews

Harland et al, 2008 (positive quality), a systematic review, meta-analysis and regression of RCTs, determined the effect of a daily intake of circa 25g soy protein on blood lipids in adults with normal or mildly elevated cholesterolemia. Randomized controlled trials published from January 1995 to September 2007 were identified by searching Medline with additional searches in Embase, SciSearch and Current Contents as well as hand searches and review of reference lists. Search terms used were “SOY(A)” and “CHOLESTEROL or BLOOD LIPIDS”. A total of 172 RCTs were identified in searches. Inclusion criteria for the review were:

An original RCT, parallel or crossover design, published in a peer-reviewed journal and included a suitable (non-soy protein) control treatment

Soy protein intake was CA 25g (range 10-40g) and could be derived from ISP, soy protein concentrates or soy foods

Volunteers were healthy or mild hypercholesterolemic, with weight loss less than 2kg per day and average BMI<30kg/m^2

Study duration was a minimum of four weeks or one menstrual cycle. Thirty RCTs containing 42 treatment arms (N=2,913 adults) were included in analyses.

Average soy protein intake in the 30 studies was 26.9g (range 15-40g); study duration was from four to 52 weeks; study population average age range was 27-67 years. The main source of soy protein was ISP (17 studies), and in the remaining studies soy foods either of a traditional nature or prepared specifically for the study were used (13 studies). Soy protein inclusion led to reductions in standard difference in mean LDL, TC and blood TG of 0.23mmol/L (95% CI: -0.160, -0.306, P<0.0001), 0.22mmol/L (95% CI: -0.142, -0.291, P<0.0001) and 0.08mmol/L (95% CI: -0.004, -0.158; P=0.04), respectively. There was increase in HDL-C of 0.071mmol/L (95% CI: -0.002, 0.144), which did not reach significance (P=0.057). Meta-regression analysis indicated no dose response relationship between soy protein intake in the range of 15-40g and standard difference in LDL or HDL. The authors concluded that the inclusion of soy protein (circa 25g) into the diet of adults with normal or mild hypercholesterolemia resulted in small, significant reductions in TC and LDL-C and TGs. (Note: Authors from HarlandHall Associates and Nutrilicious.)

Reynolds et al, 2006 (positive quality) examined the effect of soy protein supplementation on serum lipid levels by pooling the results from RCTs of isolated soy

protein supplementation. English language articles were retrieved by searching MEDLINE (1966 to February 2005) using the following medical subject headings: Lipids, lipoproteins, LDL-C, HDL-C, VLDL-C, cholesterol, soybean proteins and soybeans. Bibliographies of the retrieved articles were also reviewed. 147 studies were reviewed for inclusion. Each study had to have been a RCT; been conducted in adults; used concurrent control groups; have limited intervention differences between groups to soy protein supplementation in the form of isolated soy protein; and reported changes in serum lipids (TG, TC, LDL-C or HDL-C) from baseline to follow-up and the corresponding variances or sufficient data to estimate them. 27 reports (totaling 41 comparisons; N=1,756 adults) were included in analyses. Soy intake ranged from 20 to >61g per day, and isoflavone intake ranged from 2 to 192mg per day. Mean age range was 22-67 years and duration of intervention ranged from 3 to 52 weeks. Of the 31 trials that reported on the hypercholesterolemic status, 19 were conducted in participants with hyperlipidemia (as defined by the study), nine were conducted in participants with normal lipid levels and three trials included participants with and without hyperlipidemia. Soy protein supplementation was associated with a significant reduction in mean serum TC (-5.26mg/dl, 95% CI: -7.14, -3.38; P<0.0001), LDL-C (-4.25mg/dL; 95% CI: -6.00, -2.50; P<0.0001) and TG (-6.26mg/dL, 95% CI: -9.14, -3.38; P<0.0001) and a significant increase in HDL-C (0.77mg/dL, 95% CI: 0.20, 1.34; P=0.008). Soy protein supplementation reduced total and LDL-C levels consistently in all subgroups. However, the effect size of soy protein supplementation on TC and LDL-C was slightly greater in participants with a mean baseline TC level of <240mg/dL and LDL-C level of <160mg/dL compared with those with elevated cholesterol levels (TC ≥240mg/dL or LDL-C ≥160mg/dL) and among pre- or peri-menopausal women compared with post-menopausal women. In contrast, the effect of soy protein supplementation on HDL-C was slightly greater in participants with elevated TC levels at baseline (TC ≥240mg/dL) compared with participants with TC levels <240mg/dL. Meta-regression analyses showed a dose-response relation between soy protein and isoflavone supplementation and net changes in serum lipids. The authors concluded that soy protein supplementation reduces serum lipids among adults with or without hypercholesterolemia and replacing foods high in saturated fat, trans-saturated fat, and cholesterol with soy protein may have a beneficial effect on coronary risk factors. (Note: Partially supported by grant from NIH.)

Zhan et al, 2005 (neutral quality) conducted a meta-analysis to identify and quantify the effects of soy protein containing isoflavones on the lipid profile. Randomized controlled trials published from 1995 to 2002 were identified from PUBMED and examination of cited references. Forty-six studies were reviewed for inclusion. Studies were selected for analysis if they met the following criteria:

They provided the amount of soy isoflavones

They were controlled and had either a randomized crossover or a parallel design

They provided initial lipid profile concentrations.

Further, studies were excluded if whole soybean rather than soy protein was used. Twenty-three studies (providing 52 comparisons; N=1,381 adults) were included in analyses. In nine studies with 27 comparisons, the subjects had hypercholesterolemia at baseline according to the definitions of the original study. Sixteen studies used isolated soy protein containing isoflavones, three used

tablets containing extracted isoflavones and three used textured soy food. Isoflavone concentrations contained in soy protein averaged 80mg per day. The trials varied in length from three to 26 weeks. Most control groups received casein or whey; the control group received meat or milk in three trials. Soy protein with isoflavones intact was associated with significant decreases in serum TC (by 0.22mmol/L, or 3.77%), LDL-C (by 0.21mmol/L, or 5.25%), and TG (by 0.10mmol/L, or 7.27%) and significant increases in serum HDL-C (by 0.04mmol/L or 3.03%). Subjects with hypercholesterolemia had greater reductions of TC than did normal subjects. The TC concentrations of the former decreased by 0.25mmol/L (95% CI: -0.33, -0.17; P<0.0001) and those of the latter decreased by 0.17mmol/L (95% CI: -0.25, -0.08; P<0.0001). Initial lipid concentrations did not influence changes in LDL-C or TG; those with normal and high initial lipids levels had similar, significant net changes. However, soy protein containing isoflavones had a significant effect on HDL-C among subjects with hypercholesterolemia (net change = 0.10mmol/L; 95% CI: 0.06, 0.13; P<0.0001), but no significant effect on HDL-C was observed among participants with normal initial lipid levels. The authors concluded that soy protein containing isoflavones significantly reduced serum TC, LDL-C and TG, and significantly increased HDL-C and changes were related to initial serum lipid concentrations of the subjects. (Note: Supported by the Centre of Research and Promotion of Women's Health.)

Weggemans et al, 2003 (positive quality) examined the effect of soy-associated isoflavones on cholesterol concentrations in trials substituting soy protein with dairy or animal protein. Studies were identified by MEDLINE searches (1995 to June 2002) and reviewing reference lists. Search terms were soy OR isoflavones AND cholesterol. One hundred forty eight studies were reviewed for inclusion. Inclusion criteria included: Composition of the experimental diets differed only in the amount of soy and animal proteins and in the amount of soy-associated isoflavones; participants were weight stable; minimum two weeks feeding trial; and parallel or Latin Square crossover design. Ten studies (providing 21 comparisons; N=959 adults) were included in analyses. The intake of soy-associated isoflavones increased by one-95mg per day, and the intake of soy protein increased by 19-60g per day. During the soy treatment period, subjects were provided with isolated soy protein, a soy protein supplement, textured soy protein or tofu. During the control treatment period, casein, dry milk, a milk protein supplement, dairy and egg protein or cooked lean meat were given, if necessary, in combination with other foods to balance the change in macronutrient intake. Average age ranged from 41-67 years, and baseline cholesterol concentration ranged from 5.42 to 6.60mmol/L. Feeding daily 36g soy protein with 52mg soy-associated isoflavones on average decreased LDL-C by -0.17±0.04mmol/L (mean ± SE) and increased HDL-C by 0.03±0.01mmol/L. There was no dose-response relation between soy-associated isoflavones and changes in LDL-C (R= -0.33, P=0.14) (Pearson correlation coefficient) or HDL-C (R= -0.07, P=0.76) or their ratio. Correlations between changes in soy protein and blood cholesterol and lipoprotein concentrations were also not significant. No significant effect of baseline cholesterol on cholesterol lowering was observed; the authors noted the small range in baseline cholesterol values. Replacing dairy and animal proteins with soy protein led to 4% lower LDL-C concentrations and significantly increased HDL-C concentrations by 3%. The authors concluded that changes in soy-associated isoflavones or in soy protein amount are not related to decreases in LDL or increases in HDL-C. (Note: Sponsored by Unilever Research and Development.)

Primary Citations

Liao et al, 2007 (positive quality), an RCT, examined the effects of a soy-based diet compared with a traditional low-calorie diet on weight loss and blood lipid levels in 30 obese adults (mean BMI 29-30kg/m^2; 80% female) in China. Participants were randomized to two groups: The soy-based low-calorie group consumed soy protein as the only protein source, and the traditional low-calorie group consumed two-thirds animal protein and the rest plant protein in a 1,200kcal per day diet for eight weeks. Anthropometric data were acquired every week, and biochemical data from before and after the eight-week experiment were compared. Body weight, BMI, body fat percentage and waist circumference significantly decreased in both groups (all P<0.05), but there were no differences between groups. Serum TC concentrations and LDL-C concentrations decreased in the soy-based group and were significantly different from measurements in the traditional group (P<0.05 for both). The changes in TC for the soy and traditional groups were -23.7±15.7 and -18±18.0mg/dL, respectively, and the changes in LDL-C were -15.4 ±7.7 and -9.0±16.5mg/dL, respectively. No significant change in serum TG levels or serum HDL-C levels was found in the soy or traditional group. The authors concluded that a weight-loss diet containing high-quality soy products as the main source of protein could improve hyperlipidemia associated with obesity during a weight-loss program.

Pan et al, 2008 (neutral quality) evaluated the association between soy protein intake and the risk of MetS and its components (including hypertriglyceridemia and low HDL-C) in a cross-sectional analysis of 2,811 adults (58% female; age 58.4+6.0 years) from the Nutrition and Health of Aging Population Project in China. Blood samples were collected during physical examinations at local health stations or community clinics. Data on nutrient intake in the year prior to enrollment were derived from a quantitative FFQ that was administered during a personal interview. The FFQ included 74 food items and groups. Seven soy food items responsible for the majority of soy consumption were listed within the questionnaire, including fresh and dried soybeans, tofu, soy milk, jelly bean curd, soy sauce and other processed soy products. In the total sample, soy protein intake was not associated with hypertriglyceridemia (P=0.749) or low HDL-C (P=0.906); similarly, no significant relationships were observed when men and women were analyzed separately.

Overview table

Author, Year, Study Design, Class, Rating	Study Description/Location	Soy Protein Association (Pos, Neg, None)
Harland et al. 2008 Study Design: Meta-analysis : Systematic Review Class: M Positive quality	30 studies.	Soy protein (circa 25g, range 10 to 40g): (-) TC, (-) LDL-C, (-) TG, Ø HDL.

Liao et al 2007 Study Design: randomized intervention trial Class: A Positive quality	Location: China.	Weight loss diet with soy protein: (-) TC, (-) LDL-C, Ø TG, Ø HDL-C.
Pan et al 2008 Study Design: cross sectional study Class: D Neutral quality	Nutrition and Health of Aging Population Project. Location: China.	Soy protein intake: Ø hypertriglyceridemia, Ø low HDL-C.
Reynolds et al. 2006 Study Design: Meta-analysis Class: M Positive quality	27 studies.	Isolated soy protein supplementation (20 to >61g per day): (-) TC, (-) LDL-C, (-) TG, (+) HDL.
Weggemans RM and Trautwein EA, 2003 Study Design: Meta-analysis Class: M Positive quality	10 studies.	Soy protein (19-60g per day) with isoflavones compared to dairy or other animal protein sources: Ø LDL-C, Ø HDL-C.
Zhan and Ho 2005 Study Design: Meta-analysis Class: M Neutral quality	23 studies.	Soy protein with isoflavones: (-) TC, (-) LDL-C, (-) TG, Ø HDL-C.

Search plan and results

Inclusion criteria

- January 2000 to September 2009
- Prospective cohort studies on colorectal, breast and prostate cancers
- All study types for other health outcomes
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates

- *Ages:* Children two to 18 years; Adults 19 years and older
- *Populations:* Healthy, those with elevated chronic disease risk.

Exclusion criteria

- Medical treatment or therapy
- Systematic reviews and meta-analyses on colorectal, breast and prostate cancers
- Narrative reviews
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "overweight"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mh:NoExp] OR “heart diseases”[mh] OR "Coronary Disease"[Mesh] OR “blood pressure”[mh] OR “chronic disease”[mh] OR obesity[mh] OR "Body Weights and Measures"[mh]) AND ("Soybean Proteins"[Mesh] OR "Vegetable Proteins"[Mesh]) Limit Eng/humans ("Soybean Proteins"[Mesh] OR "Vegetable Proteins"[Mesh]) AND ("Prostatic Neoplasms"[Mesh] OR "Breast Neoplasms"[Mesh] OR "Colorectal Neoplasms"[mesh]) clinical trials "Cohort Studies"[Mesh]

Date searched: 09/19/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 343
- Total articles identified to review from electronic databases: 86
- Articles identified via handsearch or other means: 8
- Number of Primary Articles Identified: 19
- Number of Review Articles Identified: 5
- Total Number of Articles Identified: 24
- Number of Articles Reviewed but Excluded: 70

Included articles (References)

What is the relationship between the intake of vegetable protein, including soy protein and chronic disease?

1. Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. *Am J Clin Nutr*. 2008 Feb; 87 (2): 339-346. PMID: 18258623. (Hand search)
2. Kelemen LE, Kushi LH, Jacobs DR Jr, Cerhan JR. Associations of dietary protein with disease and mortality in a prospective study of postmenopausal women. *Am J Epidemiol*. 2005 Feb 1; 161 (3): 239-249. PMID: 15671256.
3. Lee SA, Shu XO, Li H, Yang G, Cai H, Wen W, Ji BT, Gao J, Gao YT, Zheng

W. Adolescent and adult soy food intake and breast cancer risk: Results from the Shanghai Women's Health Study. *Am J Clin Nutr*. 2009 Jun; 89 (6): 1, 920-1, 926. Epub 2009 Apr 29. PMID: 19403632; PMCID: PMC2683002.

4. Sluijs I, Beulens JW, van der A DL, Spijkerman AM, Grobbee DE, van der Schouw YT. Dietary intake of total, animal, and vegetable protein and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-NL study. *Diabetes Care.* 2010 Jan; 33(1): 43-48. Epub 2009 Oct 13. PMID: 19825820; PMCID: PMC2797984. (Hand search)
5. Song Y, Manson JE, Buring JE, Liu S. A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: The women's health study. *Diabetes Care*. 2004 Sep; 27 (9): 2, 108-2, 115. PMID: 15333470. (Hand search)
6. Nagata C. Ecological study of the association between soy product intake and mortality from cancer and heart disease in Japan. *Int J Epidemiol*. 2000 Oct; 29 (5): 832-836. PMID: 11034965.

What is the relationship between the intake of vegetable protein and blood pressure among adults without hypertension?

1. Stamler J, Liu K, Ruth KJ, Pryer J, Greenland P. Eight-year blood pressure change in middle-aged men: Relationship to multiple nutrients. *Hypertension.* 2002 May; 39 (5): 1, 000-1, 0006. PMID: 12019283. (Hand search)
2. Wang YF, Yancy WS Jr, Yu D, Champagne C, Appel LJ, Lin PH. The relationship between dietary protein intake and blood pressure: results from the PREMIER study. *J Hum Hypertens*. 2008 Nov; 22 (11): 745-754. Epub 2008 Jun 26. PMID: 18580887.
3. Steffen LM, Kroenke CH, Yu X, Pereira MA, Slattery ML, Van Horn L, Gross MD, Jacobs DR Jr. Associations of plant food, dairy product, and meat intakes with 15-year incidence of elevated blood pressure in young black and white adults: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr.* 2005 Dec; 82 (6): 1, 169-1, 177; quiz 1, 363-1, 364. PMID: 16332648. (Hand search)
4. Elliott P, Stamler J, Dyer AR, Appel L, Dennis B, Kesteloot H, Ueshima H, Okayama A, Chan Q, Garside DB, Zhou B. Association between protein intake and blood pressure: The INTERMAP Study. *Arch Intern Med.* 2006 Jan 9; 166 (1): 79-87. PMID: 16401814.
5. Umesawa M, Sato S, Imano H, Kitamura A, Shimamoto T, Yamagishi K, Tanigawa T, Iso H. Relations between protein intake and blood pressure in Japanese men and women: The Circulatory Risk in Communities Study (CIRCS). *Am J Clin Nutr*. 2009 Aug; 90 (2): 377-384. Epub 2009 Jun 10. PMID: 19515740.

What is the relationship between the intake of soy protein and blood pressure among adults without hypertension?

1. Teede HJ, Dalais FS, Kotsopoulos D, Liang YL, Davis S, McGrath BP. Dietary soy has both beneficial and potentially adverse cardiovascular effects: A placebo-controlled study in men and postmenopausal women. *J Clin Endocrinol Metab.* 2001 Jul; 86 (7): 3, 053-3, 060. PMID: 11443167.
2. Liao FH, Shieh MJ, Yang SC, Lin SH, Chien YW. Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in

overweight adults. *Nutrition.* 2007 Jul-Aug; 23 (7-8): 551-556. Epub 2007 Jun 15. PMID: 17574819.
3. Pan A, Franco OH, Ye J, Demark-Wahnefried W, Ye X, Yu Z, Li H, Lin X. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in middle-aged and elderly Chinese. *J Nutr.* 2008 Dec; 138 (12): 2, 413-2, 421. PMID: 19022966.

What is the relationship between the intake of soy protein and body weight?

Systematic Review

1. Cope MB, Erdman JW Jr, Allison DB. The potential role of soy foods in weight and adiposity reduction: An evidence-based review. *Obes Rev.* 2008 May; 9 (3): 219-235. Review. PMID: 18419671. (Hand search)

Primary Citations

1. Liao FH, Shieh MJ, Yang SC, Lin SH, Chien YW. Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in overweight adults. *Nutrition*. 2007 Jul-Aug; 23 (7-8): 551-556. Epub 2007 Jun 15. PMID: 17574819.
2. McVeigh BL, Dillingham BL, Lampe JW, Duncan AM. Effect of soy protein varying in isoflavone content on serum lipids in healthy young men. *Am J Clin Nutr.* 2006 Feb; 83 (2): 244-251. PMID: 16469981.
3. Pan A, Franco OH, Ye J, Demark-Wahnefried W, Ye X, Yu Z, Li H, Lin X. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in middle-aged and elderly Chinese. *J Nutr.* 2008 Dec; 138 (12): 2, 413-2, 421. PMID: 19022966.

Systematic Reviews / Meta-Analyses

1. Yang G, Shu XO, Jin F, Zhang X, Li HL, Li Q, Gao YT, Zheng W. Longitudinal study of soy food intake and blood pressure among middle-aged and elderly Chinese women. *Am J Clin Nutr*. 2005 May; 81 (5): 1, 012-1, 017. PMID: 15883423.
2. Harland JI, Haffner TA. Systematic review, meta-analysis and regression of randomized controlled trials reporting an association between an intake of circa 25g soy protein per day and blood cholesterol. *Atherosclerosis*. 2008 Sep; 200 (1): 13-27. Epub 2008 Apr 15. Review. PMID: 18534601.

What is the relationship between the intake of soy protein and blood lipids among adults without hyperlipidemia?

1. Reynolds K, Chin A, Lees KA, Nguyen A, Bujnowski D, He J. A meta-analysis of the effect of soy protein supplementation on serum lipids. *Am J Cardiol*. 2006 Sep 1; 98 (5): 633-640. Epub 2006 Jul 12. PMID: 16923451. (Hand search)
2. Weggemans RM, Trautwein EA. Relation between soy-associated isoflavones and LDL and HDL cholesterol concentrations in humans: A meta-analysis. *Eur J Clin Nutr.* 2003 Aug; 57 (8): 940-946. PMID: 12879088.
3. Zhan S, Ho SC. Meta-analysis of the effects of soy protein containing isoflavones on the lipid profile. *Am J Clin Nutr.* 2005 Feb; 81 (2): 397-408. PMID: 15699227.

Primary Citations

1. Liao FH, Shieh MJ, Yang SC, Lin SH, Chien YW. Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in overweight adults. *Nutrition. 2007* Jul-Aug; 23 (7-8): 551-556. Epub 2007 Jun 15. PMID: 17574819.
2. Pan A, Franco OH, Ye J, Demark-Wahnefried W, Ye X, Yu Z, Li H, Lin X. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in middle-aged and elderly Chinese. *J Nutr*. 2008 Dec; 138 (12): 2, 413-2, 421. PMID: 19022966.
3. He J, Gu D, Wu X, Chen J, Duan X, Chen J, Whelton PK. Effect of soybean protein on blood pressure: A randomized, controlled trial. *Ann Intern Med.* 2005 Jul 5; 143 (1):1-9. PMID: 15998749.
4. Alonso A, Beunza JJ, Bes-Rastrollo M, Pajares RM, Martínez-González MA. Vegetable protein and fiber from cereal are inversely associated with the risk of hypertension in a Spanish cohort. *Arch Med Res*. 2006 Aug; 37 (6): 778-786. PMID: 16824939.
5. Halton TL, Willett WC, Liu S, Manson JE, Albert CM, Rexrode K, Hu FB. Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med*. 2006 Nov 9; 355 (19): 1, 991-2, 002. PMID: 17093250. (Hand search)

Excluded articles

Article	Reason for Exclusion
Ashton EL, Dalais FS, Ball MJ. Effect of meat replacement by tofu on CHD risk factors including copper induced LDL oxidation. *J Am Coll Nutr.* 2000 Nov-Dec; 19 (6): 761-767. PMID: 11194529.	Included in Zhan, 2005.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Hu FB, Willett WC. Dietary soya intake alters plasma antioxidant status and lipid peroxidation in postmenopausal women with the metabolic syndrome. *Br J Nutr.* 2007 Oct; 98 (4): 807-813. Epub 2007 May 17. PMID: 17506931.	Participants diagnosed with metabolic syndrome.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Hu FB, Willett WC. Soy consumption, markers of inflammation, and endothelial function: A cross-over study in postmenopausal women with the metabolic syndrome. *Diabetes Care*. 2007 Apr; 30 (4): 967-973. PMID: 17392557.	Participants diagnosed with metabolic syndrome.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Padyab M, Hu FB, Willett WC. Soy inclusion in the diet improves features of the metabolic syndrome: a randomized crossover study in postmenopausal women. *Am J Clin Nutr.* 2007 Mar; 85 (3): 735-741. PMID: 17344494.	Participants diagnosed with metabolic syndrome.
Azadbakht L, Shakerhosseini R, Atabak S, Jamshidian M, Mehrabi Y, Esmaill-Zadeh A. Beneficiary effect of dietary soy protein on lowering plasma levels of lipid and improving kidney function in type II diabetes with nephropathy. *Eur J Clin Nutr.* 2003 Oct; 57 (10): 1, 292-1, 294. PMID: 14506491.	Participants diagnosed with type 2 diabetes with nephropathy.

Badger TM, Ronis MJ, Simmen RC, Simmen FA. Soy protein isolate and protection against cancer. *J Am Coll Nutr.* 2005 Apr; 24 (2): 146S-149S. PMID: 15798082.	Publication is a summary of a review presented at a professional meeting.
Blum A, Lang N, Vigder F, Israeli P, Gumanovsky M, Lupovitz S, Elgazi A, Peleg A, Ben-Ami M. Effects of soy protein on endothelium-dependent vasodilatation and lipid profile in postmenopausal women with mild hypercholesterolemia. *Clin Invest Med.* 2003 Feb; 26 (1): 20-26. PMID: 12659466.	Participants had mild hypercholesterolemia; included in Harland, 2008.
Brown BD, Thomas W, Hutchins A, Martini MC, Slavin JL. Types of dietary fat and soy minimally affect hormones and biomarkers associated with breast cancer risk in premenopausal women. *Nutr Cancer.* 2002; 43 (1): 22-30. PMID: 12467131.	Does not answer question: examined biomarkers associated with breast cancer, not incidence of breast cancer (not a prospective cohort study).
Chan YH, Lau KK, Yiu KH, Li SW, Chan HT, Tam S, Shu XO, Lau CP, Tse HF. Isoflavone intake in persons at high risk of cardiovascular events: Implications for vascular endothelial function and the carotid atherosclerotic burden. *Am J Clin Nutr.* 2007 Oct; 86 (4): 938-945. PMID: 17921368.	Participants (94%) had CAD or stroke; does not answer question: Outcomes were carotid intima-media thickness and flow-mediated dilation
Chen ST, Ferng SH, Yang CS, Peng SJ, Lee HR, Chen JR. Variable effects of soy protein on plasma lipids in hyperlipidemic and normolipidemic hemodialysis patients. *Am J Kidney Dis.* 2005 Dec; 46 (6): 1, 099-1, 106. PMID: 16310576.	Participants were hemodialysis patients.
Chiechi LM, Secreto G, Vimercati A, Greco P, Venturelli E, Pansini F, Fanelli M, Loizzi P, Selvaggi L. The effects of a soy rich diet on serum lipids: the Menfis randomized trial. *Maturitas*. 2002 Feb 26; 41 (2): 97-104. PMID: 11836040.	Dropout rate higher than inclusion criteria.
Cicero AF, Minardi M, Mirembe S, Pedro E, Gaddi A. Effects of a new low dose soy protein/beta-sitosterol association on plasma lipid levels and oxidation. *Eur J Nutr.* 2004 Oct; 43 (5): 319-322. Epub 2004 Jan 26. PMID: 15309453.	Participants were hypercholesterolemic; does not answer question: Tested a formulation of soy protein with added beta-sitosterol.
Cuevas AM, Irribarra VL, Castillo OA, Yañez MD, Germain AM. Isolated soy protein improves endothelial function in postmenopausal hypercholesterolemic women. *Eur J Clin Nutr.* 2003 Aug; 57 (8): 889-894. PMID: 12879082.	Participants were hypercholesterolemic.
Cupisti A, D'Alessandro C, Ghiadoni L, Morelli E, Panichi V, Barsotti G. Effect of a soy protein diet on serum lipids of renal transplant patients. *J Ren Nutr.* 2004 Jan; 14 (1): 31-35. PMID: 14740328.	Participants had renal transplantation.
Desroches S, Mauger JF, Ausman LM, Lichtenstein AH, Lamarche B. Soy protein favorably affects LDL size independently of isoflavones in hypercholesterolemic men and women. *J Nutr.* 2004 Mar; 134 (3): 574-579. PMID: 14988449.	Participants were hypercholesterolemic.

Dewell A, Weidner G, Sumner MD, Barnard RJ, Marlin RO, Daubenmier JJ, Chi C, Carroll PR, Ornish D. Relationship of dietary protein and soy isoflavones to serum IGF-1 and IGF binding proteins in the Prostate Cancer Lifestyle Trial. *Nutr Cancer.* 2007; 58 (1): 35-42. PMID: 17571965.	Participants were diagnosed with prostate cancer.
Dillingham BL, McVeigh BL, Lampe JW, Duncan AM. Soy protein isolates of varying isoflavone content exert minor effects on serum reproductive hormones in healthy young men. *J Nutr.* 2005 Mar; 135 (3): 584-591. PMID: 15735098.	Does not answer question: Examined soy protein intake on reproductive hormones.
Engelman HM, Alekel DL, Hanson LN, Kanthasamy AG, Reddy MB. Blood lipid and oxidative stress responses to soy protein with isoflavones and phytic acid in postmenopausal women. *Am J Clin Nutr.* 2005 Mar; 81 (3): 590-596. PMID: 15755827.	Does not answer question: Examined impact of soy protein components (isoflavones and phytate) on blood lipids and oxidative stress.
Gardner CD, Messina M, Kiazand A, Morris JL, Franke AA. Effect of two types of soy milk and dairy milk on plasma lipids in hypercholesterolemic adults: A randomized trial. *J Am Coll Nutr.* 2007 Dec; 26 (6): 669-677. PMID: 18187432.	Participants were hypercholesterolemic; included in Harland, 2008.
Gardner CD, Newell KA, Cherin R, Haskell WL. The effect of soy protein with or without isoflavones relative to milk protein on plasma lipids in hypercholesterolemic postmenopausal women. *Am J Clin Nutr*. 2001 Apr; 73 (4): 728-735. PMID: 11273847.	Participants were hypercholesterolemic; included in Weggemans, 2003.
Genovese MI, Lajolo FM. Isoflavones in soy-based foods consumed in Brazil: Levels, distribution, and estimated intake. *J Agric Food Chem*. 2002 Oct 9; 50 (21): 5, 987-5, 993. PMID: 12358470.	Does not include health outcomes in analyses.
Giampietro PG, Bruno G, Furcolo G, Casati A, Brunetti E, Spadoni GL, Galli E. Soy protein formulas in children: No hormonal effects in long-term feeding. *J Pediatr Endocrinol Metab.* 2004 Feb;17 (2): 191-196. PMID: 15055353.	Does not answer question: Examined hormonal and metabolic effects of long-term soy protein formula feeding.
Goldin BR, Brauner E, Adlercreutz H, Ausman LM, Lichtenstein AH. Hormonal response to diets high in soy or animal protein without and with isoflavones in moderately hypercholesterolemic subjects. *Nutr Cancer*. 2005; 51 (1): 1-6. PMID: 15749623.	Participants were hypercholesterolemic; does not answer question: Examined hormonal response to diets high in soy or animal protein.
Grainger EM, Schwartz SJ, Wang S, Unlu NZ, Boileau TW, Ferketich AK, Monk JP, Gong MC, Bahnson RR, DeGroff VL, Clinton SK. A combination of tomato and soy products for men with recurring prostate cancer and rising prostate specific antigen. *Nutr Cancer*. 2008; 60 (2): 145-154. PMID: 18444145.	Participants diagnosed with prostate cancer.

Greany KA, Nettleton JA, Wangen KE, Thomas W, Kurzer MS. Consumption of isoflavone-rich soy protein does not alter homocysteine or markers of inflammation in postmenopausal women. *Eur J Clin Nutr.* 2008 Dec; 62 (12): 1, 419-1, 425. Epub 2007 Sep 5. PMID: 17805230.	Does not answer question: Does not examine outcome of interest (examines homocysteine, C-reactive protein and adhesion molecules).
Greany KA, Nettleton JA, Wangen KE, Thomas W, Kurzer MS. Probiotic consumption does not enhance the cholesterol-lowering effect of soy in postmenopausal women. *J Nutr.* 2004 Dec; 134 (12): 3, 277-3, 283. PubMed PMID: 15570025.	Participants were hypercholesterolemic; included in Harland, 2008.
Hamilton-Reeves JM, Rebello SA, Thomas W, Kurzer MS, Slaton JW. Effects of soy protein isolate consumption on prostate cancer biomarkers in men with HGPIN, ASAP, and low-grade prostate cancer. *Nutr Cancer*. 2008; 60 (1): 7-13. PMID: 18444130.	Not a prospective cohort study examining incidence of prostate cancer. Outcomes were prostate cancer biomarkers.
Hamilton-Reeves JM, Rebello SA, Thomas W, Slaton JW, Kurzer MS. Soy protein isolate increases urinary estrogens and the ratio of 2:16alpha-hydroxyestrone in men at high risk of prostate cancer. *J Nutr.* 2007 Oct; 137 (10): 2, 258-2, 263. PMID: 17885008.	Not a prospective cohort study examining incidence of prostate cancer. Outcomes were prostate cancer biomarkers.
Hamilton-Reeves JM, Rebello SA, Thomas W, Slaton JW, Kurzer MS. Isoflavone-rich soy protein isolate suppresses androgen receptor expression without altering estrogen receptor-beta expression or serum hormonal profiles in men at high risk of prostate cancer. *J Nutr.* 2007 Jul; 137 (7): 1, 769-1, 775. PMID: 17585029.	Not a prospective cohort study examining incidence of prostate cancer. Outcomes were prostate cancer biomarkers.
Harrison RA, Sagara M, Rajpura A, Armitage L, Birt N, Birt CA, Yamori Y. Can foods with added soya-protein or fish-oil reduce risk factors for coronary disease? A factorial randomised controlled trial. *Nutr Metab Cardiovasc Dis*. 2004 Dec; 14 (6): 344-350. PMID: 15853118.	Participants had elevated total cholesterol or blood pressure.
Hartman JW, Tang JE, Wilkinson SB, Tarnopolsky MA, Lawrence RL, Fullerton AV, Phillips SM. Consumption of fat-free fluid milk after resistance exercise promotes greater lean mass accretion than does consumption of soy or carbohydrate in young, novice, male weightlifters. *Am J Clin Nutr.* 2007 Aug; 86 (2): 373-381. PMID: 17684208.	Does not answer question: Does not examine relationship between vegetable protein and health (examined consumption of various isocaloric drinks on lean mass accretion following resistance training).
Hoie LH, Guldstrand M, Sjoholm A, Graubaum HJ, Gruenwald J, Zunft HJ, Lueder W. Cholesterol-lowering effects of a new isolated soy protein with high levels of nondenaturated protein in hypercholesterolemic patients. *Adv Ther.* 2007 Mar-Apr; 24 (2): 439-447. PMID: 17565935.	Participants were hypercholesterolemic; included in Harland, 2008.
Hoie LH, Morgenstern EC, Gruenwald J, Graubaum HJ, Busch R, Lüder W, Zunft HJ. A double-blind placebo-controlled clinical trial compares the cholesterol-lowering effects of two different soy protein preparations in hypercholesterolemic subjects. *Eur J Nutr.* 2005 Mar; 44 (2): 65-71. Epub 2004 Apr 5. PMID: 15309422.	Participants were hypercholesterolemic; included in Harland, 2008.

Hori G, Wang MF, Chan YC, Komatsu T, Wong Y, Chen TH, Yamamoto K, Nagaoka S, Yamamoto S. Soy protein hydrolyzate with bound phospholipids reduces serum cholesterol levels in hypercholesterolemic adult male volunteers. *Biosci Biotechnol Biochem*. 2001 Jan; 65 (1): 72-78. PMID: 11272848.	Participants were hypercholesterolemic.
Jenkins DJ, Kendall CW, Jackson CJ, Connelly PW, Parker T, Faulkner D, Vidgen E, Cunnane SC, Leiter LA, Josse RG. Effects of high- and low-isoflavone soyfoods on blood lipids, oxidized LDL, homocysteine, and blood pressure in hyperlipidemic men and women. *Am J Clin Nutr*. 2002 Aug; 76 (2): 365-372. PMID: 12145008.	Participants were hyperlipidemic; included in Weggemans, 2003.
Jenkins DJ, Kendall CW, D'Costa MA, Jackson CJ, Vidgen E, Singer W, Silverman JA, Koumbridis G, Honey J, Rao AV, Fleshner N, Klotz L. Soy consumption and phytoestrogens: effect on serum prostate specific antigen when blood lipids and oxidized low-density lipoprotein are reduced in hyperlipidemic men. *J Urol.* 2003 Feb; 169 (2): 507-511. PMID: 12544298.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Garsetti M, Rosenberg-Zand RS, Jackson CJ, Agarwal S, Rao AV, Diamandis EP, Parker T, Faulkner D, Vuksan V, Vidgen E. Effect of soy protein foods on low-density lipoprotein oxidation and ex vivo sex hormone receptor activity: A controlled crossover trial. *Metabolism.* 2000 Apr; 49 (4): 537-543. PMID: 10778882.	Participants were hyperlipidemic; included in Harland, 2008.
Jenkins DJ, Wong JM, Kendall CW, Esfahani A, Ng VW, Leong TC, Faulkner DA, Vidgen E, Greaves KA, Paul G, Singer W. The effect of a plant-based low-carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. *Arch Intern Med.* 2009 Jun 8; 169 (11): 1, 046-1, 054. Erratum in: Arch Intern Med. 2009 Sep 14; 169 (16): 1, 490. PMID: 19506174.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Faulkner DA, Kemp T, Marchie A, Nguyen TH, Wong JM, de Souza R, Emam A, Vidgen E, Trautwein EA, Lapsley KG, Josse RG, Leiter LA, Singer W. Long-term effects of a plant-based dietary portfolio of cholesterol-lowering foods on blood pressure. *Eur J Clin Nutr*. 2008 Jun; 62 (6): 781-788. Epub 2007 Apr 25. PMID: 17457340.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Marchie A, Faulkner D, Vidgen E, Lapsley KG, Trautwein EA, Parker TL, Josse RG, Leiter LA, Connelly PW. The effect of combining plant sterols, soy protein, viscous fibers, and almonds in treating hypercholesterolemia. *Metabolism*. 2003 Nov; 52 (11): 1, 478-1, 483. PMID: 14624410.	Participants were hypercholesterolemic; included in Cope, 2008.
Jenkins DJ, Kendall CW, Vidgen E, Mehling CC, Parker T, Seyler H, Faulkner D, Garsetti M, Griffin LC, Agarwal S, Rao AV, Cunnane SC, Ryan MA, Connelly PW, Leiter LA, Vuksan V, Josse R. The effect on serum lipids and oxidized low-density lipoprotein of supplementing self-selected low-fat diets with soluble-fiber, soy and vegetable protein foods. *Metabolism.* 2000 Jan; 49 (1): 67-72. PMID: 10647066.	Participants were hyperlipidemic.

Jenkins DJ, Kendall CW, Faulkner D, Vidgen E, Trautwein EA, Parker TL, Marchie A, Koumbridis G, Lapsley KG, Josse RG, Leiter LA, Connelly PW. A dietary portfolio approach to cholesterol reduction: combined effects of plant sterols, vegetable proteins, and viscous fibers in hypercholesterolemia. *Metabolism*. 2002 Dec; 51 (12): 1, 596-1, 604. PMID: 12489074.	Participants were hypercholesterolemic.
Jones PJ, Raeini-Sarjaz M, Jenkins DJ, Kendall CW, Vidgen E, Trautwein EA, Lapsley KG, Marchie A, Cunnane SC, Connelly PW. Effects of a diet high in plant sterols, vegetable proteins, and viscous fibers (dietary portfolio) on circulating sterol levels and red cell fragility in hypercholesterolemic subjects. *Lipids.* 2005 Feb; 40 (2): 169-174. PMID: 15884765.	Participants were hypercholesterolemic.
Kreijkamp-Kaspers S, Kok L, Bots ML, Grobbee DE, Lampe JW, van der Schouw YT. Randomized controlled trial of the effects of soy protein containing isoflavones on vascular function in postmenopausal women. *Am J Clin Nutr.* 2005 Jan; 81 (1): 189-195. PMID: 15640479.	Dropout rate higher than inclusion criteria.
Lichtenstein AH, Jalbert SM, Adlercreutz H, Goldin BR, Rasmussen H, Schaefer EJ, Ausman LM. Lipoprotein response to diets high in soy or animal protein with and without isoflavones in moderately hypercholesterolemic subjects. *Arterioscler Thromb Vasc Biol.* 2002 Nov 1; 22 (11): 1, 852-1, 858. PMID: 12426215.	Participants were hypercholesterolemic; included in Reynolds, 2006.
Luiking YC, Deutz NE, Jäkel M, Soeters PB. Casein and soy protein meals differentially affect whole-body and splanchnic protein metabolism in healthy humans. *J Nutr.* 2005 May; 135 (5): 1, 080-1, 087. PMID: 15867285.	Does not answer question: study examined protein metabolism, not relationship between protein and selected health outcomes.
Ma Y, Chiriboga D, Olendzki BC, Nicolosi R, Merriam PA, Ockene IS. Effect of soy protein containing isoflavones on blood lipids in moderately hypercholesterolemic adults: A randomized controlled trial. *J Am Coll Nutr.* 2005 Aug; 24 (4): 275-285. PMID: 16093405.	Participants were hypercholesterolemic.
Mackey R, Ekangaki A, Eden JA. The effects of soy protein in women and men with elevated plasma lipids. *Biofactors*. 2000; 12 (1-4): 251-257. PMID: 11216493.	Participants were hyperlipidemic.
Maskarinec G. Soy foods for breast cancer survivors and women at high risk for breast cancer? *J Am Diet Assoc.* 2005 Oct; 105 (10): 1, 524-1, 528. PMID: 16183350.	Publication is Commentary.
Matthan NR, Jalbert SM, Ausman LM, Kuvin JT, Karas RH, Lichtenstein AH. Effect of soy protein from differently processed products on cardiovascular disease risk factors and vascular endothelial function in hypercholesterolemic subjects. *Am J Clin Nutr.* 2007 Apr; 85 (4): 960-966. Erratum in: *Am J Clin Nutr.* 2007 Aug; 86 (2): 525. PMID: 17413093.	Participants were hypercholesterolemic; included in Harland, 2008.

McVeigh BL, Dillingham BL, Lampe JW, Duncan AM. Effect of soy protein varying in isoflavone content on serum lipids in healthy young men. *Am J Clin Nutr.* 2006 Feb; 83 (2): 244-251. PMID: 16469981.	**Included in body weight review, but excluded from cholesterol review because included in Harland, 2008.
Merritt JC. Metabolic syndrome: soybean foods and serum lipids. *J Natl Med Assoc.* 2004 Aug; 96 (8): 1, 032-1, 041. PubMed PMID: 15303407; Central PMCID: PMC2568482.	Study design is narrative review.
Möllsten AV, Dahlquist GG, Stattin EL, Rudberg S. Higher intakes of fish protein are related to a lower risk of microalbuminuria in young Swedish type 1 diabetic patients. *Diabetes Care*. 2001 May; 24 (5): 805-810. PMID: 11347734.	Participants were diagnosed with type 1 diabetes.
Nagata C, Shimizu H, Takami R, Hayashi M, Takeda N, Yasuda K. Association of blood pressure with intake of soy products and other food groups in Japanese men and women. *Prev Med.* 2003 Jun; 36 (6): 692-697. PMID: 12744912.	Does not answer question: Examined soy food intake, not soy protein.
Puska P, Korpelainen V, Høie LH, Skovlund E, Smerud KT. Isolated soya protein with standardized levels of isoflavones, cotyledon soya fibres and soya phospholipids improves plasma lipids in hypercholesterolaemia: A double-blind, placebo-controlled trial of a yoghurt formulation. *Br J Nutr.* 2004 Mar; 91 (3): 393-401. PMID: 15005825.	Does not answer question: Examined yogurt formulation containing isolated soya protein, isoflavones, cotyledon soya fibers and soya phospholipids.
Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M; American Heart Association Nutrition Committee. Soy protein, isoflavones, and cardiovascular health: An American Heart Association Science Advisory for professionals from the Nutrition Committee. *Circulation.* 2006 Feb 21; 113 (7): 1, 034-1, 044. Epub 2006 Jan 17. PMID: 16418439.	Publication is AHA Science Advisory; reference list was reviewed.
Sagara M, Kanda T, NJelekera M, Teramoto T, Armitage L, Birt N, Birt C, Yamori Y. Effects of dietary intake of soy protein and isoflavones on cardiovascular disease risk factors in high risk, middle-aged men in Scotland. *J Am Coll Nutr.* 2004 Feb; 23 (1): 85-91. PMID: 14963058.	Included in Harland, 2008.
Sanders TA, Dean TS, Grainger D, Miller GJ, Wiseman H. Moderate intakes of intact soy protein rich in isoflavones compared with ethanol-extracted soy protein increase HDL but do not influence transforming growth factor beta(1) concentrations and hemostatic risk factors for coronary heart disease in healthy subjects. *Am J Clin Nutr.* 2002 Aug; 76 (2): 373-377. PMID: 12145009.	Does not answer question; design of the study does not allow for comparison between diets with and without soy protein. The study addresses the impact of isoflavones from soy on CHD risk.
Shahbazian H, Reza A, Javad S, Heshmatollah S, Mahmood L, Ali A, Hosain HM. Beneficial effects of soy protein isoflavones on lipid and blood glucose concentrations in type 2 diabetic subjects. *Saudi Med J.* 2007 Apr; 28 (4): 652-654. PMID: 17457503.	Participants diagnosed with type 2 diabetes.

Sirtori CR, Eberini I, Arnoldi A. Hypocholesterolaemic effects of soya proteins: Results of recent studies are predictable from the Anderson meta-analysis data. *Br J Nutr*. 2007 May; 97 (5): 816-822. Review. PMID: 17408521.	Not a systematic review or original research study (examines previous research using a predictive model).
Spence LA, Lipscomb ER, Cadogan J, Martin B, Wastney ME, Peacock M, Weaver CM. The effect of soy protein and soy isoflavones on calcium metabolism in postmenopausal women: A randomized crossover study. *Am J Clin Nutr*. 2005 Apr; 81 (4): 916-922. PMID: 15817872.	Does not answer question: Outcome was calcium metabolism, not selected health outcome.
St-Onge MP, Claps N, Wolper C, Heymsfield SB. Supplementation with soy-protein-rich foods does not enhance weight loss. *J Am Diet Assoc.* 2007 Mar; 107 (3): 500-505. PMID: 17324670.	Dropout rate higher than inclusion criteria.
Taku K, Umegaki K, Sato Y, Taki Y, Endoh K, Watanabe S. Soy isoflavones lower serum total and LDL cholesterol in humans: A meta-analysis of 11 randomized controlled trials. *Am J Clin Nutr.* 2007 Apr; 85 (4): 1, 148-1, 156. Erratum in: *Am J Clin Nutr*. 2007 Sep; 86 (3): 809. PMID: 17413118.	Does not answer question: Examined soy isoflavones, not soy protein.
Teede HJ, Dalais FS, Kotsopoulos D, Liang YL, Davis S, McGrath BP. Dietary soy has both beneficial and potentially adverse cardiovascular effects: A placebo-controlled study in men and postmenopausal women. *J Clin Endocrinol Metab.* 2001 Jul; 86 (7): 3, 053-3, 060. PMID: 11443167.	** Included in blood pressure review but excluded from cholesterol review because included in Harland, 2008 and Weggemans, 2003.
Teede HJ, Giannopoulos D, Dalais FS, Hodgson J, McGrath BP. Randomized, controlled, cross-over trial of soy protein with isoflavones on blood pressure and arterial function in hypertensive subjects. *J Am Coll Nutr.* 2006 Dec; 25 (6): 533-540. PMID: 17229901.	Participants were hypertensive.
Tonstad S, Smerud K, Høie L. A comparison of the effects of two doses of soy protein or casein on serum lipids, serum lipoproteins and plasma total homocysteine in hypercholesterolemic subjects. *Am J Clin Nutr.* 2002 Jul; 76 (1): 78-84. PMID: 12081819.	Participants were hypercholesterolemic.
Trock BJ, Hilakivi-Clarke L, Clarke R. Meta-analysis of soy intake and breast cancer risk. *J Natl Cancer Inst.* 2006 Apr 5; 98 (7): 459-471. PMID: 16595782.	Studies included in meta-analysis were excluded based on SC criteria; no prospective cohort studies with soy protein included in review.
Wang Y, Jones PJ, Ausman LM, Lichtenstein AH. Soy protein reduces triglyceride levels and triglyceride fatty acid fractional synthesis rate in hypercholesterolemic subjects. Atherosclerosis. 2004 Apr;173 (2): 269-275. PMID: 15064101.	Participants were hypercholesterolemic.
Wangen KE, Duncan AM, Xu X, Kurzer MS. Soy isoflavones improve plasma lipids in normocholesterolemic and mildly hypercholesterolemic postmenopausal women. Am *J Clin Nutr*. 2001 Feb; 73 (2): 225-231. PMID: 11157317.	Included in Zhan, 2005.

Weghuber D, Widhalm K. Effect of three-month treatment of children and adolescents with familial and polygenic hypercholesterolaemia with a soya-substituted diet. *Br J Nutr*. 2008 Feb; 99 (2): 281-286. Epub 2007 Aug 13. PMID: 17697400.	Participants were children and adolescents with familial or polygenic hypercholesterolemia.
Xu X, Duncan AM, Wangen KE, Kurzer MS. Soy consumption alters endogenous estrogen metabolism in postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2000 Aug; 9 (8): 781-786. PMID: 10952094.	Does not answer question: Examines soy consumption and estrogen metabolism.
Yildirir A, Tokgozoglu SL, Oduncu T, Oto A, Haznedaroglu I, Akinci D, Koksal G, Sade E, Kirazli S, Kes S. Soy protein diet significantly improves endothelial function and lipid parameters. *Clin Cardiol.* 2001 Nov; 24 (11): 711-716. PMID: 11714128.	Participants were hypercholesterolemic

CHAPTER 23. SOY PROTEIN – BLOOD PRESSURE

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF SOY PROTEIN AND BLOOD PRESSURE AMONG ADULTS WITHOUT HYPERTENSION?

Conclusion statement

A limited and inconsistent body of evidence shows that soy protein intake does not provide any unique benefits in blood pressure control.

Grade

Limited

Evidence summary overview

This review included five studies examining the relationship between soy protein and blood pressure (BP) or hypertension (HTN) among adults without HTN published since 2000. Three randomized controlled trials (RCTs) (He, 2005; Liao, 2007; Teede, 2002), one prospective cohort study (Yang, 2005) and one cross-sectional study (Pan, 2008) were included in the review. All of the studies were conducted outside of the US.

He et al, (2005) and Teede et al, (2002) conducted RCTs that included 40g of soy protein consumed per day over three months. In both studies, participants receiving soy protein supplementation experienced a significant decrease in SBP and DBP compared to the control groups. Liao and colleagues (2007) did not observe significant changes in SBP or DBP among participants consuming soy protein as the only protein source vs. a control diet with animal and plant protein for eight weeks; the groups consumed an isocaloric diet providing 1,200kcal per day

In the Shanghai Women's Health Study, SBP and DBP were lower in women who consumed ≥25g soy protein per day than in women consuming <2.5g per day (Yang, 2005). In cross-sectional analyses of the Nutrition and Health of Aging Population Project in China, soy protein intake and elevated BP were inversely associated in men, but not women (Pan, 2008); median soy protein in quartile one and quartile four of this study were 3g per day and 16g per day, respectively.

Evidence summary paragraphs

He et al, 2005 (positive quality), a double-blind, RCT conducted in the People's Republic of China, examined the effect of soybean protein supplementation on BP. Participants were adults with pre-hypertension or stage 1 HTN (initial N=302, final N=276; approximately 50% female; age 35 to 64 years) who were randomly assigned to receive 40g of isolated soybean protein supplement per day in cookies for 12 weeks or 40g of complex carbohydrate from wheat in cookies during the same period. Compliance was measured by participants returning uneaten cookies (93% compliance for each group). Participants were instructed to reduce other food intake so that total energy intake would remain constant. Blood pressure was assessed by study personnel at baseline, six weeks and 12 weeks. At baseline, mean (SD) SBP and DBP were 135.0 (10.9) mmHg and 84.7 (6.9) mmHg, respectively. Compared with the control group, the net changes in SBP and DBP were -4.31mmHg (95% CI: -2.11, -6.51mmHg; P<0.001) and -2.76mmHg (95% CI: -1.35, -4.16mm Hg; P<0.001),

respectively, after the 12-week intervention. For both SBP and DBP, the net reduction was greater in those with HTN than in those who were normotensive. The interaction between hypertensive status and BP effect of soybean protein was significant for both SBP (P=0.01) and DBP (P=0.007). The net changes in SBP and DBP reductions were -7.88mmHg (95% CI: -4.66, -11.1mmHg) and -5.27mmHg (95% CI: -3.05, -7.49mmHg), respectively, in persons with HTN and -2.34mmHg (95% CI: 0.48, -5.17mmHg) and -1.28mmHg (95% CI: 0.52, -3.07mmHg), respectively, in those without HTN. (The study was not designed to have sufficient statistical power to test for a BP reduction effect within sub-groups.) The authors concluded that soybean protein supplementation resulted in a reduction in SBP and DBP. Further, they suggested that increased intake of soybean protein may play an important role in preventing and treating HTN.

Teede et al, 2002 (positive quality) determined the effect of dietary soy supplementation on lipid parameters, BP, arterial compliance and endothelial function in an RCT in Australia. Participants were normotensive men and postmenopausal women (initial N=213, final N=179; 54% male; age 50 to 75 years) who received either soy protein isolate (40g soy protein, 118mg isoflavones) or casein placebo for three months. Participants consumed the supplements twice daily (in beverage form) in addition to their usual diet with no other modifications. Measurements were completed at baseline and three months. After intervention in the soy group, compared with casein placebo, a significant fall in BP was observed (P<0.01) encompassing mean change (±SEM) in SBP (-7.5±1.2 vs. -3.6±1.1mmHg, P<0.05), DBP (-4.3±0.8 vs. -1.9±0.7mmHg, P<0.05) and mean BP (-5.5±1 vs. -0.9±1mmHg, P<0.008). The authors concluded that soy improved BP in normotensive men and postmenopausal women.

Liao et al, 2007 (positive quality), an RCT, examined the effects of a soy-based diet compared with a traditional low-calorie diet on weight loss and blood lipid levels in 30 obese adults (mean BMI 29-30kg/m^2; 80% female) in China. Participants were randomized to two groups: The soy-based low-calorie group consumed soy protein as the only protein source, and the traditional low-calorie group consumed two-thirds animal protein and the rest plant protein in a 1,200kcal per day diet for eight weeks. Anthropometric data were acquired every week, and biochemical data from before and after the eight-week experiment were compared. Systolic blood pressure and DBP were not significantly (NS) different within either group or between groups between baseline and eight weeks.

Yang et al, 2005 (neutral quality) examined the association between usual intake of soy foods and BP among 45,694 women (age 40 to 70 years) in the Shanghai Women's Health Study. Women were excluded from analyses if they had a history of HTN or reported taking anti-hypertensive medications. Usual intake of soy foods over the previous 12 months was assessed at baseline with a validated food frequency questionnaire (FFQ) during a face-to-face interview. The questionnaire included 11 soy food items (i.e., tofu, soy milk, fried bean curd, bean curd cake and other kinds of soy products), covering virtually all soy foods consumed in urban Shanghai. Fresh and dried soybeans were also included. Blood pressure was measured two to three years after the baseline survey by study personnel. Soy protein intake was inversely associated with both SBP and DBP after adjustment for age, BMI and lifestyle and other dietary factors. The adjusted mean SBP was 1.9mmHg lower (95% CI: -3.0, -0.8mmHg; P for trend =0.01) and the DBP was 0.9mmHg lower (95% CI: -1.6, -

0.2mmHg; P for trend =0.009) in women who consumed ≥25g soy protein per day than in women consuming <2.5g per day. The authors concluded that usual intake of soy foods was significantly and inversely associated with both SBP and DBP.

Pan et al, 2008 (neutral quality) evaluated the association between soy protein intake and the risk of MetS and its components in a cross-sectional analysis of 2,811 adults (58% female; age 58.4+6.0 years) from the Nutrition and Health of Aging Population in China Project. Blood pressure was measured during physical examinations at local health stations or community clinics. Data on nutrient intake in the year prior to enrollment were derived from a quantitative FFQ that was administered during a personal interview. The FFQ included 74 food items and groups. Seven soy food items responsible for the majority of soy consumption were listed within the questionnaire, including fresh and dried soybeans, tofu, soy milk, jelly bean curd, soy sauce and other processed soy products. Soy protein intake and elevated BP were inversely associated in men (OR between extreme quartiles=0.59; 95% CI: 0.37, 0.95; P for trend=0.049), but NS association was observed for women (P for trend=0.284) or for men and women combined (P for trend=0.056).

Overview table

Author, Year, Study Design, Class, Rating	Study	Location	Soy Protein Association (Pos, Neg, None)
He J, Gu D et al, 2005 Study Design: Randomized controlled trial Class: A Positive quality	Adults with prehypertension or stage 1 HTN.	The People's Republic of China.	(-) SBP, (-) DBP.
Liao et al 2007 Study Design: randomized intervention trial Class: A Positive quality	Isocaloric Weight Loss Interventions.	China.	Ø SBP, Ø DBP.
Pan et al 2008 Study Design: cross sectional study Class: D Neutral quality	Nutrition and Health of Aging Population Project.	China.	(-) ↑ BP in men, Ø ↑ BP in women.

Teede HJ, Dalais FS et al, 2001 Study Design: RCT Class: A Positive quality	Normotensive men and postmenopausal women.	Australia.	(-) BP, (-) SBP, (-) DBP.
Yang G, Shu XO et al, 2005 Study Design: Prospective cohort, longitudinal study Class: B Neutral quality	Shanghai Women's Health Study.	China.	(-) SBP, (-) DBP.

Search plan and results

Inclusion criteria

- January 2000 to September 2009
- Prospective cohort studies on colorectal, breast and prostate cancers
- All study types for other health outcomes
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children two to 18 years; Adults 19 years and older
- *Populations:* Healthy, those with elevated chronic disease risk.

Exclusion criteria

- Medical treatment or therapy
- Systematic reviews and meta-analyses on colorectal, breast and prostate cancers
- Narrative reviews
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "overweight"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mh:NoExp] OR "heart diseases"[mh] OR "Coronary Disease"[Mesh] OR "blood pressure"[mh] OR "chronic disease"[mh] OR

obesity[mh] OR "Body Weights and Measures"[mh]) AND ("Soybean Proteins"[Mesh] OR "Vegetable Proteins"[Mesh]) Limit Eng/humans ("Soybean Proteins"[Mesh] OR "Vegetable Proteins"[Mesh]) AND ("Prostatic Neoplasms"[Mesh] OR "Breast Neoplasms"[Mesh] OR "Colorectal Neoplasms"[mesh]) clinical trials "Cohort Studies"[Mesh]

Date searched: 09/19/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 343
- Total articles identified to review from electronic databases: 86
- Articles identified via handsearch or other means: 8
- Number of Primary Articles Identified: 19
- Number of Review Articles Identified: 5
- Total Number of Articles Identified: 24
- Number of Articles Reviewed but Excluded: 70

Included articles (References)

What is the relationship between the intake of vegetable protein, including soy protein and chronic disease?

1. Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. *Am J Clin Nutr*. 2008 Feb; 87 (2): 339-346. PMID: 18258623. (Hand search)
2. Kelemen LE, Kushi LH, Jacobs DR Jr, Cerhan JR. Associations of dietary protein with disease and mortality in a prospective study of postmenopausal women. *Am J Epidemiol*. 2005 Feb 1; 161 (3): 239-249. PMID: 15671256.
3. Lee SA, Shu XO, Li H, Yang G, Cai H, Wen W, Ji BT, Gao J, Gao YT, Zheng W. Adolescent and adult soy food intake and breast cancer risk: Results from the Shanghai Women's Health Study. *Am J Clin Nutr*. 2009 Jun; 89 (6): 1, 920-1, 926. Epub 2009 Apr 29. PMID: 19403632; PMCID: PMC2683002.
4. Sluijs I, Beulens JW, van der A DL, Spijkerman AM, Grobbee DE, van der Schouw YT. Dietary intake of total, animal, and vegetable protein and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-NL study. *Diabetes Care.* 2010 Jan; 33(1): 43-48. Epub 2009 Oct 13. PMID: 19825820; PMCID: PMC2797984. (Hand search)
5. Song Y, Manson JE, Buring JE, Liu S. A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: The women's health study. *Diabetes Care*. 2004 Sep; 27 (9): 2, 108-2, 115. PMID: 15333470. (Hand search)
6. Nagata C. Ecological study of the association between soy product intake and mortality from cancer and heart disease in Japan. *Int J Epidemiol*. 2000 Oct; 29 (5): 832-836. PMID: 11034965.

What is the relationship between the intake of vegetable protein and blood pressure among adults without hypertension?

1. Stamler J, Liu K, Ruth KJ, Pryer J, Greenland P. Eight-year blood pressure change in middle-aged men: Relationship to multiple nutrients. *Hypertension.* 2002 May; 39 (5): 1, 000-1, 0006. PMID: 12019283. (Hand search)

2. Wang YF, Yancy WS Jr, Yu D, Champagne C, Appel LJ, Lin PH. The relationship between dietary protein intake and blood pressure: results from the PREMIER study. *J Hum Hypertens*. 2008 Nov; 22 (11): 745-754. Epub 2008 Jun 26. PMID: 18580887.
3. Steffen LM, Kroenke CH, Yu X, Pereira MA, Slattery ML, Van Horn L, Gross MD, Jacobs DR Jr. Associations of plant food, dairy product, and meat intakes with 15-year incidence of elevated blood pressure in young black and white adults: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr.* 2005 Dec; 82 (6): 1, 169-1, 177; quiz 1, 363-1, 364. PMID: 16332648. (Hand search)
4. Elliott P, Stamler J, Dyer AR, Appel L, Dennis B, Kesteloot H, Ueshima H, Okayama A, Chan Q, Garside DB, Zhou B. Association between protein intake and blood pressure: The INTERMAP Study. *Arch Intern Med.* 2006 Jan 9; 166 (1): 79-87. PMID: 16401814.
5. Umesawa M, Sato S, Imano H, Kitamura A, Shimamoto T, Yamagishi K, Tanigawa T, Iso H. Relations between protein intake and blood pressure in Japanese men and women: The Circulatory Risk in Communities Study (CIRCS). *Am J Clin Nutr*. 2009 Aug; 90 (2): 377-384. Epub 2009 Jun 10. PMID: 19515740.

What is the relationship between the intake of soy protein and blood pressure among adults without hypertension?

1. Teede HJ, Dalais FS, Kotsopoulos D, Liang YL, Davis S, McGrath BP. Dietary soy has both beneficial and potentially adverse cardiovascular effects: A placebo-controlled study in men and postmenopausal women. *J Clin Endocrinol Metab.* 2001 Jul; 86 (7): 3, 053-3, 060. PMID: 11443167.
2. Liao FH, Shieh MJ, Yang SC, Lin SH, Chien YW. Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in overweight adults. *Nutrition.* 2007 Jul-Aug; 23 (7-8): 551-556. Epub 2007 Jun 15. PMID: 17574819.
3. Pan A, Franco OH, Ye J, Demark-Wahnefried W, Ye X, Yu Z, Li H, Lin X. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in middle-aged and elderly Chinese. *J Nutr.* 2008 Dec; 138 (12): 2, 413-2, 421. PMID: 19022966.

What is the relationship between the intake of soy protein and body weight?

Systematic Review

1. Cope MB, Erdman JW Jr, Allison DB. The potential role of soy foods in weight and adiposity reduction: An evidence-based review. *Obes Rev.* 2008 May; 9 (3): 219-235. Review. PMID: 18419671. (Hand search)

Primary Citations

1. Liao FH, Shieh MJ, Yang SC, Lin SH, Chien YW. Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in overweight adults. *Nutrition*. 2007 Jul-Aug; 23 (7-8): 551-556. Epub 2007 Jun 15. PMID: 17574819.
2. McVeigh BL, Dillingham BL, Lampe JW, Duncan AM. Effect of soy protein varying in isoflavone content on serum lipids in healthy young men. *Am J Clin*

Nutr. 2006 Feb; 83 (2): 244-251. PMID: 16469981.
3. Pan A, Franco OH, Ye J, Demark-Wahnefried W, Ye X, Yu Z, Li H, Lin X. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in middle-aged and elderly Chinese. *J Nutr.* 2008 Dec; 138 (12): 2, 413-2, 421. PMID: 19022966.

Systematic Reviews / Meta-Analyses

1. Yang G, Shu XO, Jin F, Zhang X, Li HL, Li Q, Gao YT, Zheng W. Longitudinal study of soy food intake and blood pressure among middle-aged and elderly Chinese women. *Am J Clin Nutr*. 2005 May; 81 (5): 1, 012-1, 017. PMID: 15883423.
2. Harland JI, Haffner TA. Systematic review, meta-analysis and regression of randomized controlled trials reporting an association between an intake of circa 25g soy protein per day and blood cholesterol. *Atherosclerosis*. 2008 Sep; 200 (1): 13-27. Epub 2008 Apr 15. Review. PMID: 18534601.

What is the relationship between the intake of soy protein and blood lipids among adults without hyperlipidemia?

1. Reynolds K, Chin A, Lees KA, Nguyen A, Bujnowski D, He J. A meta-analysis of the effect of soy protein supplementation on serum lipids. *Am J Cardiol*. 2006 Sep 1; 98 (5): 633-640. Epub 2006 Jul 12. PMID: 16923451. (Hand search)
2. Weggemans RM, Trautwein EA. Relation between soy-associated isoflavones and LDL and HDL cholesterol concentrations in humans: A meta-analysis. *Eur J Clin Nutr.* 2003 Aug; 57 (8): 940-946. PMID: 12879088.
3. Zhan S, Ho SC. Meta-analysis of the effects of soy protein containing isoflavones on the lipid profile. *Am J Clin Nutr.* 2005 Feb; 81 (2): 397-408. PMID: 15699227.

Primary Citations

1. Liao FH, Shieh MJ, Yang SC, Lin SH, Chien YW. Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in overweight adults. *Nutrition. 2007* Jul-Aug; 23 (7-8): 551-556. Epub 2007 Jun 15. PMID: 17574819.
2. Pan A, Franco OH, Ye J, Demark-Wahnefried W, Ye X, Yu Z, Li H, Lin X. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in middle-aged and elderly Chinese. *J Nutr*. 2008 Dec; 138 (12): 2, 413-2, 421. PMID: 19022966.
3. He J, Gu D, Wu X, Chen J, Duan X, Chen J, Whelton PK. Effect of soybean protein on blood pressure: A randomized, controlled trial. *Ann Intern Med.* 2005 Jul 5; 143 (1):1-9. PMID: 15998749.
4. Alonso A, Beunza JJ, Bes-Rastrollo M, Pajares RM, Martínez-González MA. Vegetable protein and fiber from cereal are inversely associated with the risk of hypertension in a Spanish cohort. *Arch Med Res*. 2006 Aug; 37 (6): 778-786. PMID: 16824939.
5. Halton TL, Willett WC, Liu S, Manson JE, Albert CM, Rexrode K, Hu FB. Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med*. 2006 Nov 9; 355 (19): 1, 991-2, 002. PMID: 17093250. (Hand search)

Excluded articles

Article	Reason for Exclusion
Ashton EL, Dalais FS, Ball MJ. Effect of meat replacement by tofu on CHD risk factors including copper induced LDL oxidation. *J Am Coll Nutr.* 2000 Nov-Dec; 19 (6): 761-767. PMID: 11194529.	Included in Zhan, 2005.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Hu FB, Willett WC. Dietary soya intake alters plasma antioxidant status and lipid peroxidation in postmenopausal women with the metabolic syndrome. *Br J Nutr.* 2007 Oct; 98 (4): 807-813. Epub 2007 May 17. PMID: 17506931.	Participants diagnosed with metabolic syndrome.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Hu FB, Willett WC. Soy consumption, markers of inflammation, and endothelial function: A cross-over study in postmenopausal women with the metabolic syndrome. *Diabetes Care*. 2007 Apr; 30 (4): 967-973. PMID: 17392557.	Participants diagnosed with metabolic syndrome.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Padyab M, Hu FB, Willett WC. Soy inclusion in the diet improves features of the metabolic syndrome: a randomized crossover study in postmenopausal women. *Am J Clin Nutr.* 2007 Mar; 85 (3): 735-741. PMID: 17344494.	Participants diagnosed with metabolic syndrome.
Azadbakht L, Shakerhosseini R, Atabak S, Jamshidian M, Mehrabi Y, Esmaill-Zadeh A. Beneficiary effect of dietary soy protein on lowering plasma levels of lipid and improving kidney function in type II diabetes with nephropathy. *Eur J Clin Nutr.* 2003 Oct; 57 (10): 1, 292-1, 294. PMID: 14506491.	Participants diagnosed with type 2 diabetes with nephropathy.
Badger TM, Ronis MJ, Simmen RC, Simmen FA. Soy protein isolate and protection against cancer. *J Am Coll Nutr.* 2005 Apr; 24 (2): 146S-149S. PMID: 15798082.	Publication is a summary of a review presented at a professional meeting.
Blum A, Lang N, Vigder F, Israeli P, Gumanovsky M, Lupovitz S, Elgazi A, Peleg A, Ben-Ami M. Effects of soy protein on endothelium-dependent vasodilatation and lipid profile in postmenopausal women with mild hypercholesterolemia. *Clin Invest Med.* 2003 Feb; 26 (1): 20-26. PMID: 12659466.	Participants had mild hypercholesterolemia; included in Harland, 2008.
Brown BD, Thomas W, Hutchins A, Martini MC, Slavin JL. Types of dietary fat and soy minimally affect hormones and biomarkers associated with breast cancer risk in premenopausal women. *Nutr Cancer.* 2002; 43 (1): 22-30. PMID: 12467131.	Does not answer question: examined biomarkers associated with breast cancer, not incidence of breast cancer (not a prospective cohort study).
Chan YH, Lau KK, Yiu KH, Li SW, Chan HT, Tam S, Shu XO, Lau CP, Tse HF. Isoflavone intake in persons at high risk of cardiovascular events: Implications for vascular endothelial function and the carotid atherosclerotic burden. *Am J Clin Nutr.* 2007 Oct; 86 (4): 938-945. PMID: 17921368.	Participants (94%) had CAD or stroke; does not answer question: Outcomes were carotid intima-media thickness and flow-mediated dilation

Chen ST, Ferng SH, Yang CS, Peng SJ, Lee HR, Chen JR. Variable effects of soy protein on plasma lipids in hyperlipidemic and normolipidemic hemodialysis patients. *Am J Kidney Dis.* 2005 Dec; 46 (6): 1, 099-1, 106. PMID: 16310576.	Participants were hemodialysis patients.
Chiechi LM, Secreto G, Vimercati A, Greco P, Venturelli E, Pansini F, Fanelli M, Loizzi P, Selvaggi L. The effects of a soy rich diet on serum lipids: the Menfis randomized trial. *Maturitas*. 2002 Feb 26; 41 (2): 97-104. PMID: 11836040.	Dropout rate higher than inclusion criteria.
Cicero AF, Minardi M, Mirembe S, Pedro E, Gaddi A. Effects of a new low dose soy protein/beta-sitosterol association on plasma lipid levels and oxidation. *Eur J Nutr.* 2004 Oct; 43 (5): 319-322. Epub 2004 Jan 26. PMID: 15309453.	Participants were hypercholesterolemic; does not answer question: Tested a formulation of soy protein with added beta-sitosterol.
Cuevas AM, Irribarra VL, Castillo OA, Yañez MD, Germain AM. Isolated soy protein improves endothelial function in postmenopausal hypercholesterolemic women. *Eur J Clin Nutr.* 2003 Aug; 57 (8): 889-894. PMID: 12879082.	Participants were hypercholesterolemic.
Cupisti A, D'Alessandro C, Ghiadoni L, Morelli E, Panichi V, Barsotti G. Effect of a soy protein diet on serum lipids of renal transplant patients. *J Ren Nutr.* 2004 Jan; 14 (1): 31-35. PMID: 14740328.	Participants had renal transplantation.
Desroches S, Mauger JF, Ausman LM, Lichtenstein AH, Lamarche B. Soy protein favorably affects LDL size independently of isoflavones in hypercholesterolemic men and women. *J Nutr.* 2004 Mar; 134 (3): 574-579. PMID: 14988449.	Participants were hypercholesterolemic.
Dewell A, Weidner G, Sumner MD, Barnard RJ, Marlin RO, Daubenmier JJ, Chi C, Carroll PR, Ornish D. Relationship of dietary protein and soy isoflavones to serum IGF-1 and IGF binding proteins in the Prostate Cancer Lifestyle Trial. *Nutr Cancer.* 2007; 58 (1): 35-42. PMID: 17571965.	Participants were diagnosed with prostate cancer.
Dillingham BL, McVeigh BL, Lampe JW, Duncan AM. Soy protein isolates of varying isoflavone content exert minor effects on serum reproductive hormones in healthy young men. *J Nutr.* 2005 Mar; 135 (3): 584-591. PMID: 15735098.	Does not answer question: Examined soy protein intake on reproductive hormones.
Engelman HM, Alekel DL, Hanson LN, Kanthasamy AG, Reddy MB. Blood lipid and oxidative stress responses to soy protein with isoflavones and phytic acid in postmenopausal women. *Am J Clin Nutr.* 2005 Mar; 81 (3): 590-596. PMID: 15755827.	Does not answer question: Examined impact of soy protein components (isoflavones and phytate) on blood lipids and oxidative stress.
Gardner CD, Messina M, Kiazand A, Morris JL, Franke AA. Effect of two types of soy milk and dairy milk on plasma lipids in hypercholesterolemic adults: A randomized trial. *J Am Coll Nutr.* 2007 Dec; 26 (6): 669-677. PMID: 18187432.	Participants were hypercholesterolemic; included in Harland, 2008.

Gardner CD, Newell KA, Cherin R, Haskell WL. The effect of soy protein with or without isoflavones relative to milk protein on plasma lipids in hypercholesterolemic postmenopausal women. *Am J Clin Nutr*. 2001 Apr; 73 (4): 728-735. PMID: 11273847.	Participants were hypercholesterolemic; included in Weggemans, 2003.
Genovese MI, Lajolo FM. Isoflavones in soy-based foods consumed in Brazil: Levels, distribution, and estimated intake. *J Agric Food Chem*. 2002 Oct 9; 50 (21): 5, 987-5, 993. PMID: 12358470.	Does not include health outcomes in analyses.
Giampietro PG, Bruno G, Furcolo G, Casati A, Brunetti E, Spadoni GL, Galli E. Soy protein formulas in children: No hormonal effects in long-term feeding. *J Pediatr Endocrinol Metab.* 2004 Feb;17 (2): 191-196. PMID: 15055353.	Does not answer question: Examined hormonal and metabolic effects of long-term soy protein formula feeding.
Goldin BR, Brauner E, Adlercreutz H, Ausman LM, Lichtenstein AH. Hormonal response to diets high in soy or animal protein without and with isoflavones in moderately hypercholesterolemic subjects. *Nutr Cancer*. 2005; 51 (1): 1-6. PMID: 15749623.	Participants were hypercholesterolemic; does not answer question: Examined hormonal response to diets high in soy or animal protein.
Grainger EM, Schwartz SJ, Wang S, Unlu NZ, Boileau TW, Ferketich AK, Monk JP, Gong MC, Bahnson RR, DeGroff VL, Clinton SK. A combination of tomato and soy products for men with recurring prostate cancer and rising prostate specific antigen. *Nutr Cancer*. 2008; 60 (2): 145-154. PMID: 18444145.	Participants diagnosed with prostate cancer.
Greany KA, Nettleton JA, Wangen KE, Thomas W, Kurzer MS. Consumption of isoflavone-rich soy protein does not alter homocysteine or markers of inflammation in postmenopausal women. *Eur J Clin Nutr.* 2008 Dec; 62 (12): 1, 419-1, 425. Epub 2007 Sep 5. PMID: 17805230.	Does not answer question: Does not examine outcome of interest (examines homocysteine, C-reactive protein and adhesion molecules).
Greany KA, Nettleton JA, Wangen KE, Thomas W, Kurzer MS. Probiotic consumption does not enhance the cholesterol-lowering effect of soy in postmenopausal women. *J Nutr.* 2004 Dec; 134 (12): 3, 277-3, 283. PubMed PMID: 15570025.	Participants were hypercholesterolemic; included in Harland, 2008.
Hamilton-Reeves JM, Rebello SA, Thomas W, Kurzer MS, Slaton JW. Effects of soy protein isolate consumption on prostate cancer biomarkers in men with HGPIN, ASAP, and low-grade prostate cancer. *Nutr Cancer*. 2008; 60 (1): 7-13. PMID: 18444130.	Not a prospective cohort study examining incidence of prostate cancer. Outcomes were prostate cancer biomarkers.
Hamilton-Reeves JM, Rebello SA, Thomas W, Slaton JW, Kurzer MS. Soy protein isolate increases urinary estrogens and the ratio of 2:16alpha-hydroxyestrone in men at high risk of prostate cancer. *J Nutr.* 2007 Oct; 137 (10): 2, 258-2, 263. PMID: 17885008.	Not a prospective cohort study examining incidence of prostate cancer. Outcomes were prostate cancer biomarkers.

Hamilton-Reeves JM, Rebello SA, Thomas W, Slaton JW, Kurzer MS. Isoflavone-rich soy protein isolate suppresses androgen receptor expression without altering estrogen receptor-beta expression or serum hormonal profiles in men at high risk of prostate cancer. *J Nutr.* 2007 Jul; 137 (7): 1, 769-1, 775. PMID: 17585029.	Not a prospective cohort study examining incidence of prostate cancer. Outcomes were prostate cancer biomarkers.
Harrison RA, Sagara M, Rajpura A, Armitage L, Birt N, Birt CA, Yamori Y. Can foods with added soya-protein or fish-oil reduce risk factors for coronary disease? A factorial randomised controlled trial. *Nutr Metab Cardiovasc Dis*. 2004 Dec; 14 (6): 344-350. PMID: 15853118.	Participants had elevated total cholesterol or blood pressure.
Hartman JW, Tang JE, Wilkinson SB, Tarnopolsky MA, Lawrence RL, Fullerton AV, Phillips SM. Consumption of fat-free fluid milk after resistance exercise promotes greater lean mass accretion than does consumption of soy or carbohydrate in young, novice, male weightlifters. *Am J Clin Nutr.* 2007 Aug; 86 (2): 373-381. PMID: 17684208.	Does not answer question: Does not examine relationship between vegetable protein and health (examined consumption of various isocaloric drinks on lean mass accretion following resistance training).
Hoie LH, Guldstrand M, Sjoholm A, Graubaum HJ, Gruenwald J, Zunft HJ, Lueder W. Cholesterol-lowering effects of a new isolated soy protein with high levels of nondenaturated protein in hypercholesterolemic patients. *Adv Ther.* 2007 Mar-Apr; 24 (2): 439-447. PMID: 17565935.	Participants were hypercholesterolemic; included in Harland, 2008.
Hoie LH, Morgenstern EC, Gruenwald J, Graubaum HJ, Busch R, Lüder W, Zunft HJ. A double-blind placebo-controlled clinical trial compares the cholesterol-lowering effects of two different soy protein preparations in hypercholesterolemic subjects. *Eur J Nutr.* 2005 Mar; 44 (2): 65-71. Epub 2004 Apr 5. PMID: 15309422.	Participants were hypercholesterolemic; included in Harland, 2008.
Hori G, Wang MF, Chan YC, Komatsu T, Wong Y, Chen TH, Yamamoto K, Nagaoka S, Yamamoto S. Soy protein hydrolyzate with bound phospholipids reduces serum cholesterol levels in hypercholesterolemic adult male volunteers. *Biosci Biotechnol Biochem*. 2001 Jan; 65 (1): 72-78. PMID: 11272848.	Participants were hypercholesterolemic.
Jenkins DJ, Kendall CW, Jackson CJ, Connelly PW, Parker T, Faulkner D, Vidgen E, Cunnane SC, Leiter LA, Josse RG. Effects of high- and low-isoflavone soyfoods on blood lipids, oxidized LDL, homocysteine, and blood pressure in hyperlipidemic men and women. *Am J Clin Nutr*. 2002 Aug; 76 (2): 365-372. PMID: 12145008.	Participants were hyperlipidemic; included in Weggemans, 2003.
Jenkins DJ, Kendall CW, D'Costa MA, Jackson CJ, Vidgen E, Singer W, Silverman JA, Koumbridis G, Honey J, Rao AV, Fleshner N, Klotz L. Soy consumption and phytoestrogens: effect on serum prostate specific antigen when blood lipids and oxidized low-density lipoprotein are reduced in hyperlipidemic men. *J Urol.* 2003 Feb; 169 (2): 507-511. PMID: 12544298.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Garsetti M, Rosenberg-Zand RS, Jackson CJ, Agarwal S, Rao AV, Diamandis EP, Parker T, Faulkner D, Vuksan V, Vidgen E. Effect of soy protein foods on low-density lipoprotein oxidation and ex vivo sex hormone receptor activity: A controlled crossover trial. *Metabolism.* 2000 Apr; 49 (4): 537-543. PMID: 10778882.	Participants were hyperlipidemic; included in Harland, 2008.

Jenkins DJ, Wong JM, Kendall CW, Esfahani A, Ng VW, Leong TC, Faulkner DA, Vidgen E, Greaves KA, Paul G, Singer W. The effect of a plant-based low-carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. *Arch Intern Med.* 2009 Jun 8; 169 (11): 1, 046-1, 054. Erratum in: Arch Intern Med. 2009 Sep 14; 169 (16): 1, 490. PMID: 19506174.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Faulkner DA, Kemp T, Marchie A, Nguyen TH, Wong JM, de Souza R, Emam A, Vidgen E, Trautwein EA, Lapsley KG, Josse RG, Leiter LA, Singer W. Long-term effects of a plant-based dietary portfolio of cholesterol-lowering foods on blood pressure. *Eur J Clin Nutr*. 2008 Jun; 62 (6): 781-788. Epub 2007 Apr 25. PMID: 17457340.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Marchie A, Faulkner D, Vidgen E, Lapsley KG, Trautwein EA, Parker TL, Josse RG, Leiter LA, Connelly PW. The effect of combining plant sterols, soy protein, viscous fibers, and almonds in treating hypercholesterolemia. *Metabolism*. 2003 Nov; 52 (11): 1, 478-1, 483. PMID: 14624410.	Participants were hypercholesterolemic; included in Cope, 2008.
Jenkins DJ, Kendall CW, Vidgen E, Mehling CC, Parker T, Seyler H, Faulkner D, Garsetti M, Griffin LC, Agarwal S, Rao AV, Cunnane SC, Ryan MA, Connelly PW, Leiter LA, Vuksan V, Josse R. The effect on serum lipids and oxidized low-density lipoprotein of supplementing self-selected low-fat diets with soluble-fiber, soy and vegetable protein foods. *Metabolism.* 2000 Jan; 49 (1): 67-72. PMID: 10647066.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Faulkner D, Vidgen E, Trautwein EA, Parker TL, Marchie A, Koumbridis G, Lapsley KG, Josse RG, Leiter LA, Connelly PW. A dietary portfolio approach to cholesterol reduction: combined effects of plant sterols, vegetable proteins, and viscous fibers in hypercholesterolemia. *Metabolism*. 2002 Dec; 51 (12): 1, 596-1, 604. PMID: 12489074.	Participants were hypercholesterolemic.
Jones PJ, Raeini-Sarjaz M, Jenkins DJ, Kendall CW, Vidgen E, Trautwein EA, Lapsley KG, Marchie A, Cunnane SC, Connelly PW. Effects of a diet high in plant sterols, vegetable proteins, and viscous fibers (dietary portfolio) on circulating sterol levels and red cell fragility in hypercholesterolemic subjects. *Lipids.* 2005 Feb; 40 (2): 169-174. PMID: 15884765.	Participants were hypercholesterolemic.
Kreijkamp-Kaspers S, Kok L, Bots ML, Grobbee DE, Lampe JW, van der Schouw YT. Randomized controlled trial of the effects of soy protein containing isoflavones on vascular function in postmenopausal women. *Am J Clin Nutr.* 2005 Jan; 81 (1): 189-195. PMID: 15640479.	Dropout rate higher than inclusion criteria.
Lichtenstein AH, Jalbert SM, Adlercreutz H, Goldin BR, Rasmussen H, Schaefer EJ, Ausman LM. Lipoprotein response to diets high in soy or animal protein with and without isoflavones in moderately hypercholesterolemic subjects. *Arterioscler Thromb Vasc Biol.* 2002 Nov 1; 22 (11): 1, 852-1, 858. PMID: 12426215.	Participants were hypercholesterolemic; included in Reynolds, 2006.

Luiking YC, Deutz NE, Jäkel M, Soeters PB. Casein and soy protein meals differentially affect whole-body and splanchnic protein metabolism in healthy humans. *J Nutr.* 2005 May; 135 (5): 1, 080-1, 087. PMID: 15867285.	Does not answer question: study examined protein metabolism, not relationship between protein and selected health outcomes.
Ma Y, Chiriboga D, Olendzki BC, Nicolosi R, Merriam PA, Ockene IS. Effect of soy protein containing isoflavones on blood lipids in moderately hypercholesterolemic adults: A randomized controlled trial. *J Am Coll Nutr.* 2005 Aug; 24 (4): 275-285. PMID: 16093405.	Participants were hypercholesterolemic.
Mackey R, Ekangaki A, Eden JA. The effects of soy protein in women and men with elevated plasma lipids. *Biofactors*. 2000; 12 (1-4): 251-257. PMID: 11216493.	Participants were hyperlipidemic.
Maskarinec G. Soy foods for breast cancer survivors and women at high risk for breast cancer? *J Am Diet Assoc.* 2005 Oct; 105 (10): 1, 524-1, 528. PMID: 16183350.	Publication is Commentary.
Matthan NR, Jalbert SM, Ausman LM, Kuvin JT, Karas RH, Lichtenstein AH. Effect of soy protein from differently processed products on cardiovascular disease risk factors and vascular endothelial function in hypercholesterolemic subjects. *Am J Clin Nutr.* 2007 Apr; 85 (4): 960-966. Erratum in: *Am J Clin Nutr.* 2007 Aug; 86 (2): 525. PMID: 17413093.	Participants were hypercholesterolemic; included in Harland, 2008.
McVeigh BL, Dillingham BL, Lampe JW, Duncan AM. Effect of soy protein varying in isoflavone content on serum lipids in healthy young men. *Am J Clin Nutr.* 2006 Feb; 83 (2): 244-251. PMID: 16469981.	**Included in body weight review, but excluded from cholesterol review because included in Harland, 2008.
Merritt JC. Metabolic syndrome: soybean foods and serum lipids. *J Natl Med Assoc.* 2004 Aug; 96 (8): 1, 032-1, 041. PubMed PMID: 15303407; Central PMCID: PMC2568482.	Study design is narrative review.
Möllsten AV, Dahlquist GG, Stattin EL, Rudberg S. Higher intakes of fish protein are related to a lower risk of microalbuminuria in young Swedish type 1 diabetic patients. *Diabetes Care*. 2001 May; 24 (5): 805-810. PMID: 11347734.	Participants were diagnosed with type 1 diabetes.
Nagata C, Shimizu H, Takami R, Hayashi M, Takeda N, Yasuda K. Association of blood pressure with intake of soy products and other food groups in Japanese men and women. *Prev Med.* 2003 Jun; 36 (6): 692-697. PMID: 12744912.	Does not answer question: Examined soy food intake, not soy protein.
Puska P, Korpelainen V, Høie LH, Skovlund E, Smerud KT. Isolated soya protein with standardized levels of isoflavones, cotyledon soya fibres and soya phospholipids improves plasma lipids in hypercholesterolaemia: A double-blind, placebo-controlled trial of a yoghurt formulation. *Br J Nutr.* 2004 Mar; 91 (3): 393-401. PMID: 15005825.	Does not answer question: Examined yogurt formulation containing isolated soya protein, isoflavones, cotyledon soya fibers and soya phospholipids.

Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M; American Heart Association Nutrition Committee. Soy protein, isoflavones, and cardiovascular health: An American Heart Association Science Advisory for professionals from the Nutrition Committee. *Circulation.* 2006 Feb 21; 113 (7): 1, 034-1, 044. Epub 2006 Jan 17. PMID: 16418439.	Publication is AHA Science Advisory; reference list was reviewed.
Sagara M, Kanda T, NJelekera M, Teramoto T, Armitage L, Birt N, Birt C, Yamori Y. Effects of dietary intake of soy protein and isoflavones on cardiovascular disease risk factors in high risk, middle-aged men in Scotland. *J Am Coll Nutr.* 2004 Feb; 23 (1): 85-91. PMID: 14963058.	Included in Harland, 2008.
Sanders TA, Dean TS, Grainger D, Miller GJ, Wiseman H. Moderate intakes of intact soy protein rich in isoflavones compared with ethanol-extracted soy protein increase HDL but do not influence transforming growth factor beta(1) concentrations and hemostatic risk factors for coronary heart disease in healthy subjects. *Am J Clin Nutr.* 2002 Aug; 76 (2): 373-377. PMID: 12145009.	Does not answer question; design of the study does not allow for comparison between diets with and without soy protein. The study addresses the impact of isoflavones from soy on CHD risk.
Shahbazian H, Reza A, Javad S, Heshmatollah S, Mahmood L, Ali A, Hosain HM. Beneficial effects of soy protein isoflavones on lipid and blood glucose concentrations in type 2 diabetic subjects. *Saudi Med J.* 2007 Apr; 28 (4): 652-654. PMID: 17457503.	Participants diagnosed with type 2 diabetes.
Sirtori CR, Eberini I, Arnoldi A. Hypocholesterolaemic effects of soya proteins: Results of recent studies are predictable from the Anderson meta-analysis data. *Br J Nutr*. 2007 May; 97 (5): 816-822. Review. PMID: 17408521.	Not a systematic review or original research study (examines previous research using a predictive model).
Spence LA, Lipscomb ER, Cadogan J, Martin B, Wastney ME, Peacock M, Weaver CM. The effect of soy protein and soy isoflavones on calcium metabolism in postmenopausal women: A randomized crossover study. *Am J Clin Nutr*. 2005 Apr; 81 (4): 916-922. PMID: 15817872.	Does not answer question: Outcome was calcium metabolism, not selected health outcome.
St-Onge MP, Claps N, Wolper C, Heymsfield SB. Supplementation with soy-protein-rich foods does not enhance weight loss. *J Am Diet Assoc.* 2007 Mar; 107 (3): 500-505. PMID: 17324670.	Dropout rate higher than inclusion criteria.
Taku K, Umegaki K, Sato Y, Taki Y, Endoh K, Watanabe S. Soy isoflavones lower serum total and LDL cholesterol in humans: A meta-analysis of 11 randomized controlled trials. *Am J Clin Nutr.* 2007 Apr; 85 (4): 1, 148-1, 156. Erratum in: *Am J Clin Nutr*. 2007 Sep; 86 (3): 809. PMID: 17413118.	Does not answer question: Examined soy isoflavones, not soy protein.
Teede HJ, Dalais FS, Kotsopoulos D, Liang YL, Davis S, McGrath BP. Dietary soy has both beneficial and potentially adverse cardiovascular effects: A placebo-controlled study in men and postmenopausal women. *J Clin Endocrinol Metab.* 2001 Jul; 86 (7): 3, 053-3, 060. PMID: 11443167.	** Included in blood pressure review but excluded from cholesterol review because included in Harland, 2008 and Weggemans, 2003.

Teede HJ, Giannopoulos D, Dalais FS, Hodgson J, McGrath BP. Randomized, controlled, cross-over trial of soy protein with isoflavones on blood pressure and arterial function in hypertensive subjects. *J Am Coll Nutr.* 2006 Dec; 25 (6): 533-540. PMID: 17229901.	Participants were hypertensive.
Tonstad S, Smerud K, Høie L. A comparison of the effects of two doses of soy protein or casein on serum lipids, serum lipoproteins and plasma total homocysteine in hypercholesterolemic subjects. *Am J Clin Nutr.* 2002 Jul; 76 (1): 78-84. PMID: 12081819.	Participants were hypercholesterolemic.
Trock BJ, Hilakivi-Clarke L, Clarke R. Meta-analysis of soy intake and breast cancer risk. *J Natl Cancer Inst.* 2006 Apr 5; 98 (7): 459-471. PMID: 16595782.	Studies included in meta-analysis were excluded based on SC criteria; no prospective cohort studies with soy protein included in review.
Wang Y, Jones PJ, Ausman LM, Lichtenstein AH. Soy protein reduces triglyceride levels and triglyceride fatty acid fractional synthesis rate in hypercholesterolemic subjects. Atherosclerosis. 2004 Apr;173 (2): 269-275. PMID: 15064101.	Participants were hypercholesterolemic.
Wangen KE, Duncan AM, Xu X, Kurzer MS. Soy isoflavones improve plasma lipids in normocholesterolemic and mildly hypercholesterolemic postmenopausal women. Am *J Clin Nutr*. 2001 Feb; 73 (2): 225-231. PMID: 11157317.	Included in Zhan, 2005.
Weghuber D, Widhalm K. Effect of three-month treatment of children and adolescents with familial and polygenic hypercholesterolaemia with a soya-substituted diet. *Br J Nutr*. 2008 Feb; 99 (2): 281-286. Epub 2007 Aug 13. PMID: 17697400.	Participants were children and adolescents with familial or polygenic hypercholesterolemia.
Xu X, Duncan AM, Wangen KE, Kurzer MS. Soy consumption alters endogenous estrogen metabolism in postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2000 Aug; 9 (8): 781-786. PMID: 10952094.	Does not answer question: Examines soy consumption and estrogen metabolism.
Yildirir A, Tokgozoglu SL, Oduncu T, Oto A, Haznedaroglu I, Akinci D, Koksal G, Sade E, Kirazli S, Kes S. Soy protein diet significantly improves endothelial function and lipid parameters. *Clin Cardiol.* 2001 Nov; 24 (11): 711-716. PMID: 11714128.	Participants were hypercholesterolemic

CHAPTER 24. SOY PROTEIN – BODY WEIGHT

WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF SOY PROTEIN AND BODY WEIGHT?

Conclusion statement

A moderate body of consistent evidence finds no unique benefit of soy protein intake on body weight.

Grade

Moderate

Evidence summary overview

This review included four articles that examined the relationship between intake of soy protein and measures of body weight published since 2000. One systematic review (Cope, 2008), one randomized controlled trial (RCT) (Liao, 2007), one crossover trial (McVeigh, 2006) and one cross-sectional study (Pan, 2008) were included in the review.

Cope and colleagues (2008) completed a systematic review including 91 international references with data from in vitro, animal, epidemiologic and clinical studies evaluating the relationship between soy foods, including soy protein and weight loss. The authors reported that studies with overweight and obese individuals suggest that soy, as a source of dietary protein, may be used to achieve significant weight loss; however, there is no convincing evidence to show whether soy protein is better than other protein sources to achieve weight loss when prescribed at isocaloric levels. Three additional studies identified in the NEL review support the conclusion by Cope et al, (2008). In an eight-week RCT, Liao et al, (2007) compared two 1,200kcal per day diets varying in protein source (soy as the only protein source vs. animal and plant protein sources). Body weight, BMI, body fat percentage and waist circumference decreased within both groups, but there were no significant differences between groups. In a randomized crossover trial, McVeigh and colleagues (2006) did not observe a difference in body weight, BMI or percent body fat following 57 days of supplementation with milk protein isolate or soy protein isolate. Finally, in the Nutrition and Health of Aging Population Project in China, no significant association was observed between soy protein intake and central obesity.

Evidence summary paragraphs

Systematic Review

Cope et al, 2008 (neutral quality), a systematic review including 91 international references, identified and evaluated evidence regarding soy foods and weight loss. Data from in vitro, animal, epidemiologic and clinical studies were evaluated and summarized. The authors reported that studies investigating weight loss in overweight and obese humans suggest that soy, as a source of dietary protein, may be used to achieve significant weight loss; however, there is no convincing evidence to show whether soy protein is better than other protein sources to achieve weight loss. Additionally, clinical data suggest that soy protein may be as good as other protein

sources for achieving weight loss in prescribed isocaloric settings, but suggest that soy consumption does not have a clear advantage over other protein sources for weight and fat loss when prescribed at isocaloric levels. The authors noted that additional evidence is needed before making firm conclusions regarding soy foods and weight loss.

Primary Citations

Liao et al., 2007 (positive quality), an RCT, examined the effects of a soy-based diet compared with a traditional low-calorie diet on weight loss and blood lipid levels in 30 obese adults (mean BMI 29-30kg/m^2; 80% female) in China. Participants were randomized to two groups: The soy-based low-calorie group consumed soy protein as the only protein source, and the traditional low-calorie group consumed two-thirds animal protein and the rest plant protein in a 1,200kcal per day diet for eight weeks. Anthropometric data were acquired every week and biochemical data from before and after the eight-week experiment were compared. Body weight, BMI, body fat percentage, and waist circumference significantly decreased within both groups ($P<0.05$), but there were no significant differences between groups.

McVeigh et al, 2006 (neutral quality) examined the effects of soy protein varying in isoflavone content on serum lipids in healthy young men (age 27.9±5.7 years) in a randomized crossover trial in Canada. 35 of 43 participants completed the study (19% dropout rate). Participants consumed their habitual diet plus milk protein isolate (MPI), low-isoflavone soy protein isolate (low-iso SPI; 1.64±0.19mg aglycone isoflavones per day) and high isoflavone SPI (high-iso SPI; 61.7±7.4mg aglycone isoflavones per day) for 57 days each, separated by four-week washout periods. Height and weight were measured by study personnel at baseline and every study visit. Body composition was measured using bioelectrical impedance analysis (BIA) on days one and 57 of each treatment period. During the study, there were no significant effects of treatment or treatment order on anthropometric measurements, including body weight, BMI, and percentage body fat (data not provided).

Pan et al, 2008 (neutral quality) evaluated the association between soy protein intake and the risk of MetS and its components in a cross-sectional analysis of 2,811 adults (58% female; age 58.4 plus 6.0 years) from the Nutrition and Health of Aging Population in China Project. Anthropometric measurements were conducted by trained staff and physicians. Data on nutrient intake in the year prior to enrollment were derived from a quantitative food frequency questionnaire (FFQ) that was administered during a personal interview. The FFQ included 74 food items and groups. Seven soy food items responsible for the majority of soy consumption were listed within the questionnaire, including fresh and dried soybeans, tofu, soy milk, jelly bean curd, soy sauce and other processed soy products. No significant association was observed between soy protein intake and central obesity for men (P for trend=0.655), women (P for trend=0.827), or for men and women combined (P for trend=0.757).

Overview table

Author, Year, Study Design, Class, Rating	Location	Soy Protein Association (Pos, Neg, None)
Cope MB et al 2008 Study Design: Systematic Review Class: M Neutral quality		Ø
Liao et al 2007 Study Design: randomized intervention trial Class: A Positive quality	China.	Ø
McVeigh et al 2006 Study Design: randomized crossover trial Class: A Positive quality	Canada.	Ø
Pan et al 2008 Study Design: cross sectional study Class: D Neutral quality	Nutrition and Health of Aging Population Project China.	Ø

Search plan and results

Inclusion criteria

- January 2000 to September 2009
- Prospective cohort studies on colorectal, breast and prostate cancers
- All study types for other health outcomes
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children two to 18 years; Adults 19 years and older
- *Populations:* Healthy, those with elevated chronic disease risk.

Exclusion criteria

- Medical treatment or therapy
- Systematic reviews and meta-analyses on colorectal, breast and prostate cancers
- Narrative reviews
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Pubmed: ("Diabetes Mellitus, Type 2"[mh] OR "metabolic syndrome X"[mh] OR "overweight"[mh] OR "hypertension"[mh] OR "dyslipidemias"[mh] OR "cardiovascular diseases"[mh:NoExp] OR “heart diseases”[mh] OR "Coronary Disease"[Mesh] OR “blood pressure”[mh] OR “chronic disease”[mh] OR obesity[mh] OR "Body Weights and Measures"[mh]) AND ("Soybean Proteins"[Mesh] OR "Vegetable Proteins"[Mesh]) Limit Eng/humans ("Soybean Proteins"[Mesh] OR "Vegetable Proteins"[Mesh]) AND ("Prostatic Neoplasms"[Mesh] OR "Breast Neoplasms"[Mesh] OR "Colorectal Neoplasms"[mesh]) clinical trials "Cohort Studies"[Mesh]

Date searched: 09/19/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 343
- Total articles identified to review from electronic databases: 86
- Articles identified via handsearch or other means: 8
- Number of Primary Articles Identified: 19
- Number of Review Articles Identified: 5
- Total Number of Articles Identified: 24
- Number of Articles Reviewed but Excluded: 70

Included articles (References)

What is the relationship between the intake of vegetable protein, including soy protein and chronic disease?

1. Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. *Am J Clin Nutr*. 2008 Feb; 87 (2): 339-346. PMID: 18258623. (Hand search)
2. Kelemen LE, Kushi LH, Jacobs DR Jr, Cerhan JR. Associations of dietary protein with disease and mortality in a prospective study of postmenopausal women. *Am J Epidemiol*. 2005 Feb 1; 161 (3): 239-249. PMID: 15671256.
3. Lee SA, Shu XO, Li H, Yang G, Cai H, Wen W, Ji BT, Gao J, Gao YT, Zheng W. Adolescent and adult soy food intake and breast cancer risk: Results from the Shanghai Women's Health Study. *Am J Clin Nutr*. 2009 Jun; 89 (6): 1, 920-1, 926. Epub 2009 Apr 29. PMID: 19403632; PMCID: PMC2683002.
4. Sluijs I, Beulens JW, van der A DL, Spijkerman AM, Grobbee DE, van der

Schouw YT. Dietary intake of total, animal, and vegetable protein and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-NL study. *Diabetes Care.* 2010 Jan; 33(1): 43-48. Epub 2009 Oct 13. PMID: 19825820; PMCID: PMC2797984. (Hand search)

5. Song Y, Manson JE, Buring JE, Liu S. A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: The women's health study. *Diabetes Care*. 2004 Sep; 27 (9): 2, 108-2, 115. PMID: 15333470. (Hand search)
6. Nagata C. Ecological study of the association between soy product intake and mortality from cancer and heart disease in Japan. *Int J Epidemiol*. 2000 Oct; 29 (5): 832-836. PMID: 11034965.

What is the relationship between the intake of vegetable protein and blood pressure among adults without hypertension?

1. Stamler J, Liu K, Ruth KJ, Pryer J, Greenland P. Eight-year blood pressure change in middle-aged men: Relationship to multiple nutrients. *Hypertension.* 2002 May; 39 (5): 1, 000-1, 0006. PMID: 12019283. (Hand search)
2. Wang YF, Yancy WS Jr, Yu D, Champagne C, Appel LJ, Lin PH. The relationship between dietary protein intake and blood pressure: results from the PREMIER study. *J Hum Hypertens*. 2008 Nov; 22 (11): 745-754. Epub 2008 Jun 26. PMID: 18580887.
3. Steffen LM, Kroenke CH, Yu X, Pereira MA, Slattery ML, Van Horn L, Gross MD, Jacobs DR Jr. Associations of plant food, dairy product, and meat intakes with 15-year incidence of elevated blood pressure in young black and white adults: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr.* 2005 Dec; 82 (6): 1, 169-1, 177; quiz 1, 363-1, 364. PMID: 16332648. (Hand search)
4. Elliott P, Stamler J, Dyer AR, Appel L, Dennis B, Kesteloot H, Ueshima H, Okayama A, Chan Q, Garside DB, Zhou B. Association between protein intake and blood pressure: The INTERMAP Study. *Arch Intern Med.* 2006 Jan 9; 166 (1): 79-87. PMID: 16401814.
5. Umesawa M, Sato S, Imano H, Kitamura A, Shimamoto T, Yamagishi K, Tanigawa T, Iso H. Relations between protein intake and blood pressure in Japanese men and women: The Circulatory Risk in Communities Study (CIRCS). *Am J Clin Nutr*. 2009 Aug; 90 (2): 377-384. Epub 2009 Jun 10. PMID: 19515740.

What is the relationship between the intake of soy protein and blood pressure among adults without hypertension?

1. Teede HJ, Dalais FS, Kotsopoulos D, Liang YL, Davis S, McGrath BP. Dietary soy has both beneficial and potentially adverse cardiovascular effects: A placebo-controlled study in men and postmenopausal women. *J Clin Endocrinol Metab.* 2001 Jul; 86 (7): 3, 053-3, 060. PMID: 11443167.
2. Liao FH, Shieh MJ, Yang SC, Lin SH, Chien YW. Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in overweight adults. *Nutrition.* 2007 Jul-Aug; 23 (7-8): 551-556. Epub 2007 Jun 15. PMID: 17574819.
3. Pan A, Franco OH, Ye J, Demark-Wahnefried W, Ye X, Yu Z, Li H, Lin X. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in

middle-aged and elderly Chinese. *J Nutr.* 2008 Dec; 138 (12): 2, 413-2, 421. PMID: 19022966.

What is the relationship between the intake of soy protein and body weight?

Systematic Review

1. Cope MB, Erdman JW Jr, Allison DB. The potential role of soy foods in weight and adiposity reduction: An evidence-based review. *Obes Rev.* 2008 May; 9 (3): 219-235. Review. PMID: 18419671. (Hand search)

Primary Citations

1. Liao FH, Shieh MJ, Yang SC, Lin SH, Chien YW. Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in overweight adults. *Nutrition*. 2007 Jul-Aug; 23 (7-8): 551-556. Epub 2007 Jun 15. PMID: 17574819.
2. McVeigh BL, Dillingham BL, Lampe JW, Duncan AM. Effect of soy protein varying in isoflavone content on serum lipids in healthy young men. *Am J Clin Nutr.* 2006 Feb; 83 (2): 244-251. PMID: 16469981.
3. Pan A, Franco OH, Ye J, Demark-Wahnefried W, Ye X, Yu Z, Li H, Lin X. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in middle-aged and elderly Chinese. *J Nutr.* 2008 Dec; 138 (12): 2, 413-2, 421. PMID: 19022966.

Systematic Reviews / Meta-Analyses

1. Yang G, Shu XO, Jin F, Zhang X, Li HL, Li Q, Gao YT, Zheng W. Longitudinal study of soy food intake and blood pressure among middle-aged and elderly Chinese women. *Am J Clin Nutr*. 2005 May; 81 (5): 1, 012-1, 017. PMID: 15883423.
2. Harland JI, Haffner TA. Systematic review, meta-analysis and regression of randomized controlled trials reporting an association between an intake of circa 25g soy protein per day and blood cholesterol. *Atherosclerosis*. 2008 Sep; 200 (1): 13-27. Epub 2008 Apr 15. Review. PMID: 18534601.

What is the relationship between the intake of soy protein and blood lipids among adults without hyperlipidemia?

1. Reynolds K, Chin A, Lees KA, Nguyen A, Bujnowski D, He J. A meta-analysis of the effect of soy protein supplementation on serum lipids. *Am J Cardiol*. 2006 Sep 1; 98 (5): 633-640. Epub 2006 Jul 12. PMID: 16923451. (Hand search)
2. Weggemans RM, Trautwein EA. Relation between soy-associated isoflavones and LDL and HDL cholesterol concentrations in humans: A meta-analysis. *Eur J Clin Nutr.* 2003 Aug; 57 (8): 940-946. PMID: 12879088.
3. Zhan S, Ho SC. Meta-analysis of the effects of soy protein containing isoflavones on the lipid profile. *Am J Clin Nutr.* 2005 Feb; 81 (2): 397-408. PMID: 15699227.

Primary Citations

1. Liao FH, Shieh MJ, Yang SC, Lin SH, Chien YW. Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in overweight adults. *Nutrition. 2007* Jul-Aug; 23 (7-8): 551-556. Epub 2007 Jun 15. PMID: 17574819.

2. Pan A, Franco OH, Ye J, Demark-Wahnefried W, Ye X, Yu Z, Li H, Lin X. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in middle-aged and elderly Chinese. *J Nutr*. 2008 Dec; 138 (12): 2, 413-2, 421. PMID: 19022966.
3. He J, Gu D, Wu X, Chen J, Duan X, Chen J, Whelton PK. Effect of soybean protein on blood pressure: A randomized, controlled trial. *Ann Intern Med.* 2005 Jul 5; 143 (1):1-9. PMID: 15998749.
4. Alonso A, Beunza JJ, Bes-Rastrollo M, Pajares RM, Martínez-González MA. Vegetable protein and fiber from cereal are inversely associated with the risk of hypertension in a Spanish cohort. *Arch Med Res*. 2006 Aug; 37 (6): 778-786. PMID: 16824939.
5. Halton TL, Willett WC, Liu S, Manson JE, Albert CM, Rexrode K, Hu FB. Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med*. 2006 Nov 9; 355 (19): 1, 991-2, 002. PMID: 17093250. (Hand search)

Excluded articles

Article	Reason for Exclusion
Ashton EL, Dalais FS, Ball MJ. Effect of meat replacement by tofu on CHD risk factors including copper induced LDL oxidation. *J Am Coll Nutr.* 2000 Nov-Dec; 19 (6): 761-767. PMID: 11194529.	Included in Zhan, 2005.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Hu FB, Willett WC. Dietary soya intake alters plasma antioxidant status and lipid peroxidation in postmenopausal women with the metabolic syndrome. *Br J Nutr.* 2007 Oct; 98 (4): 807-813. Epub 2007 May 17. PMID: 17506931.	Participants diagnosed with metabolic syndrome.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Hu FB, Willett WC. Soy consumption, markers of inflammation, and endothelial function: A cross-over study in postmenopausal women with the metabolic syndrome. *Diabetes Care*. 2007 Apr; 30 (4): 967-973. PMID: 17392557.	Participants diagnosed with metabolic syndrome.
Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Padyab M, Hu FB, Willett WC. Soy inclusion in the diet improves features of the metabolic syndrome: a randomized crossover study in postmenopausal women. *Am J Clin Nutr.* 2007 Mar; 85 (3): 735-741. PMID: 17344494.	Participants diagnosed with metabolic syndrome.
Azadbakht L, Shakerhosseini R, Atabak S, Jamshidian M, Mehrabi Y, Esmaill-Zadeh A. Beneficiary effect of dietary soy protein on lowering plasma levels of lipid and improving kidney function in type II diabetes with nephropathy. *Eur J Clin Nutr.* 2003 Oct; 57 (10): 1, 292-1, 294. PMID: 14506491.	Participants diagnosed with type 2 diabetes with nephropathy.
Badger TM, Ronis MJ, Simmen RC, Simmen FA. Soy protein isolate and protection against cancer. *J Am Coll Nutr.* 2005 Apr; 24 (2): 146S-149S. PMID: 15798082.	Publication is a summary of a review presented at a professional meeting.

Blum A, Lang N, Vigder F, Israeli P, Gumanovsky M, Lupovitz S, Elgazi A, Peleg A, Ben-Ami M. Effects of soy protein on endothelium-dependent vasodilatation and lipid profile in postmenopausal women with mild hypercholesterolemia. *Clin Invest Med.* 2003 Feb; 26 (1): 20-26. PMID: 12659466.	Participants had mild hypercholesterolemia; included in Harland, 2008.
Brown BD, Thomas W, Hutchins A, Martini MC, Slavin JL. Types of dietary fat and soy minimally affect hormones and biomarkers associated with breast cancer risk in premenopausal women. *Nutr Cancer.* 2002; 43 (1): 22-30. PMID: 12467131.	Does not answer question: examined biomarkers associated with breast cancer, not incidence of breast cancer (not a prospective cohort study).
Chan YH, Lau KK, Yiu KH, Li SW, Chan HT, Tam S, Shu XO, Lau CP, Tse HF. Isoflavone intake in persons at high risk of cardiovascular events: Implications for vascular endothelial function and the carotid atherosclerotic burden. *Am J Clin Nutr.* 2007 Oct; 86 (4): 938-945. PMID: 17921368.	Participants (94%) had CAD or stroke; does not answer question: Outcomes were carotid intima-media thickness and flow-mediated dilation
Chen ST, Ferng SH, Yang CS, Peng SJ, Lee HR, Chen JR. Variable effects of soy protein on plasma lipids in hyperlipidemic and normolipidemic hemodialysis patients. *Am J Kidney Dis.* 2005 Dec; 46 (6): 1, 099-1, 106. PMID: 16310576.	Participants were hemodialysis patients.
Chiechi LM, Secreto G, Vimercati A, Greco P, Venturelli E, Pansini F, Fanelli M, Loizzi P, Selvaggi L. The effects of a soy rich diet on serum lipids: the Menfis randomized trial. *Maturitas*. 2002 Feb 26; 41 (2): 97-104. PMID: 11836040.	Dropout rate higher than inclusion criteria.
Cicero AF, Minardi M, Mirembe S, Pedro E, Gaddi A. Effects of a new low dose soy protein/beta-sitosterol association on plasma lipid levels and oxidation. *Eur J Nutr.* 2004 Oct; 43 (5): 319-322. Epub 2004 Jan 26. PMID: 15309453.	Participants were hypercholesterolemic; does not answer question: Tested a formulation of soy protein with added beta-sitosterol.
Cuevas AM, Irribarra VL, Castillo OA, Yañez MD, Germain AM. Isolated soy protein improves endothelial function in postmenopausal hypercholesterolemic women. *Eur J Clin Nutr.* 2003 Aug; 57 (8): 889-894. PMID: 12879082.	Participants were hypercholesterolemic.
Cupisti A, D'Alessandro C, Ghiadoni L, Morelli E, Panichi V, Barsotti G. Effect of a soy protein diet on serum lipids of renal transplant patients. *J Ren Nutr.* 2004 Jan; 14 (1): 31-35. PMID: 14740328.	Participants had renal transplantation.
Desroches S, Mauger JF, Ausman LM, Lichtenstein AH, Lamarche B. Soy protein favorably affects LDL size independently of isoflavones in hypercholesterolemic men and women. *J Nutr.* 2004 Mar; 134 (3): 574-579. PMID: 14988449.	Participants were hypercholesterolemic.
Dewell A, Weidner G, Sumner MD, Barnard RJ, Marlin RO, Daubenmier JJ, Chi C, Carroll PR, Ornish D. Relationship of dietary protein and soy isoflavones to serum IGF-1 and IGF binding proteins in the Prostate Cancer Lifestyle Trial. *Nutr Cancer.* 2007; 58 (1): 35-42. PMID: 17571965.	Participants were diagnosed with prostate cancer.

Dillingham BL, McVeigh BL, Lampe JW, Duncan AM. Soy protein isolates of varying isoflavone content exert minor effects on serum reproductive hormones in healthy young men. *J Nutr.* 2005 Mar; 135 (3): 584-591. PMID: 15735098.	Does not answer question: Examined soy protein intake on reproductive hormones.
Engelman HM, Alekel DL, Hanson LN, Kanthasamy AG, Reddy MB. Blood lipid and oxidative stress responses to soy protein with isoflavones and phytic acid in postmenopausal women. *Am J Clin Nutr.* 2005 Mar; 81 (3): 590-596. PMID: 15755827.	Does not answer question: Examined impact of soy protein components (isoflavones and phytate) on blood lipids and oxidative stress.
Gardner CD, Messina M, Kiazand A, Morris JL, Franke AA. Effect of two types of soy milk and dairy milk on plasma lipids in hypercholesterolemic adults: A randomized trial. *J Am Coll Nutr.* 2007 Dec; 26 (6): 669-677. PMID: 18187432.	Participants were hypercholesterolemic; included in Harland, 2008.
Gardner CD, Newell KA, Cherin R, Haskell WL. The effect of soy protein with or without isoflavones relative to milk protein on plasma lipids in hypercholesterolemic postmenopausal women. *Am J Clin Nutr*. 2001 Apr; 73 (4): 728-735. PMID: 11273847.	Participants were hypercholesterolemic; included in Weggemans, 2003.
Genovese MI, Lajolo FM. Isoflavones in soy-based foods consumed in Brazil: Levels, distribution, and estimated intake. *J Agric Food Chem*. 2002 Oct 9; 50 (21): 5, 987-5, 993. PMID: 12358470.	Does not include health outcomes in analyses.
Giampietro PG, Bruno G, Furcolo G, Casati A, Brunetti E, Spadoni GL, Galli E. Soy protein formulas in children: No hormonal effects in long-term feeding. *J Pediatr Endocrinol Metab.* 2004 Feb;17 (2): 191-196. PMID: 15055353.	Does not answer question: Examined hormonal and metabolic effects of long-term soy protein formula feeding.
Goldin BR, Brauner E, Adlercreutz H, Ausman LM, Lichtenstein AH. Hormonal response to diets high in soy or animal protein without and with isoflavones in moderately hypercholesterolemic subjects. *Nutr Cancer*. 2005; 51 (1): 1-6. PMID: 15749623.	Participants were hypercholesterolemic; does not answer question: Examined hormonal response to diets high in soy or animal protein.
Grainger EM, Schwartz SJ, Wang S, Unlu NZ, Boileau TW, Ferketich AK, Monk JP, Gong MC, Bahnson RR, DeGroff VL, Clinton SK. A combination of tomato and soy products for men with recurring prostate cancer and rising prostate specific antigen. *Nutr Cancer*. 2008; 60 (2): 145-154. PMID: 18444145.	Participants diagnosed with prostate cancer.
Greany KA, Nettleton JA, Wangen KE, Thomas W, Kurzer MS. Consumption of isoflavone-rich soy protein does not alter homocysteine or markers of inflammation in postmenopausal women. *Eur J Clin Nutr.* 2008 Dec; 62 (12): 1, 419-1, 425. Epub 2007 Sep 5. PMID: 17805230.	Does not answer question: Does not examine outcome of interest (examines homocysteine, C-reactive protein and adhesion molecules).
Greany KA, Nettleton JA, Wangen KE, Thomas W, Kurzer MS. Probiotic consumption does not enhance the cholesterol-lowering effect of soy in postmenopausal women. *J Nutr.* 2004 Dec; 134 (12): 3, 277-3, 283. PubMed PMID: 15570025.	Participants were hypercholesterolemic; included in Harland, 2008.

Hamilton-Reeves JM, Rebello SA, Thomas W, Kurzer MS, Slaton JW. Effects of soy protein isolate consumption on prostate cancer biomarkers in men with HGPIN, ASAP, and low-grade prostate cancer. *Nutr Cancer*. 2008; 60 (1): 7-13. PMID: 18444130.	Not a prospective cohort study examining incidence of prostate cancer. Outcomes were prostate cancer biomarkers.
Hamilton-Reeves JM, Rebello SA, Thomas W, Slaton JW, Kurzer MS. Soy protein isolate increases urinary estrogens and the ratio of 2:16alpha-hydroxyestrone in men at high risk of prostate cancer. *J Nutr.* 2007 Oct; 137 (10): 2, 258-2, 263. PMID: 17885008.	Not a prospective cohort study examining incidence of prostate cancer. Outcomes were prostate cancer biomarkers.
Hamilton-Reeves JM, Rebello SA, Thomas W, Slaton JW, Kurzer MS. Isoflavone-rich soy protein isolate suppresses androgen receptor expression without altering estrogen receptor-beta expression or serum hormonal profiles in men at high risk of prostate cancer. *J Nutr.* 2007 Jul; 137 (7): 1, 769-1, 775. PMID: 17585029.	Not a prospective cohort study examining incidence of prostate cancer. Outcomes were prostate cancer biomarkers.
Harrison RA, Sagara M, Rajpura A, Armitage L, Birt N, Birt CA, Yamori Y. Can foods with added soya-protein or fish-oil reduce risk factors for coronary disease? A factorial randomised controlled trial. *Nutr Metab Cardiovasc Dis*. 2004 Dec; 14 (6): 344-350. PMID: 15853118.	Participants had elevated total cholesterol or blood pressure.
Hartman JW, Tang JE, Wilkinson SB, Tarnopolsky MA, Lawrence RL, Fullerton AV, Phillips SM. Consumption of fat-free fluid milk after resistance exercise promotes greater lean mass accretion than does consumption of soy or carbohydrate in young, novice, male weightlifters. *Am J Clin Nutr.* 2007 Aug; 86 (2): 373-381. PMID: 17684208.	Does not answer question: Does not examine relationship between vegetable protein and health (examined consumption of various isocaloric drinks on lean mass accretion following resistance training).
Hoie LH, Guldstrand M, Sjoholm A, Graubaum HJ, Gruenwald J, Zunft HJ, Lueder W. Cholesterol-lowering effects of a new isolated soy protein with high levels of nondenaturated protein in hypercholesterolemic patients. *Adv Ther.* 2007 Mar-Apr; 24 (2): 439-447. PMID: 17565935.	Participants were hypercholesterolemic; included in Harland, 2008.
Hoie LH, Morgenstern EC, Gruenwald J, Graubaum HJ, Busch R, Lüder W, Zunft HJ. A double-blind placebo-controlled clinical trial compares the cholesterol-lowering effects of two different soy protein preparations in hypercholesterolemic subjects. *Eur J Nutr.* 2005 Mar; 44 (2): 65-71. Epub 2004 Apr 5. PMID: 15309422.	Participants were hypercholesterolemic; included in Harland, 2008.
Hori G, Wang MF, Chan YC, Komatsu T, Wong Y, Chen TH, Yamamoto K, Nagaoka S, Yamamoto S. Soy protein hydrolyzate with bound phospholipids reduces serum cholesterol levels in hypercholesterolemic adult male volunteers. *Biosci Biotechnol Biochem*. 2001 Jan; 65 (1): 72-78. PMID: 11272848.	Participants were hypercholesterolemic.
Jenkins DJ, Kendall CW, Jackson CJ, Connelly PW, Parker T, Faulkner D, Vidgen E, Cunnane SC, Leiter LA, Josse RG. Effects of high- and low-isoflavone soyfoods on blood lipids, oxidized LDL, homocysteine, and blood pressure in hyperlipidemic men and women. *Am J Clin Nutr*. 2002 Aug; 76 (2): 365-372. PMID: 12145008.	Participants were hyperlipidemic; included in Weggemans, 2003.

Jenkins DJ, Kendall CW, D'Costa MA, Jackson CJ, Vidgen E, Singer W, Silverman JA, Koumbridis G, Honey J, Rao AV, Fleshner N, Klotz L. Soy consumption and phytoestrogens: effect on serum prostate specific antigen when blood lipids and oxidized low-density lipoprotein are reduced in hyperlipidemic men. *J Urol.* 2003 Feb; 169 (2): 507-511. PMID: 12544298.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Garsetti M, Rosenberg-Zand RS, Jackson CJ, Agarwal S, Rao AV, Diamandis EP, Parker T, Faulkner D, Vuksan V, Vidgen E. Effect of soy protein foods on low-density lipoprotein oxidation and ex vivo sex hormone receptor activity: A controlled crossover trial. *Metabolism.* 2000 Apr; 49 (4): 537-543. PMID: 10778882.	Participants were hyperlipidemic; included in Harland, 2008.
Jenkins DJ, Wong JM, Kendall CW, Esfahani A, Ng VW, Leong TC, Faulkner DA, Vidgen E, Greaves KA, Paul G, Singer W. The effect of a plant-based low-carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. *Arch Intern Med.* 2009 Jun 8; 169 (11): 1, 046-1, 054. Erratum in: Arch Intern Med. 2009 Sep 14; 169 (16): 1, 490. PMID: 19506174.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Faulkner DA, Kemp T, Marchie A, Nguyen TH, Wong JM, de Souza R, Emam A, Vidgen E, Trautwein EA, Lapsley KG, Josse RG, Leiter LA, Singer W. Long-term effects of a plant-based dietary portfolio of cholesterol-lowering foods on blood pressure. *Eur J Clin Nutr*. 2008 Jun; 62 (6): 781-788. Epub 2007 Apr 25. PMID: 17457340.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Marchie A, Faulkner D, Vidgen E, Lapsley KG, Trautwein EA, Parker TL, Josse RG, Leiter LA, Connelly PW. The effect of combining plant sterols, soy protein, viscous fibers, and almonds in treating hypercholesterolemia. *Metabolism*. 2003 Nov; 52 (11): 1, 478-1, 483. PMID: 14624410.	Participants were hypercholesterolemic; included in Cope, 2008.
Jenkins DJ, Kendall CW, Vidgen E, Mehling CC, Parker T, Seyler H, Faulkner D, Garsetti M, Griffin LC, Agarwal S, Rao AV, Cunnane SC, Ryan MA, Connelly PW, Leiter LA, Vuksan V, Josse R. The effect on serum lipids and oxidized low-density lipoprotein of supplementing self-selected low-fat diets with soluble-fiber, soy and vegetable protein foods. *Metabolism.* 2000 Jan; 49 (1): 67-72. PMID: 10647066.	Participants were hyperlipidemic.
Jenkins DJ, Kendall CW, Faulkner D, Vidgen E, Trautwein EA, Parker TL, Marchie A, Koumbridis G, Lapsley KG, Josse RG, Leiter LA, Connelly PW. A dietary portfolio approach to cholesterol reduction: combined effects of plant sterols, vegetable proteins, and viscous fibers in hypercholesterolemia. *Metabolism*. 2002 Dec; 51 (12): 1, 596-1, 604. PMID: 12489074.	Participants were hypercholesterolemic.
Jones PJ, Raeini-Sarjaz M, Jenkins DJ, Kendall CW, Vidgen E, Trautwein EA, Lapsley KG, Marchie A, Cunnane SC, Connelly PW. Effects of a diet high in plant sterols, vegetable proteins, and viscous fibers (dietary portfolio) on circulating sterol levels and red cell fragility in hypercholesterolemic subjects. *Lipids.* 2005 Feb; 40 (2): 169-174. PMID: 15884765.	Participants were hypercholesterolemic.

Kreijkamp-Kaspers S, Kok L, Bots ML, Grobbee DE, Lampe JW, van der Schouw YT. Randomized controlled trial of the effects of soy protein containing isoflavones on vascular function in postmenopausal women. *Am J Clin Nutr.* 2005 Jan; 81 (1): 189-195. PMID: 15640479.	Dropout rate higher than inclusion criteria.
Lichtenstein AH, Jalbert SM, Adlercreutz H, Goldin BR, Rasmussen H, Schaefer EJ, Ausman LM. Lipoprotein response to diets high in soy or animal protein with and without isoflavones in moderately hypercholesterolemic subjects. *Arterioscler Thromb Vasc Biol.* 2002 Nov 1; 22 (11): 1, 852-1, 858. PMID: 12426215.	Participants were hypercholesterolemic; included in Reynolds, 2006.
Luiking YC, Deutz NE, Jäkel M, Soeters PB. Casein and soy protein meals differentially affect whole-body and splanchnic protein metabolism in healthy humans. *J Nutr.* 2005 May; 135 (5): 1, 080-1, 087. PMID: 15867285.	Does not answer question: study examined protein metabolism, not relationship between protein and selected health outcomes.
Ma Y, Chiriboga D, Olendzki BC, Nicolosi R, Merriam PA, Ockene IS. Effect of soy protein containing isoflavones on blood lipids in moderately hypercholesterolemic adults: A randomized controlled trial. *J Am Coll Nutr.* 2005 Aug; 24 (4): 275-285. PMID: 16093405.	Participants were hypercholesterolemic.
Mackey R, Ekangaki A, Eden JA. The effects of soy protein in women and men with elevated plasma lipids. *Biofactors*. 2000; 12 (1-4): 251-257. PMID: 11216493.	Participants were hyperlipidemic.
Maskarinec G. Soy foods for breast cancer survivors and women at high risk for breast cancer? *J Am Diet Assoc.* 2005 Oct; 105 (10): 1, 524-1, 528. PMID: 16183350.	Publication is Commentary.
Matthan NR, Jalbert SM, Ausman LM, Kuvin JT, Karas RH, Lichtenstein AH. Effect of soy protein from differently processed products on cardiovascular disease risk factors and vascular endothelial function in hypercholesterolemic subjects. *Am J Clin Nutr.* 2007 Apr; 85 (4): 960-966. Erratum in: *Am J Clin Nutr.* 2007 Aug; 86 (2): 525. PMID: 17413093.	Participants were hypercholesterolemic; included in Harland, 2008.
McVeigh BL, Dillingham BL, Lampe JW, Duncan AM. Effect of soy protein varying in isoflavone content on serum lipids in healthy young men. *Am J Clin Nutr.* 2006 Feb; 83 (2): 244-251. PMID: 16469981.	**Included in body weight review, but excluded from cholesterol review because included in Harland, 2008.
Merritt JC. Metabolic syndrome: soybean foods and serum lipids. *J Natl Med Assoc.* 2004 Aug; 96 (8): 1, 032-1, 041. PubMed PMID: 15303407; Central PMCID: PMC2568482.	Study design is narrative review.
Möllsten AV, Dahlquist GG, Stattin EL, Rudberg S. Higher intakes of fish protein are related to a lower risk of microalbuminuria in young Swedish type 1 diabetic patients. *Diabetes Care*. 2001 May; 24 (5): 805-810. PMID: 11347734.	Participants were diagnosed with type 1 diabetes.

Nagata C, Shimizu H, Takami R, Hayashi M, Takeda N, Yasuda K. Association of blood pressure with intake of soy products and other food groups in Japanese men and women. *Prev Med.* 2003 Jun; 36 (6): 692-697. PMID: 12744912.	Does not answer question: Examined soy food intake, not soy protein.
Puska P, Korpelainen V, Høie LH, Skovlund E, Smerud KT. Isolated soya protein with standardized levels of isoflavones, cotyledon soya fibres and soya phospholipids improves plasma lipids in hypercholesterolaemia: A double-blind, placebo-controlled trial of a yoghurt formulation. *Br J Nutr.* 2004 Mar; 91 (3): 393-401. PMID: 15005825.	Does not answer question: Examined yogurt formulation containing isolated soya protein, isoflavones, cotyledon soya fibers and soya phospholipids.
Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M; American Heart Association Nutrition Committee. Soy protein, isoflavones, and cardiovascular health: An American Heart Association Science Advisory for professionals from the Nutrition Committee. *Circulation.* 2006 Feb 21; 113 (7): 1, 034-1, 044. Epub 2006 Jan 17. PMID: 16418439.	Publication is AHA Science Advisory; reference list was reviewed.
Sagara M, Kanda T, NJelekera M, Teramoto T, Armitage L, Birt N, Birt C, Yamori Y. Effects of dietary intake of soy protein and isoflavones on cardiovascular disease risk factors in high risk, middle-aged men in Scotland. *J Am Coll Nutr.* 2004 Feb; 23 (1): 85-91. PMID: 14963058.	Included in Harland, 2008.
Sanders TA, Dean TS, Grainger D, Miller GJ, Wiseman H. Moderate intakes of intact soy protein rich in isoflavones compared with ethanol-extracted soy protein increase HDL but do not influence transforming growth factor beta(1) concentrations and hemostatic risk factors for coronary heart disease in healthy subjects. *Am J Clin Nutr.* 2002 Aug; 76 (2): 373-377. PMID: 12145009.	Does not answer question; design of the study does not allow for comparison between diets with and without soy protein. The study addresses the impact of isoflavones from soy on CHD risk.
Shahbazian H, Reza A, Javad S, Heshmatollah S, Mahmood L, Ali A, Hosain HM. Beneficial effects of soy protein isoflavones on lipid and blood glucose concentrations in type 2 diabetic subjects. *Saudi Med J.* 2007 Apr; 28 (4): 652-654. PMID: 17457503.	Participants diagnosed with type 2 diabetes.
Sirtori CR, Eberini I, Arnoldi A. Hypocholesterolaemic effects of soya proteins: Results of recent studies are predictable from the Anderson meta-analysis data. *Br J Nutr*. 2007 May; 97 (5): 816-822. Review. PMID: 17408521.	Not a systematic review or original research study (examines previous research using a predictive model).
Spence LA, Lipscomb ER, Cadogan J, Martin B, Wastney ME, Peacock M, Weaver CM. The effect of soy protein and soy isoflavones on calcium metabolism in postmenopausal women: A randomized crossover study. *Am J Clin Nutr*. 2005 Apr; 81 (4): 916-922. PMID: 15817872.	Does not answer question: Outcome was calcium metabolism, not selected health outcome.
St-Onge MP, Claps N, Wolper C, Heymsfield SB. Supplementation with soy-protein-rich foods does not enhance weight loss. *J Am Diet Assoc.* 2007 Mar; 107 (3): 500-505. PMID: 17324670.	Dropout rate higher than inclusion criteria.

Taku K, Umegaki K, Sato Y, Taki Y, Endoh K, Watanabe S. Soy isoflavones lower serum total and LDL cholesterol in humans: A meta-analysis of 11 randomized controlled trials. *Am J Clin Nutr.* 2007 Apr; 85 (4): 1, 148-1, 156. Erratum in: *Am J Clin Nutr*. 2007 Sep; 86 (3): 809. PMID: 17413118.	Does not answer question: Examined soy isoflavones, not soy protein.
Teede HJ, Dalais FS, Kotsopoulos D, Liang YL, Davis S, McGrath BP. Dietary soy has both beneficial and potentially adverse cardiovascular effects: A placebo-controlled study in men and postmenopausal women. *J Clin Endocrinol Metab.* 2001 Jul; 86 (7): 3, 053-3, 060. PMID: 11443167.	** Included in blood pressure review but excluded from cholesterol review because included in Harland, 2008 and Weggemans, 2003.
Teede HJ, Giannopoulos D, Dalais FS, Hodgson J, McGrath BP. Randomized, controlled, cross-over trial of soy protein with isoflavones on blood pressure and arterial function in hypertensive subjects. *J Am Coll Nutr.* 2006 Dec; 25 (6): 533-540. PMID: 17229901.	Participants were hypertensive.
Tonstad S, Smerud K, Høie L. A comparison of the effects of two doses of soy protein or casein on serum lipids, serum lipoproteins and plasma total homocysteine in hypercholesterolemic subjects. *Am J Clin Nutr.* 2002 Jul; 76 (1): 78-84. PMID: 12081819.	Participants were hypercholesterolemic.
Trock BJ, Hilakivi-Clarke L, Clarke R. Meta-analysis of soy intake and breast cancer risk. *J Natl Cancer Inst.* 2006 Apr 5; 98 (7): 459-471. PMID: 16595782.	Studies included in meta-analysis were excluded based on SC criteria; no prospective cohort studies with soy protein included in review.
Wang Y, Jones PJ, Ausman LM, Lichtenstein AH. Soy protein reduces triglyceride levels and triglyceride fatty acid fractional synthesis rate in hypercholesterolemic subjects. Atherosclerosis. 2004 Apr;173 (2): 269-275. PMID: 15064101.	Participants were hypercholesterolemic.
Wangen KE, Duncan AM, Xu X, Kurzer MS. Soy isoflavones improve plasma lipids in normocholesterolemic and mildly hypercholesterolemic postmenopausal women. Am *J Clin Nutr*. 2001 Feb; 73 (2): 225-231. PMID: 11157317.	Included in Zhan, 2005.
Weghuber D, Widhalm K. Effect of three-month treatment of children and adolescents with familial and polygenic hypercholesterolaemia with a soya-substituted diet. *Br J Nutr*. 2008 Feb; 99 (2): 281-286. Epub 2007 Aug 13. PMID: 17697400.	Participants were children and adolescents with familial or polygenic hypercholesterolemia.
Xu X, Duncan AM, Wangen KE, Kurzer MS. Soy consumption alters endogenous estrogen metabolism in postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2000 Aug; 9 (8): 781-786. PMID: 10952094.	Does not answer question: Examines soy consumption and estrogen metabolism.
Yildirir A, Tokgozoglu SL, Oduncu T, Oto A, Haznedaroglu I, Akinci D, Koksal G, Sade E, Kirazli S, Kes S. Soy protein diet significantly improves endothelial function and lipid parameters. *Clin Cardiol.* 2001 Nov; 24 (11): 711-716. PMID: 11714128.	Participants were hypercholesterolemic