2010 Dietary Guidelines Advisory Committee:

Systematic Reviews of the Fatty Acids and Cholesterol 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 Fatty Acids and Cholesterol 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.

Archived from www.NEL.gov on March 21, 2017

TABLE OF CONTENTS

Archived from www.NEL.gov on March 21, 2017

ACKNOWLEDGEMENTS

CHAPTER 1. OVERVIEW AND NEEDS FOR FUTURE RESEARCH

OVERVIEW

The Dietary Guidelines Advisory Committee (DGAC) 2010 first reviewed the 2005 DGAC Report to inform their review process. Several lines of evidence indicate that the type of fat is more important in decreasing metabolic and cardiovascular disease (CVD) risk than the total amount of fat in the diet; therefore, the committee focused their review on the metabolic effect of specific types of fats and fatty acids. Topics in this section on fatty acids and cholesterol that were considered by the 2005 DGAC include:

- Saturated fatty acids (SFA)
- Cholesterol
- Monounsaturated fatty acids (MUFA)
- Omega-6 (n-6) polyunsaturated fatty acids (PUFA)
- Stearic acid
- Trans fatty acids
- Omega-3 (n-3) fatty acids from plants and seafood.

Prior DGAC made recommendations about dietary fat consumption targeting atherosclerotic CVD as the primary disease of concern. The 2010 DGAC continues this focus, but considered additional disease outcomes and intermediate markers of these outcomes. Type 2 diabetes (T2D), as affected by dietary fat, is a new consideration for the 2010 DGAC. Other new questions considered by the 2010 DGAC examined maternal intake of n-3 fatty acids from seafood and the effect on breast milk composition and infant health outcomes; and health effects related to consumption of whole foods high in fat, with the examples being nuts and chocolate *(pending completion of copyediting)*.

For the majority of topics, the conclusions expressed in the 2010 DGAC report are informed by evidence compiled for the 2005 DGAC report, but are based primarily on Nutrition Evidence Library (NEL) evidence gathered and reviewed since 2004. For new or extended topics, the search was extended back further to capture a larger body of evidence, particularly related to diabetic-risk populations. For some topics, a combination of NEL and American Dietetic Association's (ADA) Evidence Analysis Library (EAL) reviews were conducted. For each of the NEL systematic reviews, randomized controlled or clinical trials (RCTs), large non-randomized observational studies, meta-analyses and systematic reviews were included. Health subjects and those with elevated chronic disease risk, including risk of CVD, T2D, and other metabolic risk indicators, were considered for the review.

NEEDS FOR FUTURE RESEARCH

1. Determine the benefits and risks of MUFA vs. PUFA as an isocaloric substitute for SFA (see below). Confirm the metabolic pathways through which dietary SFA affect serum lipids, especially as some SFA (e.g., stearic acid) do not appear to affect blood lipid levels.
   - **Rationale:** The growing data to support a risk of T2D from SFA consumption indicates the need for fat-modified diets in persons with pre-diabetes, including those with metabolic syndrome, and with established diabetes. Since the ages

7

of onset of T2D now include childhood, studies from adolescence through middle age would be useful to define when SFA-reduced diets would be most effective. Conduct feeding studies using cholesterol from sources other than eggs and funded by non-industry sponsors. Conduct research on low- and high-risk consumers of dietary cholesterol and determine a better definition of hypo- and hyper-responders to dietary cholesterol, with respective underlying genetic polymorphisms. Identify additional subgroups in which dietary cholesterol appears especially harmful with regard to cardiovascular risk"

- **Rationale:** Most of the feeding studies with serum lipid and lipoprotein endpoints used eggs as the primary source of cholesterol, and many of the studies were funded by industry. Since the proportion of dietary cholesterol in the US diet supplied by eggs has declined to less than 25%, feeding trials on other dietary sources of cholesterol would be useful. Persons with T2D appear to be a subgroup in which dietary cholesterol is particularly harmful and better understanding of the mechanisms and magnitude of risk is essential, as eggs are an important, low-fat source of protein in T2D patients.

2. Determine the mechanism by which dietary MUFA improve serum lipids, glucose metabolism, insulin levels, homeostatic model assessment (HOMA scores), inflammatory markers and blood pressure in both healthy persons and in persons with T2D. Studies of replacing carbohydrates or other dietary fat with MUFA should include isocaloric substitutions, so as not to be confounded by differences in energy.

- **Rationale**: Understanding the mechanism by which MUFA improve risk of CVD and T2D will enhance our ability to make specific recommendations for MUFA consumption in healthy and at-risk individuals.

3. Determine the mechanism by which dietary PUFA improve serum lipids, glucose metabolism, insulin levels, HOMA scores, inflammatory markers, and blood pressure in both healthy persons and in persons with T2D. Studies of replacing carbohydrates or other dietary fat with PUFA should include isocaloricsubstitutions, so as not to be confounded by differences in energy.

- **Rationale:** Understanding the mechanism by which PUFA improve risk of CVD and T2D will enhance our ability to make specific recommendations for PUFA consumption in healthy and at-risk individuals. PUFA and MUFAhave similar benefits as substitutes for SFA and trans fatty acids. Additional isocaloric comparisons of MUFA vs. PUFA on metabolic intermediates and especially on clinical outcomes are needed to differentiate these two classes of fatty acids.

4. Examine stearic acid for its benefits as a solid fat, in contrast to liquid oils high in MUFA and PUFA; include other potential metabolic effects of stearic acid, such as inflammation and coagulation.

- **Rationale**: The benefit of stearic acid is that it has a high melting point and therefore is solid at room temperature, unlike other fatty acids that do not raise blood cholesterol (e.g., MUFA, PUFA). Comparisons of intermediate markers and other effects of stearic acid vs. MUFA and PUFA would clarify ways that it could be best used in a calorie and nutrient-balanced diets.

5. Characterize the difference in metabolic effects and intermediate markers between industrial and ruminant trans fatty acids (rTFA).

- **Rationale**: Since rTFA and industrial trans fatty acids (iTFA) have different

8

chemical structures, better characterization of their metabolic effects though further feeding studies would be warranted.

6. Conduct randomized controlled trials and prospective observational studies in persons with and without CVD on plant compared to marine n-3 fatty acids. Examine diets rich in plant n-3 fatty acids in subjects with and without adequate intake of n-3 fatty acids from marine sources. Examine the mechanism of action of marine vs. plant n-3 fatty acids for
synergies and inhibition.

   - **Rationale**: Although there is consistent data on the benefits of n-3 fatty acids from seafood consumption, there is no research on comparing marine vs. plant n-3 fatty acids on intermediate markers and CVD outcomes.

7. Investigate further the opposing interactions of high eicosapentaenoic acid(EPA) and docosahexaenoic acid (DHA) vs. high methyl mercury, especially in dietary patterns in which these consumptions coexist. Investigate high vs. low DHA-consuming mothers and infants and the long-term effects on intelligence and other cognitive outcomes.

   - **Rationale**: All aspects of the risk to benefit ratio of consumption of EPA + DHA and methyl mercury, both of which can be present in varying amounts in different types of seafood, should be further elucidated. Docosahexaenoic acid appears to be the active nutrient in seafood that provides benefits in infant development. Further studies of the role of DHA in neurodevelopment and dose-response relationships between DHA and health and development outcomes would be useful.

8. Conduct RCTs comparing different types of nuts on intermediate markers, such as serum lipids, and classify each specific type of nut as more or less associated with CVD risk reduction.

   - **Rationale**: Additional randomized trials will be required over longer periods of time to determine if nuts confer long-term benefits. It is difficult to distinguish benefits to health and to intermediate metabolites between different types of nuts.

9. Elucidate further the role of polyphenolic compounds as major active ingredients in the health benefits of chocolate. Test different chocolate formulations that are commonly consumed by the general public.

   - **Rationale**: Many chocolate and cocoa studies used formulations of chocolate that are not readily available to the consumer and were sponsored by industry. In order to determine the real health benefits of chocolate consumption, chocolate formulations that are available to, and consumed by, the general public need to be tested.

CHAPTER 2. SPECIFIC FATS, FATTY ACIDS, AND CHOLESTEROL – CHOLESTEROL

WHAT IS THE EFFECT OF DIETARY CHOLESTEROL INTAKE ON RISK OF CARDIOVASCULAR DISEASE?

Conclusion statement

Moderate evidence from epidemiologic studies relates dietary cholesterol intake to clinical cardiovascular disease (CVD) end-points. Many randomized clinical trials on dietary cholesterol use eggs as the dietary source. Independent of other dietary factors, evidence suggests that consumption of one egg per day is not associated with risk of coronary heart disease or stroke in healthy adults, although consumption of more than seven eggs per week has been associated with increased risk. An important distinction is that among individuals with type 2 diabetes, increased dietary cholesterol intake is associated with CVD risk.

Grade

Moderate

Evidence summary overview

The Nutrition Evidence Library (NEL) systematic review identified 16 studies published since 1999 that evaluated the effect of dietary cholesterol intake on cardiovascular disease (CVD) risk conducted in the US, Europe, Mexico and Japan. These studies focused on dietary cholesterol, in the absence of dietary saturated fat. Eight randomized controlled trials (RCTs), including two methodologically strong studies (Ballesteros, 2004; Knopp, 2003) and six methodologically neutral studies (Goodrow, 2006; Greene, 2005; Harman, 2008; Mutungi, 2008; Reaven, 2001; Tannock, 2005) with sample size ranging from 28 to 201 subjects were reviewed. Five prospective cohort studies, including four methodologically strong studies (Djousse, 2008; Hu, 1999; Qureshi, 2007; Tanasescu, 2004) and one methodologically neutral study (Nakamura, 2006) ranging in size from 5,687 to 80,082 subjects, were reviewed. One meta-analysis of 17 studies was methodologically strong (Weggemans, 2001), and two systematic reviews, one methodologically strong pooled analysis of 167 cholesterol feeding studies in 3,519 subjects (McNamara, 2000) and one methodologically neutral review of eight prospective cohort studies on dietary cholesterol and six prospective cohort studies on eggs (Kritchevsky and Kritchevsky, 2000) met the eligibility criteria and were reviewed. The majority of these articles reported on comparisons of egg vs. egg substitute or no egg intake. In studies comparing eggs vs. egg substitute, one randomized controlled trial (Ballesteros, 2004) and one pooled analysis (McNamara, 2000) showed that low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol increased in hyper-responders, but did not change in hypo-responders; overall, the LDL:HDL did not change in hypo- or hyper-responders. Identification of hypo-and hyper-responders showed inter-individual variation to dietary cholesterol that may result in differing health outcomes for individuals with different genetic predispositions.

10

Harman et al, (2008) found that LDL-C decreased in both egg and egg substitute groups and two studies in elderly adults (Greene, 2005; Goodrow, 2006) indicated that LDL-C and HDL-C were not affected by egg intake. Two RCTs showed an increase in LDL-C diameter in the egg group (Ballesteros, 2004; Greene, 2005). Two RCTs in 65 insulin-sensitive and 75 insulin-resistant subjects determined that egg consumption was associated with increased LDL-C, but only in insulin-sensitive subjects (Knopp, 2003; Tannock, 2005). However, Reaven et al, (2001) found that high cholesterol intake did not increase LDL-C in either insulin-sensitive or insulin-resistant sub-groups. All studies that measured HDL-C found that HDL-C was increased with egg consumption, and one such study was in a carbohydrate (CHO)-restricted diet background (Mutungi, 2008). One study assessed markers of inflammation and found increased C-reactive protein (CRP) and serum amyloid A with high egg consumption, but found no difference in circulating cytokines (Tannock, 2005). One meta-analysis of 17 studies indicated that high dietary cholesterol intake increased the total cholesterol (TC):HDL-C ratio. However, this effect was attenuated in the low saturated fatty acid (SFA) subgroup (Weggemans, 2001).

In the prospective cohort studies, Djousse et al, (2001) found that egg consumption up to six eggs per week in the Physicians' Health Study was not associated with risk of all-cause mortality, but consumption of more than seven eggs per week was associated with a 23% increased risk of death. In the Japan Public Health Center study, egg consumption was not associated with coronary heart disease (CHD) incidence (Nakamura, 2006). In Nutrition and Health Examination Examination Survey I (NHANES I), no relationship was established between egg consumption (more than six eggs per week) and risk of stroke or ischemic stroke, and risk of myocardial infarction (MI) and all-cause mortality was not different between egg and non-egg consumption groups (Qureshi, 2007). A combined analysis of the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS), found no significant (NS) association between egg consumption and risk of CHD or stroke in men or women (Hu, 1999). A review of epidemiological studies (Kritchevsky and Kritchevsky, 2000) showed there was no association between consumption of one egg per day and risk of cardiovascular disease (CVD), but only in non-diabetic men and women. Furthermore, three methodologically strong prospective cohort studies warned that egg consumption was associated with increased CVD risk in subjects with type 2 diabetes (T2D) (Djousse, 2001; Hu, 1999; Tanasescu, 2004) and this warrants further investigation.

Evidence summary paragraphs

Ballesteros et al, 2004 (positive quality) This was a randomized crossover trial conducted in Mexico to evaluate the effects of dietary cholesterol provided by whole eggs on plasma lipids and LDL-C atherogenicity in a pediatric population. Children were divided into two groups and randomly assigned to either the egg or egg substitute intervention for 30 days followed by a three-week washout period, followed by the opposite intervention for 30 days. The children consumed either two whole eggs (providing 518mg additional dietary cholesterol) or the equivalent amount of egg whites with added color, served scrambled for breakfast in the school cafeteria. On weekends, eggs and egg substitute were packed for consumption and parents were

11

instructed on proper administration. Sixty children [30 boys (aged 10.6±1.6 years) and 30 girls (aged 10.2±1.5 years)] were enrolled in the study; 54 children (25 boys and 29 girls) completed the trial. Children were classified as hyporesponders (N=36), defined as no increase or <0.05mmol/L increase in plasma cholesterol for 100mg cholesterol, or hyperresponders (N=18), defined as an increase of >0.06mmol/L in plasma cholesterol for 100mg cholesterol. During the egg consumption period, the hyperresponders had an elevation of both LDL-C (from 1.54±0.38 to 1.93±0.36mmol/L) and HDL-C (from 1.23±0.26 to 1.35±0.29mmol/L), while hyporesponders had NS alterations in plasma LDL-C or HDL-C. All subjects, however, had an increase in LDL peak diameter (P<0.01) and a decrease in the smaller LDL sub-fractions (P<0.01) during the egg consumption period

Djousse et al, 2008 (positive quality) This was a prospective cohort study (a component of the Physicians' Health Study) conducted in the US to examine the association between egg consumption and the risk of CVD and mortality. Information on egg consumption was obtained at baseline, 24, 48, 72, 96 and 120 months using a semi-quantitative food frequency questionnaire (FFQ). A total of 21,327 American male physicians (mean age 53.7±9.5 years, range 40-85 years) were included in the analysis. After an average follow-up of 20 years, a total of 1,550 new MI, 1,342 incident strokes and 5,169 deaths occurred in the cohort. Egg consumption was not associated with incident MI, total stroke or types of stroke. While egg consumption of up to six eggs per week was not associated with the risk of all-cause mortality, consumption of seven or more eggs per week was associated with a 23% increased risk of death after controlling for confounders (P for trend<0.0001). In addition, compared with the lowest category of egg consumption, intake of seven or more per week was associated with 22% increased risk of death in the absence of prevalent diabetes whereas a two-fold increased risk of death was observed in the presence of prevalent diabetes (P for interaction between diabetes and egg consumption was 0.029 in the parsimonious model and 0.09 in the multivariable adjusted model).

Goodrow et al, 2006 (neutral quality) This was a randomized crossover trial conducted in the US to investigate the effects of egg consumption on serum concentrations of lutein, zeaxanthin, lipids and lipoprotein cholesterol in older adults. The 18-week trial consisted of four phases: Phase I (baseline period in which participants were instructed to limit their consumption of foods high in lutein and zeaxanthin and to avoid eggs or high-egg content foods), phase II (five-week intervention during which subjects consumed either no egg or egg substitute or one egg per day in addition to their normal diet), phase III (four-week washout period similar to phase I), and phase IV (five-week crossover intervention from phase II). A seven-day diet record was obtained from each subject during each phase of the study. Thirty-three subjects [seven men (mean age 77±4 years) and 26 women (mean age 81±2 years)] were enrolled and completed the trial. After the egg consumption period, serum lutein increased by 26% and serum zeaxanthin increased by 38% (both P<0.001), while serum concentrations of TC, LDL-C, HDL-C and triglycerides (TG) were not affected.

Greene et al, 2005 (neutral quality) This was a randomized crossover trial conducted in the US to evaluate the effects of a cholesterol challenge on plasma cholesterol, LDL

size and LDL susceptibility to oxidation in the elderly. Subjects were assigned to either the equivalent of three eggs per day (containing approximately 640mg of dietary cholesterol) or the same volume of egg substitute for 30 days, followed by a three-week washout period, and then assigned to the opposite intervention for 30 days. A seven-day dietary record was collected during each period. Forty-two older adults (13 men over 60 years of age, 29 postmenopausal women, no age specified) enrolled and completed the trial. In both men and women, TC ($P<0.05$), LDL-C ($P<0.05$), HDL-C ($P<0.001$) and LDL particle size ($P<0.05$) increased during the egg consumption period. However, there were no differences between egg and egg substitute consumption periods with regard to LDL:HDL ratio, plasma TGs, apo-B concentration and the parameters of LDL oxidation.

Harman et al, 2008 (neutral quality) This was an RCT conducted in the United Kingdom to compare the combined effects of two energy-restricted diets, with and without added dietary cholesterol (two eggs per day) on weight loss, plasma lipids, and lipoproteins. Fifty-three subjects were randomly assigned to one of two parallel dietary interventions: An energy restricted diet (reduced by 500-1,000kcal per day) which included two eggs (N=27) or no eggs (N=26) per day for 12 weeks. All subjects received dietetic counseling and an individualized diet plan, and weight loss was monitored through regular meetings with a dietitian. A seven-day food diary was completed at baseline and after six weeks. Forty-five subjects completed the trial, 24 in the group consuming eggs (eight male, 17 female, mean age 44.9±8.4 years) and 21 in the control group (six male, 15 female, mean age 43.0±10.5 years). Energy intake fell by 25 and 29% in the egg-fed and non-egg-fed groups, resulting in a moderate weight loss of 3.4kg ($P<0.05$) and 4.4kg ($P<0.05$), respectively. The concentration of plasma LDL-C decreased in the non-egg-fed group after six weeks ($P<0.01$) and in the egg-fed and non-egg-fed at 12 weeks relative to baseline, however, there were no other significant changes in plasma lipoproteins or LDL particle size.

Hu et al, 1999 (positive quality) This was an analysis of two prospective cohort studies, the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS), to examine the effect of egg consumption on CVD outcomes in men and women. A total of 37,851 men (aged 40-75 years) and 80,082 women (aged 34-59 years) were followed for incident nonfatal MI, fatal CHD and stroke. Dietary intake of eggs was determined by validated FFQ. There were 866 cases of CHD and 258 cases of stroke in men during the 8-year follow-up, and 939 cases of CHD and 563 cases of stroke in women during the 14-year follow-up. After adjustment for age and other CHD risk factors, there was NS association between egg consumption and risk of CHD or stroke in men or women. The relative risk (RR) of CHD across categories of intake was 1.08 (P for trend=0.75) for the highest egg consumption group (more than one egg per day) for men, and 0.82 (P for trend=0.95) for women. However, when sub-groups were analyzed, there was a significant association between egg intake and risk of CHD in subjects with T2D (RR=2.02, P for trend=0.04, for men and RR=1.49, P for trend=0.008, for women), which warrants further investigation.

Knopp et al, 2003 (positive quality) This was a randomized crossover trial to determine if insulin resistance influences the serum lipoprotein response to dietary cholesterol and SFA. Specifically, this was a double-blinded, randomized, three-period

Archived from www.NEL.gov on March 21, 2017

crossover clinical trial with three four-week intervention periods with four-week washout. Subjects were divided based on body mass index (BMI) and insulin sensitivity to three groups: Insulin sensitive (IS, N=65); insulin resistant (IR, N=75; and obese insulin-resistant (OIR, N=58). The intervention was consumption of zero, two or four eggs per day with a background National Cholesterol Education Program (NCEP) Step 1 diet (monitored by three-day food records). Consumption of four eggs per day was associated with an increase in LDL-C in the IS (increased 7.8%) and IR (increased 3.3%) groups (both P<0.05), but not the OIR group (NS). However, HDL-C levels also increased significantly in all groups: 8.8%, 5.2%, and 3.6% in IS, IR and OIR groups, respectively. Additionally, there were significantly decreased TG levels (-5.5%) with consumption of four eggs per day in the IS group. A limitation of this study was that the IR and OIR groups had significantly higher LDL-C at baseline than the IS group.

Kritchevsky and Kritchevsky 2000 (neutral quality) This was a semi-systematic review of epidemiological studies that examine the relationship between dietary cholesterol and heart disease risk. The summary of epidemiological evidence relating dietary cholesterol to CVD risk covered eight prospective cohort studies from 1981-1999. When the full-range of confounding factors including dietary fat and fiber were taken into account, the association between dietary cholesterol and heart disease risk was small (6% increased risk for 200mg per 1,000kcal per day difference in cholesterol intake). The summary of epidemiological evidence relating egg consumption to CVD risk covered six prospective cohort studies. Taking into account dietary confounding factors, there was no association between egg consumption at levels up to one or more egg per day and risk of CHD in non-diabetic men and women.

Mutungi et al, 2008 (neutral quality) This was an RCT conducted in the US to compare the effects of a CHO-restricted diet high in cholesterol (provided by eggs) to one low in cholesterol (provided by egg substitutes) on the variables of metabolic syndrome. The CHO-restricted diet was composed of 10-15% of energy as CHO, 25-30% as protein (PRO), and 55-60% as fat and energy intake was not restricted. Subjects received weekly follow-up counseling and education and body mass and compliance were measured at visits. Three-day food records were obtained at baseline and five-day food records were completed during weeks one, six and 12. 31 males, age 40-70 years old, enrolled in the study; 28 completed the 12-week trial. Energy intake decreased in both groups from 10,243±4,040 to 7,968±2,401kJ (P<0.05) compared with baseline, and all subjects had reduced body weight and waist circumference (WC) (P<0.0001). The plasma TG concentration was reduced from 1.34±0.66 to 0.83±0.30mmol/L after 12 weeks (P<0.001) in all subjects. The plasma HDL-C concentration increased in the egg consumption group from 1.23±0.39 to 1.47±0.38mmol/L (P<0.01), whereas HDL-C did not change in the egg substitute consumption group; however, the plasma LDL-C concentration, as well as the LDL-C:HDL-C ratio, did not change during the intervention.

Nakamura et al, 2006 (neutral quality) This was a prospective cohort study conducted in Japan to examine the association between egg consumption and TC concentration, and CHD incidence. Two cohorts were analyzed: Cohort I, composed of 54,350 residents in four specific prefectures of Japan, aged 40-59 in 1990, and cohort II,

composed of 62,288 residents in five specific prefectures of Japan, aged 40-69 in 1993-1994. Egg consumption was assessed through FFQs and subjects were followed through December 2001. Egg consumption was not associated with the risk of CHD, although TC was significantly related to the risk of CHD; the multivariate hazard ratio (HR) of CHD in subjects with TC >2,400 vs. <1,800mg/L was 2.17 (95% CI: 1.22, 3.85, P for trend=0.0018).

Qureshi et al, 2007 (positive quality) This was a prospective cohort study conducted in the US to study the association between egg intake and 20-year risk of CVD and mortality in subjects from the NHANES-I Epidemiologic Follow-up Study (NHEFS). Egg consumption was categorized into no or less than one egg, one to six eggs or greater than six eggs per week, during four follow-up periods in 1982-1984, 1986, 1987 and 1992. A total of 9,734 adults (3,756 males, 5,978 females, aged 25-74 years at the time of the original study) were included in the analysis. After adjusting for several factors, no relationship was observed between consuming more than six eggs per week and risk of stroke (RR=0.9, 95% CI: 0.7-1.1); there was also no relationship between more than six eggs per week and risk of ischemic stroke (RR = 0.9, 95% CI: 0.7-1.1). Subjects with higher egg intake had NS difference than lower intake groups in RR for risk of MI (RR=1.0, 95% CI: 0.9-1.3) or all-cause mortality (RR=1.0, 95% CI: 0.9-1.1). There was an increased risk for MI in some of the diabetic subjects who consumed more than six eggs per week (RR=2.0, 95% CI: 1.0-3.8), however, this same risk was not observed for either type of stroke.

Reaven et al, 2001 (neutral quality) This was an RCT of post-menopausal women to test the effects of increasing levels of dietary cholesterol intake on TC and LDL-C. Subjects were 65 healthy, post-menopausal women, 31 defined as insulin resistant (IR) and 34 as insulin sensitive (IS). Subjects were studied over a 12-week period: Four weeks of low-cholesterol baseline, four-week washout, and four weeks on 319mg, 523mg or 941mg cholesterol per day. The designated amount of cholesterol was obtained from eggs. The changes in TC and LDL-C in response to increments in dietary cholesterol up to the highest dose were not statistically significant and there were no differences between the IS and IR groups.

Tanasescu et al, 2004 (positive quality) This was a prospective cohort study, using a sub-population from the Nurses' Health Study, conducted in the US to assess the relationship between different types of dietary fat and cholesterol and the risk of CVD among women with T2D. The Nurses' Health Study started in 1986 with follow-up questionnaires sent every two years until 1996. Dietary fat and cholesterol were assessed through semiquantitative FFQs. A total of 5,672 female nurses (between the ages of 30-55 years in 1976) had reported a physician's diagnosis of diabetes at age >30 years on any follow-up questionnaire and were included in the analysis. Between 1980 and 1998, 619 new cases of CVD (non-fatal MI, fatal CHD and stroke) were identified. The RR of CVD for an increase of 200mg cholesterol per 1,000kcal was 1.37 (95% CI: 1.12-1.68, P=0.003). Each 5% of energy intake from SFA, as compared with equivalent energy from CHO, was associated with a 29% greater risk of CVD (RR=1.29, 95% CI: 1.02-1.63, P=0.04). The P:S ratio (polyunsaturated fat (PUFA) to SFA) was inversely associated with the risk of fatal CVD. Replacement of 5% of energy from SFA with equivalent energy from CHO or monounsaturated fat (MUFA)

was associated with a 22% or 37% lower risk of CVD, respectively.

Tannock et al, 2005 (neutral quality) This was a randomized crossover trial to examine the effects of dietary cholesterol on markers of inflammation in 201 subjects divided into three a priori defined groups: Lean insulin-sensitive (LIS), N=66; lean insulin-resistant (LIR), N=78; and obese insulin resistant (OIR), N=59. For this analysis, subjects ingested zero or four eggs per day for four weeks in random order, with a background NCEP Step 1 diet (monitored by three-day food records) and four-week washout. Egg feeding was associated with significant increases in both CRP and serum amyloid A (SAA) in the LIS group (both $P<0.01$) but not in the LIR or OIR groups, although CRP and SAA were significantly higher in the latter two groups at baseline. Egg feeding was associated with a significant increase in HDL-C for all three groups. Egg feeding also was associated with a significant increase in non-HDL-C in LIS subjects ($P<0.01$); however, there was no correlation between the changes in non-HDL-C or changes in either CRP or SAA in this group. Circulating cytokines (IL-1b, IL-6, IL-8 and TNF-a) were not increased with egg feeding in any groups. Overall, a limitation of this analysis is that it is based on the same study population as that of Knopp et al; however, the outcomes and conclusions regarding egg consumption are different and more general measures are provided (e.g., there is no measure of LDL-C, only non-HDL-C).

Weggemans et al, 2001 (positive quality) This was a meta-analysis to examine the effects of dietary cholesterol on the ratio of total to HDL-C. Studies were identified in MEDLINE and Biological Abstracts searches (1974-1999). Of 222 studies identified, 17 studies with 556 subjects met the inclusion criteria. The meta-analysis included men and women with a wide age range from North America, Europe and South Africa. The analysis showed that addition of 100mg cholesterol per day increased the ratio of TC to HDL-C by 0.02 units (95% CI: 0.01-0.03); TC by 2.2mg/dL (95% CI: 1.8-2.5mg/dL); and HDL-C by 0.3mg/dL (95% CI: 0.2-0.4mg/dL). However, when subjects were divided into two sub-groups based on PUFA and SFA intake (PUFA:SFA <0.7 or >0.7), the association between dietary cholesterol and increased serum LDL-C was attenuated in the low SFA group, with a statistically significant difference between high and low SFA groups.

16

Overview table

Author, Year, Study Design, Class, Rating	Study Description and Duration	Study Population, Demographics and Location	Intervention Protocol	Significant Outcomes	Limitations
Ballesteros et al 2004 Study Design: Randomized Crossover Trial Class: A Rating: Positive quality	30-day intervention followed by a three-week washout period, followed by the opposite intervention for 30 days.	N=60 children [30 boys (aged 10.6±1.6 years) and 30 girls (aged 10.2±1.5 years)] enrolled. N=54 children (25 boys, 29 girls) completed the trial. Location: Mexico.	Children were divided into two groups and randomly assigned to either egg or egg substitute intervention for 30 days followed by a three-week washout period, followed by the opposite intervention for 30 days. Children consumed either two whole eggs (providing 518mg additional dietary cholesterol) or the equivalent amount of egg whites with added color, served scrambled for breakfast in the school cafeteria. On weekends, eggs and egg substitute were packed for consumption and parents were instructed on proper administration.	Children were classified as hyporesponders (N=36), defined as no ↑ or <0.05mmol/L ↑ in plasma cholesterol for 100mg cholesterol or hyperresponders (N=18), defined as an ↑ of >0.06mmol/L in plasma cholesterol for 100mg cholesterol. During egg consumption period, hyperresponders had an ↑ of both LDL-C (from 1.54±0.38 to 1.93±0.36mmol/L) and HDL-C (from 1.23±0.26 to 1.35±0.29mmol/L), while hyporesponders had NS alterations in plasma LDL-C or HDL-C. All subjects, however, had an ↑ in LDL peak diameter (P<0.01) and a ↓ in the smaller LDL sub-fractions (P<0.01) during the egg consumption period.	Sponsored by the American Egg Board.

Djousse et al 2008 Study Design: Prospective Cohort Study Class: B Rating: Positive quality	Physicians' Health Study. Average follow-up of 20 years.	21,327 American male physicians. Mean age: 53.7±9.5 years, range 40-85 years. Location: United States.	Examined association between egg consumption and risk of CVD and mortality. Information on egg consumption obtained at baseline, 24, 48, 72, 96 and 120 months using a semi-quantitative FFQ.	After an average follow-up of 20 years, a total of 1,550 new MI, 1,342 incident strokes and 5,169 deaths occurred in the cohort. Egg consumption not associated with incident MI, total stroke or types of stroke. While egg consumption of up to six eggs per week was not associated with risk of all-cause mortality, consumption of ≥seven eggs per week was associated with a 23% ↑ risk of death after controlling for confounders (P for trend <0.0001). In addition, compared with lowest category of egg consumption, intake of ≥seven per week was associated with 22% ↑ risk of death in the absence of prevalent diabetes, whereas a two-fold ↑ risk of death was observed in the presence of prevalent diabetes (P for interaction between diabetes and egg consumption was 0.029 in the parsimonious model and 0.09 in the multivariable adjusted model).	Study substituted missing values at baseline using reported egg consumption at 24 months in 113 individuals. Lack of detailed dietary data prevented adjustment for energy and other major nutrients. Sample consisting of male physicians limits generalizability of the findings. Unable to examine the effects of SFA, markers of insulin resistance, lipid and other nutrients or relevant biomarkers on the observed positive association in diabetic subjects.

Goodrow et al 2006 Study Design: Randomized Crossover Trial Class: A Rating: Neutral quality	Duration: 18 weeks.	N=33 older adults [seven men (mean age 77±4 years) and 26 women (mean age 81±2 years)] enrolled and completed the trial. Location: United States.	The 18-week trial consisted of four phases: Phase I (baseline period; participants instructed to limit consumption of foods ↑ in lutein and zeaxanthin and avoid eggs or ↑-egg content foods) Phase II (five-week intervention; subjects consumed either no egg or egg substitute or one egg per day in addition to their normal diet) Phase III (four-week washout period similar to phase I) Phase IV (five-week crossover intervention from phase II). A seven-day diet record obtained from each subject during each phase of the study.	After egg consumption period, serum lutein ↑ by 26% and serum zeaxanthin ↑ by 38% (both P<0.001), while serum concentrations of TC, LDL-C, HDL-C and TG were not affected.	Sample size was relatively small, most subjects were female and the age range was very broad. Sponsored by the American Egg Board.
Greene CM et al 2005 Study Design: Randomized Crossover Trial Class: A Rating: Neutral quality	Two 30-day intervention periods separated by a three-week washout period.	N=42 older adults (13 men >60 years of age, 29 postmenopausal women) enrolled and completed the trial. Age not specified. Location: United States	Subjects assigned to either equivalent of three eggs per day (containing ~640mg dietary cholesterol) or same volume of egg substitute for 30 days, followed by a three week washout period, and then assigned to opposite intervention for 30 days. Seven-day dietary record collected during each period.	In both men and women, TC (P<0.05), LDL-C (P<0.05), HDL-C (P<0.001) and LDL particle size (P<0.05) ↑ during the egg consumption period. However, no differences between egg and egg substitute consumption periods with regard to LDL:HDL ratio, plasma tTG, apo-B concentration and parameters of LDL oxidation.	Relatively small sample size, predominantly composed of females; subjects not well described. Significant differences in WC and HDL-C concentrations between men and women at baseline. Sponsored by the American Egg Board/Egg Nutrition Center.

| Harman et al 2008

Study Design: Randomized Controlled Trial

Class: A

Rating:

Neutral quality | Duration: 12 weeks. | N=53 subjects randomly assigned.

N=45 subjects completed trial:

N=24 in group consuming eggs (eight male, 17 female, mean age 44.9±8.4 years)

N=21 in control group (six male, 15 female, mean age 43.0±10.5 years).

Location: United Kingdom. | Subjects were randomly assigned to one of two parallel dietary interventions:

1) An energy restricted diet (↓ by 500-1,000kcal per day) which included two eggs (N=27)

2) No eggs (N=26) per day for 12 weeks.

All subjects received dietetic counseling and individualized diet plan and weight loss monitored through regular meetings with a dietitian.

Seven-day food diary completed at baseline and after six weeks. | Energy intake ↓ by 25 and 29% in the egg-fed and non-egg-fed groups, resulting in a moderate weight ↓ of 3.4kg (P<0.05) and 4.4kg (P<0.05), respectively.

Concentration of plasma LDL-C ↓ in the non-egg-fed group after six weeks (P<0.01) and in the egg-fed and non-egg-fed at 12 weeks relative to baseline, however, no other significant Δ in plasma lipoproteins or LDL particle size. | Study was not sufficiently controlled or statistically powered.

Supported by the British Egg Industry Council. |
|---|---|---|---|---|---|

Hu FB, Stampfer MJ et al, 1999 Study Design: Prospective Cohort Study Class: B Rating: Positive quality	Analysis of: 1) Health Professionals Follow-up Study (HPFS); eight-year follow-up 2) Nurses Health Study (NHS); 14-year follow-up.	N=37,851 men (aged 40-75 years). N=80,082 women (aged 34-59 years).	Followed for incident non-fatal MI, fatal CHD and stroke. Egg intake determined with FFQ.	N=866 cases of CHD and 258 cases of stroke in men in eight-year follow-up. RR of CHD across categories of intake was 1.08 (P for trend =0.75) for highest egg consumption group (> one egg per day) for men. N=939 cases of CHD and 563 cases of stroke in women during the 14-year follow-up. RR of CHD across categories of intake was 0.82 (P for trend =0.95) for highest egg consumption group for women. After adjustment for age and other CHD risk factors, NS association between egg consumption and risk of CHD or stroke in men or women. In subjects with T2D, positive association between egg intake and CHD risk (RR=2.02, P for trend=0.04, for men and RR=1.49, P for trend=0.008, for women).	None.

Knopp RH, Retzlaff B et al, 2003 Study Design: Randomized Controlled Trial Class: A Rating: Positive quality	Double-blinded, randomized, three-period crossover clinical trial with three four-week intervention periods with four-week washout.	Subjects divided based on BMI and insulin sensitivity to three groups: N=65 Insulin sensitive (IS) N=75 Insulin resistant (IR) N=58 Obese, insulin-resistant (OIR).	Consumption of zero, two or four eggs per day. Background NCEP Step 1 diet (monitored by three-day food records).	Consumption of four eggs per day associated with ↑ LDL-C in IS (7.8%) and IR (3.3%) groups (both P<0.05), but not OIR group (NS). HDL-C levels ↑ significantly in all groups: 8.8%, 5.2% and 3.6% in IS, IR and OIR groups, respectively, with consumption of four eggs per day. Significantly ↓ TG (-5.5%) with consumption of four eggs per day in IS group.	None.
Kritchevsky SB and Kritchevsky D, 2000 Study Design: Meta-analysis or Systematic Review Class: M Rating: Neutral quality	Summary of epidemiological evidence relating dietary cholesterol and egg intake to CVD.	N=8 prospective cohort studies relating dietary cholesterol and risk of CVD. N=6 prospective cohort studies relating egg consumption and risk of CVD.	Dietary cholesterol. Egg cholesterol.	Association between dietary cholesterol and heart disease risk is small. 6% ↑ CVD risk for 200mg per 1,000kcal per day difference in cholesterol intake. No association between egg consumption at >one egg per day and risk of CVD in non-diabetic men and women.	None.

McNamara DJ, 2000 Study Design: Meta-analysis or Systematic Review Class: M Rating: Positive quality	Pooled quantitative analysis.	N=167 articles on cholesterol feeding studies in 3,519 subjects. 1960-2000. Studies limited to cross-over design with cholesterol intake sole variable.	Studies used dietary cholesterol concentrations from ↑ (100-300mg per day) to ↓ (3-5g per day) intakes adjusted for body weight to 70kg and plasma cholesterol to 100mg per day Δ.	Plasma cholesterol ↑ by 2.2mg/dL for 100mg per day cholesterol intake. Hyper-responders: Plasma cholesterol ↑ by 3.9mg/dL for 100mg per day. Hypo-responders: Plasma cholesterol ↑ by 1.4mg/dL for 100mg per day. NS Δ in LDL:HDL ratio (2.60 to 2.61).	None.
Mutungi et al 2008 Study Design: Randomized Controlled Trial Class: A Rating: Neutral quality	Duration: 12 weeks.	N=31 males enrolled. N=28 completed the trial. Age: 40-70 years. Location: United States.	Compared effects of a CHO-restricted diet ↑ in cholesterol (provided by eggs) to one ↓ in cholesterol (provided by egg substitutes) on the variables of metabolic syndrome. CHO-restricted diet composed of 10-15% of energy as CHO, 25-30% as PRO and 55-60% as fat; energy intake not restricted. Subjects received weekly follow-up counseling and education and body mass and compliance measured at visits. Three-day food records obtained at baseline and five-day food records completed during weeks one, six and 12.	Energy intake ↓ in both groups from 10,243±4,040 to 7,968±2,401kJ (P<0.05) compared with baseline, and all subjects had ↓ body weight and WC (P<0.0001). Plasma TG concentration was ↓ from 1.34±0.66 to 0.83±0.30mmol/L after 12 weeks (P<0.001) in all subjects. Plasma HDL-C concentration ↑ in egg consumption group from 1.23±0.39 to 1.47±0.38mmol/L (P<0.01), whereas HDL-C did not Δ in egg substitute consumption group; however, no Δ in the plasma LDL-C concentration or LDL:HDL ratio.	All male subjects and sample not well described; unclear if sample was representative. Sponsored by the Egg Nutrition Center.

Nakamura et al 2006 Study Design: Prospective Cohort Study Class: B Rating: Neutral quality	Duration: Subjects followed through December 2001.	Two cohorts were analyzed: Cohort I, composed of 54,350 residents in four specific prefectures of Japan, aged 40-59 in 1990 Cohort II, composed of 62,288 residents in five specific prefectures of Japan, aged 40-69 in 1993-1994. Location: Japan.	Examined association between egg consumption and TC concentration and CHD incidence. Egg consumption assessed through FFQ.	Egg consumption was not associated with risk of CHD, although TC was significantly related to risk of CHD; the multivariate HR of CHD in subjects with TC >2,400 vs. <1,800mg/L was 2.17 (95% CI: 1.22, 3.85, P for trend=0.0018).	Egg consumption only measured at baseline and was measured in days per week rather than number of eggs per week. Portion sizes not specified, total energy intake could not be used as a covariate in the analyses. TC concentration was only available for some of the subjects.

Qureshi et al 2007 Study Design: Prospective Cohort Study Class: B Rating: Positive quality	Duration: 20-year follow-up.	N=9,734 adults (3,756 males, 5,978 females) included in analysis, from the NHANES-I Epidemiologic Follow-up Study (NHEFS). Age: 25-74 years at time of original study. Location: United States.	Studied the association between egg intake and risk of CVD and mortality. Egg consumption was categorized into no or six eggs per week, during four follow-up periods in 1982-1984, 1986, 1987 and 1992.	After adjusting for several factors, no relationship observed between consuming >six eggs per week and risk of stroke (RR=0.9, 95% CI: 0.7-1.1); there was also no relationship between >six eggs per week and risk of ischemic stroke (RR=0.9, 95% CI: 0.7-1.1). Subjects with higher egg intake had NS difference than lower intake groups in RR for risk of MI (RR=1.0, 95% CI: 0.9-1.3) or all-cause mortality (RR=1.0, 95% CI: 0.9-1.1). ↑ risk for MI in some of the diabetic subjects who consumed >six eggs per week (RR=2.0, 95% CI: 1.0-3.8), however, this same risk not observed for either type of stroke.	None.
Reaven GM, Abbasi F et al, 2001 Study Design: Randomized Controlled Trial Class: A Rating: Neutral quality		N=65 healthy, postmenopausal women (31 insulin resistant, 34 insulin sensitive).	12-week trial: Four weeks of low-cholesterol baseline Four-week washout Four weeks on 319mg, 523mg, or 941mg cholesterol per day. Cholesterol was from eggs.	Δ in TC and LDL-C in response to increments in dietary cholesterol up to the highest dose were not statistically significant. No differences between IS and IR groups.	None.

Tanasescu et al 2004 Study Design: Prospective Cohort Study Class: B Rating: Positive quality	Nurses' Health Study. Duration: 18-year follow-up.	N=5,672 female nurses who reported a physician's diagnosis of diabetes at age >30 years on any follow-up questionnaire. Age: 30-55 years in 1976. Location: United States.	Assessed relationship between different types of dietary fat and cholesterol and risk of CVD among women with T2D. Nurses' Health Study started in 1986 with follow-up questionnaires sent every two years until 1996. Dietary fat and cholesterol assessed through semi-quantitative FFQ.	Between 1980 and 1998, 619 new cases of CVD (nonfatal MI, fatal CHD and stroke) were identified. RR of CVD for an ↑ of 200mg cholesterol per 1,000kcal was 1.37 (95% CI: 1.12-1.68, P=0.003). Each 5% of energy intake from SFA, as compared with equivalent energy from CHO, was associated with a 29% ↑ risk of CVD (RR=1.29, 95% CI: 1.02-1.63, P=0.04). P:S ratio inversely associated with risk of fatal CVD. Replacement of 5% of energy from SFA with equivalent energy from CHO or MUFA was associated with a 22% or 37% ↓ risk of CVD, respectively.	Assessment of MUFA was difficult due to shared food sources of SFA and MUFA.

Tannock LR, O'Brien KD et al, 2005 Study Design: Randomized Controlled Trial Class: A Rating: Neutral quality		N=201 subjects divided into three defined groups: 1) N=66 Lean insulin-sensitive (LIS) 2) N=78 Lean insulin-resistant (LIR) 3) N=59 Obese insulin resistant (OIR).	Zero or four eggs per day for four weeks. Background NCEP Step 1 diet (monitored by three-day food records). Four-week washout.	Egg feeding associated with significant ↑ in CRP and SAA in LIS group (both P<0.01), but not in LIR or OIR groups. Egg feeding associated with significant ↑ in HDL-C for all three groups. Egg feeding associated with significant ↑ in non-HDL-C in LIS group (P<0.01). No correlation between Δ in non-HDL-C or Δ in CRP or SAA in LIS group. Circulating cytokines (IL-1b, IL-6, IL-8 and TNF-a) not ↑ with egg feeding in any groups.	None.
Weggemans RM, Zock PL et al, 2001 Study Design: Meta-analysis or Systematic Review Class: M Rating: Positive quality	Studies identified in MEDLINE and Biological Abstracts (1974-1999).	Men and women with a wide age range from North America, Europe and South Africa. Location: International.	N=17 with 556 subjects met inclusion criteria (of 222 studies identified).	Addition of 100mg cholesterol per day: ↑ ratio of TC:HDL-C by 0.02 units (95% CI: 0.01-0.03) ↑ TC by 2.2mg/dL (95% CI: 1.8-2.5mg/dL) ↑ HDL-C by 0.3mg/dL (95% CI: 0.2-0.4mg/dL). Association between dietary cholesterol and ↑ LDL-C attenuated in the ↓ SFA, vs. ↑ SFA, group (P=0.03).	None.

Research recommendations

The potential for dietary cholesterol to increase CVD risk in individuals with type 2 diabetes warrants further investigation.

Search plan and results

Inclusion Criteria

Subjects/Population

- *Age:* Two years through adult
- *Setting:* US and International
- *Health status:* Healthy and those with elevated chronic disease risk (CHD/CVD, type 2 diabetes, metabolic syndrome and obesity).

Search Criteria

- *Study design preferences:* RCT or clinical controlled studies, large non-randomized observational studies, meta-analysis and systematic reviews. Feeding period must be greater than four weeks
- *Size of study groups:* The sample size must be 10 or more subjects for each study group. For example, this would include 10 patients in the intervention group and 10 patients in the control or comparison group
- *Study dropout rate:* Less than 20%; preference for smaller dropout rates
- *Year range*: 1999 to present
- *Languages:* Limited to articles in English
- *Other:* Article must be published in peer-reviewed journal.

Exclusion Criteria

Subjects/Population

- *Age:* Infants/children less than two years
- *Setting:* Inpatients.

Search Criteria

- *Size of study groups:* Sample sizes less than 10
- *Study designs:* Cross-sectional; feeding periods less than four weeks
- *Study dropout rate:* If the dropout rate in a study is 20% or greater
- *Year range:* Prior to January 2000
- *Authorship:* Studies by same author with similar in content
- *Languages:* Articles not in English
- *Other:* Animal studies; abstracts or presentations.

Search Terms and Electronic Databases Used

PubMed:

"Cholesterol, Dietary" [MeSH Major Topic]

"Cholesterol, Dietary" [MeSH] AND "Lipoproteins, LDL" [MeSH] AND "Cholesterol, LDL" [MeSH]

"Cholesterol, Dietary" [MeSH] AND "Cardiovascular Disease" [MeSH]

"Cholesterol, Dietary" [MeSH] AND "Inflammation" [MeSH]

Eggs Cardiovascular Disease (Key Words)

Eggs LDL Cholesterol (Key Words)

Eggs Inflammation (Key Words)

Date Searched: 07/20/2009

Summary of Articles Identified to Review

- Total hits from all electronic database searches: 61
- Total articles identified to review from electronic databases: 30
- Articles identified via handsearch or other means: 1
- Number of Primary Articles Identified: 13
- Number of Review Articles Identified: 3
- Total Number of Articles Identified: 16
- Number of Articles Reviewed but Excluded: 14

Included Articles (References)

Systematic Review/Meta-Analyses

1. Kritchevsky SB, Kritchevsky D. Egg consumption and coronary heart disease: An epidemiologic overview. J Am Coll Nutr. 2000 Oct; 19(5 Suppl): 549S-555S. Review. PMID: 11023006.
2. McNamara DJ. The impact of egg limitations on coronary heart disease risk: Do the numbers add up? J Am Coll Nutr. 2000 Oct; 19(5 Suppl): 540S-548S. Review. PMID: 11023005.
3. 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.

Primary Articles

1. Ballesteros MN, Cabrera RM, Saucedo Mdel S, Fernandez ML. Dietary cholesterol does not increase biomarkers for chronic disease in a pediatric population from northern Mexico. Am J Clin Nutr. 2004 Oct; 80(4): 855-861. PMID: 15447890.
2. 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.
3. Harman NL, Leeds AR, Griffin BA. Increased dietary cholesterol does not increase plasma low density lipoprotein when accompanied by an energy-restricted diet and weight loss. Eur J Nutr. 2008 Sep; 47(6): 287-293. Epub 2008 Aug 26. Erratum in: Eur J Nutr. 2008 Oct; 47(7): 408. PMID: 18726564.
4. Goodrow EF, Wilson TA, Houde SC, Vishwanathan R, Scollin PA, Handelman G, Nicolosi RJ. Consumption of one egg per day increases serum lutein and zeaxanthin concentrations in older adults without altering serum lipid and lipoprotein cholesterol concentrations. J Nutr. 2006 Oct; 136(10): 2, 519-2, 524.

29

PMID: 16988120.

5. Greene CM, Zern TL, Wood RJ, Shrestha S, Aggarwal D, Sharman MJ, Volek JS, Fernandez ML. Maintenance of the LDL cholesterol:HDL cholesterol ratio in an elderly population given a dietary cholesterol challenge. J Nutr. 2005 Dec; 135(12): 2, 793-2, 788. PMID: 16317122.

6. Hu FB, Stampfer MJ, Rimm EB, Manson JE, Ascherio A, Colditz GA, Rosner BA, Spiegelman D, Speizer FE, Sacks FM, Hennekens CH, Willett WC. A prospective study of egg consumption and risk of cardiovascular disease in men and women. JAMA. 1999 Apr 21;281(15):1, 387-1, 394. PMID: 10217054.

7. Knopp RH, Retzlaff B, Fish B, Walden C, Wallick S, Anderson M, Aikawa K, Kahn SE. Effects of insulin resistance and obesity on lipoproteins and sensitivity to egg feeding. Arterioscler Thromb Vasc Biol. 2003 Aug 1; 23(8): 1, 437-1, 443. Epub 2003 Jun 19. PMID: 12816878.

8. Mutungi G, Ratliff J, Puglisi M, Torres-Gonzalez M, Vaishnav U, Leite JO, Quann E, Volek JS, Fernandez ML. Dietary cholesterol from eggs increases plasma HDL cholesterol in overweight men consuming a carbohydrate-restricted diet. J Nutr. 2008 Feb; 138(2): 272-276. PMID: 18203890.

9. A prospective study of egg consumption and risk of cardiovascular disease in men and women. JAMA. 1999 Apr 21; 281(15): 1, 387-1, 394. PMID: 10217054.

10. 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.

11. 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.

12. Reaven GM, Abbasi F, Bernhart S, Coulston A, Darnell B, Dashti N, Kim H, Kulkarni K, Lamendola C, McLaughlin T, Osterlund L, Schaff P, Segrest J. Insulin resistance, dietary cholesterol, and cholesterol concentration in postmenopausal women. Metabolism. 2001 May; 50(5): 594-597. PMID: 11319723.

13. Tanasescu M, Cho E, Manson JE, Hu FB. Dietary fat and cholesterol and the risk of cardiovascular disease among women with type 2 diabetes. Am J Clin Nutr. 2004 Jun; 79(6): 999-1, 005. PMID: 15159229.

14. Tannock LR, O'Brien KD, Knopp RH, Retzlaff B, Fish B, Wener MH, Kahn SE, Chait A. Cholesterol feeding increases C-reactive protein and serum amyloid A levels in lean insulin-sensitive subjects. Circulation. 2005 Jun 14; 111(23): 3, 058-3, 062. Epub 2005 Jun 6. PMID: 15939816.

Excluded Articles

Article	Reason for Exclusion
Burnett JR, Huff MW. Cholesterol absorption inhibitors as a therapeutic option for hypercholesterolaemia. *Expert Opin Investig Drugs.* 2006 Nov; 15(11): 1, 337-1, 351. Review. PMID: 17040195.	Does not address question: Examines cholesterolabsorption inhibitors as therapeutic intervention.
Carr TP, Jesch ED. Food components that reduce cholesterol absorption. *Adv Food Nutr Res.* 2006; 51: 165-204. Review. PMID: 17011476.	Food Science review.
Coico R, Woodruff-Pak DS. Immunotherapy for Alzheimer's disease: harnessing our knowledge of T cell biology using a cholesterol-fed rabbit model. *J Alzheimers Dis.* 2008 Dec; 15(4): 657-671. Review. PMID: 19096163.	Alzheimer's disease is not a health outcome that is included in this question.
Devaraj S, Jialal I. The role of dietary supplementation with plant sterols and stanols in the prevention of cardiovascular disease. *Nutr Rev.* 2006 Jul; 64(7 Pt 1): 348-354. Review. PMID: 16910223.	Covers plant sterols and stanols as dietary supplements to inhibit cholesterol absorption.
Herron KL, McGrane MM, Waters D, Lofgren IE, Clark RM, Ordovas JM, Fernandez ML. The ABCG5 polymorphism contributes to individual responses to dietary cholesterol and carotenoids in eggs. *J Nutr.* 2006 May; 136(5): 1, 161-1, 165. PMID: 16614398.	This article better addresses question 3.1 on genetic polymorphisms.
Hovenkamp E, Demonty I, Plat J, Lütjohann D, Mensink RP, Trautwein EA. Biological effects of oxidized phytosterols: a review of the current knowledge. *Prog Lipid Res.* 2008 Jan; 47(1): 37-49. Epub 2007 Nov 1. Review. PMID: 18022398.	Narrative review of the cardioprotective effects of oxidized phytosterols.
Ikeda I. Multifunctional effects of green tea catechins on prevention of the metabolic syndrome. *AsiaPac J Clin Nutr.* 2008; 17 Suppl 1: 273-274. Review. PMID: 18296354.	Narrative review of beneficial effects of green tea catechins to prevent symptoms of metabolic syndrome.

Kassis AN, Vanstone CA, Abu M, Weis SS, Jones PJ. Efficacy of plant sterols is not influenced by dietary cholesterol intake in hypercholesterolemic individuals. *Metabolism.* 2008 Mar; 57(3): 339-346. PMID: 18249205.	Article is focused on the use of plant sterols, not dietary cholesterol.
Khoury J, Haugen G, Tonstad S, Frøslie KF, Henriksen T. Effect of a cholesterol-lowering diet during pregnancy on maternal and fetal Doppler velocimetry: The CARRDIP study. *Am J Obstet Gynecol.* 2007 Jun; 196(6): 549.e1-7. PMID: 17547890.	Subjects are pregnant women.
Lucenteforte E, Talamini R, Montella M, Dal Maso L, Tavani A, Deandrea S, Pelucchi C, Greggi S, Zucchetto A, Barbone F, Parpinel M, Franceschi S, La Vecchia C, Negri E. Macronutrients, fatty acids and cholesterol intake and endometrial cancer. *Ann Oncol.* 2008 Jan; 19(1): 168-172. Epub 2007 Sep 24. PMID: 17895258.	This article is excluded based on the new formulation of the question that does not address cancer as a health outcome.
Paxman JR, Richardson JC, Dettmar PW, Corfe BM. Alginate reduces the increased uptake of cholesterol and glucose in overweight male subjects: a pilot study. *Nutr Res.* 2008 Aug; 28(8): 501-505. PMID: 19083452.	Treatment, not dietary, study.
Ratliff J, Mutungi G, Puglisi MJ, Volek JS, Fernandez ML. Carbohydrate restriction (with or without additional dietary cholesterol provided by eggs) reduces insulin resistance and plasma leptin without modifying appetite hormones in adult men. *Nutr Res.* 2009 Apr; 29(4): 262-268. PMID: 19410978.	All subjects in this study were on a carbohydrate restricted diet, both EGG and control groups.
Riechman SE, Andrews RD, Maclean DA, Sheather S. Statins and dietary and serum cholesterol are associated with increased lean mass following resistance training. *J Gerontol A Biol Sci Med Sci.* 2007 Oct; 62(10): 1, 164-1, 171. PMID: 17921432.	Confounder: Resistance training.

Sutherland WH, de Jong SA, Walker RJ. Effect of dietary cholesterol and fat on cell cholesterol transfer to postprandial plasma in hyperlipidemic men. *Lipids.* 2007 Oct; 42(10): 901-911. Epub 2007 Aug 7. PMID: 17680290.	Although potentially relevant, subject N<10 per treatment group.

CHAPTER 3. SPECIFIC FATS, FATTY ACIDS, AND CHOLESTEROL – MONOUNSATURATED FATTY ACIDS ON HEALTH OUTCOMES

WHAT IS THE EFFECT OF DIETARY INTAKE OF MONOUNSATURATED FATTY ACIDS (MUFA) ON HEALTH AND INTERMEDIATE HEALTH OUTCOMES?

Conclusion statement

Strong evidence indicates that dietary monounsaturated fatty acids (MUFA) are associated with improved blood lipids related to both cardiovascular disease (CVD) and type 2 diabetes (T2D), when they are a replacement for dietary saturated fatty acids (SFA). The evidence shows that five percent energy replacement of SFA with MUFA decreases intermediate markers and the risk of CVD and T2D in healthy adults and improves insulin responsiveness in insulin resistant and T2D subjects.

Grade

Strong

Evidence summary overview

Thirteen studies published since 2004 and conducted in the US, Europe and Australia were reviewed to determine the effect of monounsaturated fat (MUFA) on health outcomes. These included one methodologically strong meta-analysis evaluating 11 prospective cohort studies (Jakobsen, 2009) and 11 randomized controlled trials (RCTs) ranging from 14 to 162 subjects, including six methodologically strong studies (Appel, 2005; Berglund, 2007; Due, 2008; Lopez, 2008; Thijssen and Mensink, 2005; and Thijssen, 2005) and five methodologically neutral studies (Allman-Farinelli, 2005; Binkoski, 2005; Clifton, 2004; Paniagua, 2007; and Rasmussen, 2006). The reviewed studies also included one methodologically strong prospective cohort study of 5,672 subjects from the Nurses' Health Study who reported a diagnosis of type 2 diabetes (T2D) (Tanasescu, 2004).

Overall, MUFA replacing saturated fat (SFA) in the diet as percent of energy leads to a decrease in low-density lipoprotein cholesterol (LDL-C) (Allman-Farinelli, 2005; Appel, 2005; Berglund, 2007), a decrease in serum triglycerides (TG) (Allman-Farinelli, 2005), a decrease in markers of inflammation (Allman-Farinelli, 2005), and a decrease in cardiovascular disease (CVD) risk (Appel, 2005; Rasmussen, 2006). Increasing MUFA intake, rather than replacing SFA with MUFA, also leads to a decrease in total cholesterol (TC) (Haban, 2004), LDL-C (Haban, 2004), LDL-C to high-density lipoprotein cholesterol (HDL-C) ratio (Due, 2008), serum TG (Brunerova, 2007), inflammatory markers (Brunerova, 2007) and fasting insulin and Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) scores (Brunerova, 2007; Due, 2008). However, Clifton et al, (2004) found a greater decrease in TC and HDL-C in women who consumed a very low-fat diet, compared with a high MUFA diet and no difference in the LDL: HDL ratio between the two diets (Clifton, 2004). Replacing SFA with MUFA, compared to replacement with carbohydrates (CHO), decreased serum TG (Appel, 2005) and increased HDL-C (Appel, 2005; Berglund, 2007). Lastly, a prospective cohort study involving a T2D subpopulation within the Nurses' Health

Study found that replacing 5% energy from SFA with equivalent energy from MUFA was associated with a 27% lower risk of CVD. The authors conclude that replacing SFA with MUFA may be more protective against CVD than replacement with CHO (Tanasescu, 2004).

Comparing substitution of SFA with MUFA vs. polyunsaturated fat (PUFA) showed a greater decrease in TC and LDL-C with PUFA substitution (Binkoski, 2005). Furthermore, a pooled analysis of 11 prospective cohort studies showed that risk of coronary events and coronary death was lowest with 5% energy substitution of SFA with PUFA; PUFA substitution resulted in the greatest decrease, with MUFA showing somewhat less, and CHO showing the least improvement when substituted for SFA (Jakobsen, 2009). In a comparison of individual fatty acids, oleic acid was no different than stearic or linoleic acid in its effect on measures of serum lipids or lipoproteins and markers of inflammation (Thijssen and Mensink, 2005; Thijssen, 2005).

Evidence summary paragraphs

Allman-Farinelli et al, 2005 (neutral quality) This was a randomized, extra-period crossover trial, conducted in Australia. The study compared the effect of a SFA-rich diet with a MUFA-rich diet on the concentrations of factor VII coagulant activity factor, fibrinogen, plasminogen, activator inhibitor-1 and blood lipids. Subjects consumed either the SFA-rich diet (20.8% energy as fat) for five weeks and crossed over to the MUFA-rich diet (20.3% energy as fat) for 10 weeks or the opposite diets with no washout period between diets. Fifteen of the 18 initial subjects (five males, 10 females; aged 35-69 years) completed the study. Subjects completed three-day food diaries on two occasions during each intervention. Weight was maintained throughout the study. Dietary compliance was confirmed by a significant increase in both plasma phospholipids and neutral lipid oleic acid (P<0.0001) on the MUFA diet. Factor VIIc was lower (97±1%) on the MUFA diet (P<0.05) compared to the SFA diet (99±1). Low-density lipoprotein cholesterol (3.47±0.06mmol per L) was lower (P<0.001) compared to SFA (4.01±0.07mmol per L) and TG levels were also lower (P<0.01) on the MUFA - rich diet (144.0±4.6mmol per L) compared to the SFA diet (145.1±4.9mmol per L). There were no differences between diets for fibrinogen and insulin concentrations or plasminogen activator inhibitor-1 activity.

Appel et al, 2005 (positive quality) This was the Omni Heart randomized, three-period crossover trial conducted in the US. The study compared the effect of three reduced SFA, on blood pressure (BP) and serum lipids in 191 healthy adults with stage I hypertension (HTN) or pre-hypertension (PHTN). The three six-week interventions included a diet rich in CHO, a diet rich in protein (about half from plant sources) and a diet rich in unsaturated fat (predominantly MUFA); all were reduced in SFA, cholesterol and sodium, and rich in fruits, vegetables, fiber, potassium and other minerals at the recommended levels. One hundred sixty one subjects were included in this analysis (45% women, mean age 53.6±10.9 years). Blood pressure, LDL-C and estimated CHD risk were lower on each diet compared to baseline. Compared with the CHO-rich diet, the unsaturated fat diet decreased systolic blood pressure (SBP) by 1.3mmHg (P=0.005) and by 2.9mmHg among those with HTN (P=0.02), had no effect on LDL-C, increased HDL-C by 1.1mg per dL (0.03mmol per L, P=0.03) and lowered TG by 9.6mg per dL (0.11mmol per L, P=0.02).

35

Berglund et al, 2007 (positive quality) This was a randomized crossover trial conducted in the US. The study compared MUFA with CHO as a replacement for SFA in subjects with a high metabolic risk profile. Three diets were fed in a double-blind, three-way crossover with each lasting seven-weeks with a rest period of four to six weeks between each intervention. The three diets reflected the typical pattern of the US population. Two were modified to replace 7% of energy from SFA with either CHO (primarily complex) on the CHO-replacement diet or with MUFA on the MUFA-replacement diet. All food was provided except for a self-selected meal [following the NCEP Step I guidelines] on Saturday evenings. Blood samples were drawn at weeks five, six and seven of each intervention. Eighty five of the initial 110 subjects completed all three interventions (33 females, 52 males and mean age 35.5±9.2 years, range 21-61 years). Relative to the average American diet, LDL-C was lower with both the CHO-replacement diet (-7.0%) and MUFA-replacement diet (-6.3%), whereas the difference in HDL-C was smaller during the MUFA-replacement diet (-4.3%) than during the CHO-replacement diet (-7.2%). Lipoprotein (a) concentrations increased with both the CHO-replacement diet (20%) and MUFA-replacement diet (11%) relative to the average American diet.

Binkoski et al, 2005 (neutral quality) This was a randomized crossover trial conducted in the US. The study evaluated the effect of a trans fat-free MUFA-rich vegetable oil on lipid and lipoprotein levels and measures of oxidative stress. Thirty one subjects (12 men, 19 women and 25-64 years of age) with moderate hypercholesterolemia enrolled and completed the trial. Subjects were randomized to one of three, four-week dietary interventions with a two-week washout period. Two of the experimental diets provided 30% fat, with olive oil or NuSun sunflower oil contributing one-half of the fat (8.3% vs. 7.9% SFA, 17.2% vs. 14.2% MUFA, and 4.3% vs. 7.7% PUFA, respectively). NuSun is mid-oleic sunflower oil developed by standard hybrid breeding that contains a similar proportion of and substantially greater proportion PUFAs and less SFA compared than olive oil. The third diet was an average American diet (AAD) (34% fat, 11.2% SFA, 14.9% MUFA and 7.8% PUFA). The test fats were incorporated in sauces, spreads, baked goods, granola and salad dressings. The NuSun sunflower oil diet significantly reduced total and LDL-C levels, as well as apolipoprotein A-1 levels compared with the average American diet ($P<0.001$, $P=0.0006$ and $P=0.0004$, respectively). The olive oil diet had no effect compared with the AAD. The experimental diets had no effect on TG levels, rate of oxidation, total dienes, lipid hydroperoxides or alpha-tocopherol ($P>0.05$).

Clifton et al, 2004 (neutral quality) This was an RCT with parallel design. This study investigated the effects of a very low-fat diet (VLF) vs, a high MUFA (H-MUFA) weight loss diet on body fat distribution, weight and lipid profile in overweight women without T2D [N=62, body mass index (BMI)>27kg/m2]. Subjects were matched by age and BMI and randomized to consume one of two 6,000kJ diets: 35% energy from fat, 20% energy from MUFA) (H-MUFA diet) or 12% energy from fat, 4% energy from MUFA (VLF diet) for 12 weeks. Weight loss (9.5±2.4 vs. 9.4±3.4kg, VLF vs. H-MUFA) and total fat loss (6.1±2.4 vs. 6.3±2.7kg, VLF vs. H-MUFA) did not differ in the groups. There was a diet x menopausal status interaction in lean mass changes (P=0.005) such that in premenopausal women, H-MUFA produced a lower loss of lean mass than the low-fat diet (0.4±2.3 vs. 2.9±2.7kg, P=0.006) with the opposite, but NS effect seen

36

in postmenopausal women. There was a greater decrease in total plasma cholesterol in women who consumed VLF compared with those who consumed H-MUFA (0.82±0.0.51 vs. 0.50±0.48mmol per L, P<0.001 for time, P<0.05 for diet effect). This was also true for the change in HDL-C (0.18±0.23 vs. 0.04±0.19mmol per L, VLF and H-MUFA, respectively, P<0.001 for time, P<0.05 for diet effect). The LDL/HDL ratio was reduced in both groups with no effect of diet (0.16±0.51 vs. 0.16±0.45, VLF and H-MUFA, respectively, P<0.05). Authors conclude that weight, total fat mass and regional fat mass loss did not differ in the two groups of women, but there was an apparent preservation of lean mass in premenopausal women consuming H-MUFA.

Due et al, 2008 (positive quality) This was an RCT with parallel design to compare the effect on weight-loss maintenance and change in CVD and diabetic risk factors of three diets (Willett's new Healthy Eating Pyramid, the Official Nordic Dietary Guidelines and the average Danish diet) in a six-month controlled dietary maintenance program, for 154 non-diabetic overweight or obese subjects [mean±SD BMI): 31.5±2.6kg/m2] men (N=55) and women (N=76) aged 28.2±4.8 years in Denmark. Subjects were randomly assigned to a diet providing a moderate amount of fat (35-45% of energy) and >20% of fat as MUFA (MUFA diet; N=54), to a low-fat (20-30% of energy) diet (LF diet; N=51), or to a control diet (35% of energy as fat; N=26). Protein constituted 10-20% of energy in all three diets. All foods were provided from a purpose-built supermarket. The attrition rate was higher for MUFA (28%) group than for the LF group (16%) and control group (8%) (MUFA compared with control: P<0.05). All groups regained weight (MUFA: 2.5±0.7kg; LF: 2.2±0.7kg; and control: 3.8±0.8kg; NS). Body fat regain was lower in the LF (0.6±0.6%) and MUFA (1.6±0.6%) groups than in the control group (2.6±0.5%, P<0.05). In the MUFA group, fasting insulin decreased by 2.6±3.5pmol per L, the HOMA-IR by 0.17±0.13, and the ratio of LDL:HDL by 0.33±0.13; in the LF group, these variables increased by 4.3±3.0pmol per L (P<0.08) and 0.17±0.10 (P<0.05) and decreased by 0.02±0.09 (P=0.005), respectively; and in the control group, increased by 14.0±4.3pmol per L (P<0.001), 0.57±0.17 (P<0.001) and 0.05±0.14 (P=0.036), respectively. Dietary adherence was high on the basis of fatty acid changes in adipose tissue. Diet composition had no major effect on preventing weight regain. Both the LF and MUFA diets produced less body fat regain than did the control diet, and the dropout rate was lowest in the LF diet group. Fasting insulin decreased and the HOMA-IR and ratio of LDL to HDL improved with the MUFA diet.

Jakobsen et al, 2009 (positive quality) This pooled analysis evaluated the associations between energy intake from MUFA, PUFA and CHO replacing energy from SFA to prevent CHD. Data from 11 American and European cohort studies involving 344,696 persons were pooled and analyzed for incident of CHD as outcome measures. During four to 10-year follow-up, there were 5,249 coronary events and 2,155 coronary deaths. The analysis found that for every 5% lower energy intake from SFAs and a concomitant higher energy intake from PUFAs or CHOs, there was a significant inverse association between these energy sources and risk of coronary events, with hazard ratios (HR) as follows for PUFAs: HR: 0.87 (95% CI: 0.77, 0.97); HR for coronary deaths= +0.74 (95% CI: 0.61, 0.89) and for CHOs: HR: 1.07 (95% CI: 1.01, 1.14); HR for coronary deaths=0.96 (95% CI: 0.82, 1.13), respectively. There was indication of a positive association between substitution of MUFAs and risk of

37

coronary events (HR: 1.19; 95% CI: 1.00, 1.42), but not risks of coronary deaths. There was also a modest, but significant, association between substitution of CHO and risk of coronary events (HR: 1.07; 95% CI: 1.01, 1.14), but not risk of coronary deaths. There was no effect modification by gender or age. The authors conclude that replacing SFAs with PUFAs rather than MUFAs or CHOs prevents CHD over a wide range of intakes. The country and demographics of subjects not described. The type of CHO in the diet was not taken into account in this analysis (i.e., extent of processing, fiber content, or glycemic index, although discussed).

Lopez et al, 2008 (positive quality) This was a randomized, single-blinded, crossover trial of 14 healthy men in Spain to determine the degree to which unsaturation of dietary fatty acids influences the postprandial control of insulin secretion and insulin sensitivity. The postprandial response to high-fat meals enriched in SFAs or MUFAs was assessed using mixed meals with common foods. The isocaloric diet interventions included 9% more fat, replacing CHO in the control NCEP diet, and were as follows:

1. NCEP Step I
2. High butter (MUFA:SFA, 0.48:1.0)
3. Refined olive oil (ROO) (MUFA:SFA, 5.43:1.0)
4. High palmitic sunflower oil (HPSO) (MUFA:SFA, 2.42:1.0)
5. Mixture of vegetable and fish oils (VEFO) (MUFA:SFA, 7.08:1.0).

Subjects were normo-triglyceridemic and had normal fasting blood glucose (FBG) and glucose tolerance. Results showed that high fat meals increased the postprandial concentrations of insulin, TG, and free fatty acids (FFAs), and they increased postprandial b-cell activity as assessed by the insulinogenic index (IGI), a surrogate measure of first-phase insulin secretion; IGI/HOMA-IR ratio; AUCinsulin/AUCglucose ratio; and HOMA of b-cell function (HOMA-B). High fat meals also decreased postprandial insulin sensitivity assessed by a glucose and TG tolerance test meal (GTTTM)-determined insulin sensitivity test and the postprandial Belfiore indices for glycemia and blood FFAs. These effects were significantly improved, in a linear relationship, when MUFAs were substituted for SFAs; subjects became less insulin resistant postprandially as the proportion of MUFAs, compared with SFAs, in dietary fats increased (VEFO>ROO>HPSO>butter). When the early postprandial insulin response was used as a measure of b-cell activity, it decreased as the ratio of MUFA/SFA increased. Overall the findings suggest that b-cell function and insulin sensitivity progressively improve in the postprandial state as the proportion of MUFAs, relative to SFAs, increases in the diet, suggesting that MUFAs moderate the postprandial hyperactivity of the pancreatic b-cell. The underlying mechanism likely involves different insulinotropic potentials of individual FFA (e.g., oleic acid has been reported to elicit half the insulin secretion from b-cells as palmitic or stearic acids).

Paniagua et al, 2007 (neutral quality) This was a randomized crossover study on offspring of obese, T2D patients recruited from diabetic patients' records at primary care centers in Cordoba Spain. Fifty-nine potential subjects were recruited, but 27 subjects either did not meet the inclusion criteria or refused to participate. Qualifying subjects underwent an oral glucose tolerance test (OGTT), after which 11 insulin resistant (IR) subjects (four men, seven women) remained in the study. Subjects had a BMI=25kg/m2. Subjects were randomly assigned to three groups and underwent three

38

diet periods of 28 days in a crossover design:

1. Diet high in SFA (SAT): Increased 15% energy as SFA
2. Diet high in MUFA (MUFA): Increased 15% energy as MUFA
3. Diet high in CHO: Increased 18% energy as CHO.

Body weight and resting energy expenditure were not changed over any of the diet interventions. Fasting serum glucose decreased during the MUFA and CHO diet periods compared with SAT diet (5.02 ± 0.1, 5.03 ± 0.1, 5.50 ± 0.2mmol per L, respectively, ANOVA<0.05). The MUFA diet improved insulin sensitivity indicated by lower HOMA-IR, compared to CHO and SAT diets (2.32 ± 0.3, 2.52 ± 0.4, 2.72 ± 0.4, respectively, ANOVA<0.01). Compared to a CHO breakfast, the AUC of postprandial glucose and insulin were lower with MUFA or SAT breakfasts (11.9 ± 2.7, 7.8 ± 1.3, 5.84 ± 1.2mmol x 180minutes per L, ANOVA< 0.05; and $2,667\pm329$, $1,004\pm147$, $1,253\pm140$, pmol x 180minutes per L, ANOVA<0.01, respectively). Integrated glucagon-like peptide-1 increased with MUFA and SAT breakfasts compared with isocaloric CHO breakfast. Fasting and postprandial HDL-C increased with MUFA diet and the AUC of TG decreased with CHO diet. Fasting proinsulin decreased, while stimulated ratio PI/I was not changed by MUFA diet. Overall, weight maintenance with a MUFA rich diet improves HOMA-IR and fasting proinsulin levels in IR subjects.

Rasmussen et al, 2006 (neutral quality) This was a randomized controlled, parallel, multi-center study. This trial investigated whether dietary MUFA, compared to SFA affects BP in healthy subjects (N=162, 76 women and 86 men) over a three-month period. A secondary purpose was to investigate if addition of long chain n-3 fatty acids would affect BP. Subjects followed one of two isoenergetic diets: One rich in MUFA (MUFA diet, 8%of energy as SFAs, 23% as MUFAs and 6% as PUFAs) and the other rich in SFA (SFA diet, 17% of energy as SFAs, 14% as MUFAs and 6% as PUFAs). Each group was further randomly assigned to receive supplementation with fish oil (3.6g n-3 fatty acids per day) or placebo. Adherence to the diets was not different between groups. Body weight remained unchanged during the study. Systolic BP and diastolic BP (DBP) decreased with the MUFA diet [-2.2% (P=0.009) and -3.8% (P=0.0001), respectively], but did not change with the SFA diet [-1.0% (P=0.2084) and -1.1% (P=0.2116)]. The MUFA diet caused a significantly lower DBP than did the SFA diet (P=0.0475). The favorable effects of MUFA on DBP disappeared at a total fat intake above the median (>37% of energy). The addition of n-3 fatty acids influenced neither SBP nor DBP.

Tanasescu et al, 2004 (positive quality) This study used data from the prospective cohort Nurses' Health Study conducted in the US to assess the relationship between different types of dietary fat and cholesterol and the risk of CVD among women with T2D. The Nurses' Health Study started in 1986 with follow-up questionnaires sent every two years. Dietary fat and cholesterol were assessed through semi-quantitative food-frequency questionnaire (FFQ). Five thousand six hundred seventy two female nurses (30-55 years in 1976) who had reported a physician's diagnosis of diabetes at age >30 years on any follow-up questionnaire were included in the analysis. Between 1980-1998, 619 new cases of CVD (non-fatal MI, fatal CHD and stroke) were identified. Relative risks of CVD were estimated from Cox proportional hazards analysis after adjustment for potential confounders. The relative risk of CVD for an

increase of 200mg cholesterol per 1,000kcal was 1.37 (95% CI: 1.12-1.68, P=0.003). Each 5% of energy intake from SFA, as compared with equivalent energy from CHO, was associated with a 29% greater risk of CVD (RR=1.29, 95% CI: 1.02-1.63, P=0.04). The PUFA: SFA (P:S) ratio was inversely associated with risk of fatal CVD. Replacement of 5% energy from SFA with equivalent energy from CHO or MUFA was associated with a 22% or 37% lower risk of CVD, respectively. Overall, an increased intake of cholesterol and SFA and a low P:S was related to increased CVD risk in women with T2D. Among women with T2D, replacement of SFA with MUFA may be more protective against CVD than replacement with CHOs.

Thijssen et al, 2005a (positive quality) and Thijssen and Mensink, 2005b (positive quality) This was a randomized multiple crossover study conducted in the Netherlands that compared the effects of fat types: Stearic, oleic (MUFA) and linoleic acids on platelet aggregation, coagulation, fibrinolysis and hematological variables in 45 healthy subjects (18 men and 27 women, mean age 51 years, range 28-66 years). Subjects consumed three test diets in random order over three five-week periods and after each intervention period, there was a washout period of at least one week when participants consumed their habitual diets. The test diets contained approximately 35% of energy from fat, and each diet contained 7% of energy as linoleic, stearic acid or oleic acid. Subjects visited a dietitian at least once every week to receive a new supply of products and to be weighed. Individual allowances were adjusted when subjects' weight differed by 1.5kg from the initial weight during week 1- or 2kg during the following weeks. Thijssen et al, 2005b found that in men (N=18), ex vivo platelet aggregation time as measured by filtragometry (P=0.036 for diet effects) was favorably prolonged during consumption of the PUFA diet compared with the stearic acid diet (P=0.040). No effect was found in women (N=27 After the high linoleic diet, the number of erythrocytes was lower and the mean platelet volume of the subjects decreased during consumption of the stearic acid diet by 0.32fL compared with the oleic acid diet (P<0.001) and by 0.35fL compared with the linoleic acid diet (P<0.001). The effects on coagulation and fibrinolytic variables did not differ among the other two fatty acids. Thijssen and Mensink, 2005b, found NS differences in serum LDL-C (P=0.137 for diet effects) or HDL-C (P=0.866). Very-low-density lipoprotein (VLDL) particle sizes and lipoprotein subclass distributions also did not differ significantly between the three diets. (abSame Study; two publications).

Overview table

Author, Year, Study Design, Class, Rating	Study Description, Duration	Study Population/ Location	Intervention Protocol/Exposure levels	Significant Results	Limitations
Allman-Farinelli et al 2005 Study Design: Randomized Crossover Trial Class: A Rating: Neutral quality	Randomized extra-period crossover trial. SFA diet for five weeks. MUFA diet for 10 weeks.	N=15 healthy men and women. Age: 35-69 years. Attrition: 17%. Location: Australia.	SFA vs. MUFA Two diets: MUFA rich diet (high-oleic-acid sunflower oil) (Energy 32.6% total fat; 8.8% SFA; 20.3 % MUFA) SFA rich diet (Energy 33.1% total fat; 20.8% SFA; 9.6% MUFA) No wash out.	Factor VII was lower with MUFA fat rich diet ($P<0.05$). LDL-C ($P<0.001$) and TG ($P<0.01$) lower on the MUFA diet. MUFA diet ↑ plasma PL and neutral lipid oleic acid ($P<0.0001$). Fibrinogen, plasminogen activator inhibitor-1, insulin concentration did not between diets.	Small number of subjects. No washout periods.

Appel LJ et al 2005 Study Design: Randomized Crossover Trial Class: A Rating: Positive quality	OmniHeart. Compared the effects of three diets, for six weeks each. Washout period of two to four weeks separated the feeding periods.	N=191, healthy adults with Stage I HTN or PHTN. Mean age: 53.6 years. Attrition: ~15%. N=191 randomly assigned N=164 completed two feeding periods; N=159 completed all three diet periods N=161 included in the analysis (45% women). Location: United States.	Unsaturated fat (MUFA) vs. CHO diet. Compared the effects of three diets, each with 6% energy from SFA, on BP and serum lipids. Percent energy: CHO-rich diet: 58% CHO, 15% PRO, 27% total fat (13% MUFA) Protein-rich diet: 48% CHO, 25% PRO, 27% total fat (13% MUFA) Unsaturated fat (MUFA) rich diet: 48% CHO, 15% PRO, 37% total fat (21% MUFA) All diets were (per day): <150mg cholesterol, >30g fiber, 2,300mg Na, 4,700mg K, 500mg Mg, 1,200mg Ca.	Unsaturated fat vs. MUFA vs. CHO diet: ↓ SBP 1.3mmHg (P=0.005); 2.9mmHg in HTN subjects (P=0.02; NS effect on LDL-C; ↑ HDL-C 1.1mg per dL (0.03mmol per L; P=0.03); ↓ TG 9.6mg per dL (0.11mmol per L; P=0.02). PRO vs. CHO Protein diet: ↓ mean SBP 1.4mmHg (P=0.002); 3.5mmHg (P=0.006) in HTN subjects; ↓ LDL-C 3.3mg per dL (0.09mmol per L; P=0.01); HDL-C 1.3mg per dL (0.03mmol per L; P=0.02); TG 15.7mg per dL (0.18mmol per L; P=0.001).	None.

Berglund L, Lefevre M et al, 2007 Study Design: Randomized Crossover Trial Class: A Rating: Positive quality	Three diets fed in a double-blind, three-way crossover with each diet lasting seven weeks. Rest period of four to six weeks between each diet.	N=85, high metabolic risk profile (33 females, 52 males). Attrition: 23%. Mean age: 35.5±9.2 years (range 21-61 years); three diets. Location: United States.	Compared MUFA with CHO as a replacement for SFA. Three diets: Average American diet (AAD; reflecting the typical pattern of the US population) CHO-replacement diet (meeting the nutrient specifications of the NCEP Step I diet) MUFA fat-replacement diet (to match the SFA and PUFA content of the CHO-replacement diet, but also the total fat of the AAD; 36% energy from fat) 7% energy from SFA replaced with either CHO (primarily complex) on the CHO-replacement diet or with MUFA on the MUFA-replacement diet. All food was provided except for a self-selected meal (following the NCEP Step I guidelines) on Saturday evenings. Blood samples were drawn at weeks five, six and seven of each of the three diets.	Relative to AAD: LDL-C was lower with CHO (-7.0%) and MUFA (-6.3%) diets, compared to AAD. HDL-C differences were ↓ for MUFA (-4.3%) than CHO diet (-7.2%). Lipoprotein (a) concentration ↑ with both CHO (20%) and MUFA (11%) diets, relative to AAD.	Weights were maintained, so the issue of dietary effects on lipid concentrations under "free-living" conditions is unknown.

Binkoski AE et al 2005 Study Design: Randomized crossover trial. Class: A Rating: Neutral quality	Subjects were randomized to each diet for four-weeks. Two-week washout period.	N=31 subjects with moderate hypercholesterolemia (12 men, 19 women) Age: 25-64 years.	MUFA vs. NuSun sunflower oil Two test diets: 30% fat as olive oil NuSun sunflower oil contributing one-half of the fat (8.3% vs. 7.9% SFA, 17.2% vs. 14.2% MUFA and 4.3% vs. 7.7% PUFA, respectively). Third diet (control): Average American diet (ADD) (34% fat; 11.2% SFA; 14.9% MUFA; 7.8% PUFA).	Only the sunflower oil diet ↓ both TC and LDL-C levels compared with the other two diets; TC ↓ 4.7% and LDL-C ↓ 5.8% on the sunflower oil diet compared to the ADD. The experimental diets had no effect **on** TG levels, rate of oxidation, total dienes, lipid hydroperoxides or alpha-tocopherol.	Relatively small sample size. AAD not well-defined. Sponsored by the National Sunflower Association.
Clifton PM, Noakes M et al, 2004 Study Design: Randomized Controlled Trial Class: A Rating: Neutral quality	12-week parallel design study.	N=62 women with BMI>27kg/m^2 without diabetes. Mean age: Years±SD Very low fat: 46.9±9.9 H-MUFA: 47.1±10.7. Location: United States.	MUFA vs. CHO [both in low SFA compared to baseline] Random assignment to one of two 6,000kJ diets (%energy): High MUFA: (35% fat, 20 % MUFA) Very low-fat diet (VLF): 12% fat, 4% MUFA).	Δ in weight, LDL-C, TG, HDL/LDL ratio, BP and blood glucose did not differ between diets.	Short duration.

44

Due A et al 2008 Study Design: Randomized Controlled Trial Class: A Rating: Positive quality	Duration: Six months.	N=169. Attrition: N=131 (55 males, 76 women); 25 did not complete the six-month intervention. Age: 18-35 years (28.2± 4.8 years). BMI: 28-36kg/m^2. Location: Copenhagen, Denmark.	Three diets: Moderate fat and >20% MUFA diet, N=54, low GI and 10-20% PRO 20-30% kcals from fat; low-fat (LF diet, N=51), moderate GI and 10-20% PRO Control diet, 5% kcals from fat (N=26), high GI, 10-20% PRO three-week run-in diet.	Diet composition did not have major effects on maintenance of weight loss during the six-month dietary intervention. The MUFA and LF diets had slower rates of weight gain when compared to a Western diet. The MUFA diet may have a positive impact on diabetes risk factors. The type of diet followed may not matter as it relates to weight loss maintenance. The type of dietary fat may affect body fat composition and satiety. The MUFA diet ↓ fasting insulin and improved HOMA-IR. A diet ↑ in unsaturated fat may improve insulin resistance.	Other lifestyle factors besides diet may help with obesity prevention and weight maintenance.

Jakobsen MU, O'Reilly EJ et al, 2009 Study Design: Meta-analysis or Systematic Review Class: M Rating: Positive quality		N= 344,696 subjects. Pooled from 11 American and European cohort studies published between 1966 and 1993.	Data Analyisis. Incidents of CHD associated with energy intake from MUFA, PUFA and CHO and risk of CHD.	Follow-up: Four to 10 years 5,249 coronary events; 2,155 coronary deaths. Significant inverse associations found for PUFA or CHO as replacement sources for 5% lower energy from SFAs and risk of coronary events reported as HR for: PUFA: HR=0.87 (95% CI: 0.77, 0.97); HR for coronary deaths=+0.74 (95% CI: 0.61, 0.89). CHO: HR=1.07 (95% CI: 1.01, 1.14); HR for coronary deaths=0.96 (95% CI: 0.82, 1.13). MUFA intake was not associated with CHD.	The country and demographics of subjects not described.

Lopez S, Bermudez B et al, 2008 Study Design: Randomized Crossover Trial Class: A Rating: Positive quality		N=14 men; healthy normotrigly-ceridemic with normal glucose tolerance. Mean age: 27 years. Mean BMI: 23.9kg/m^2. Location: Spain.	Four isocaloric diets with 9% ↑ fat [replacing CHO in Step I diet as control] Control Step I High butter (MUFA:SFA, 0.48:1.0) Refined olive oil (ROO) (MUFA:SFA, 5.43:1.0) High palmitic sunflower oil (HPSO) (MUFA:SFA, 2.42:1.0) Mixture of vegetable and fish oils (VEFO) (MUFA:SFA, 7.08:1.0).	High fat meals: ↑ postprandial insulin, TG and FFAs ↑ pancreatic beta-cell activity ↓ insulin sensitivity. Postprandial insulin sensitivity ↑ and as proportion of MUFAs, (vs. SFAs) ↑: VEFO>ROO>HPSO>Butter. Beta-cell activity, measured as early postprandial insulin response, ↓ as proportion of MUFAs (vs. SFAs) ↑.	Relatively low subject number (N=14).

47

Paniagua JA, de la Sacristana AG et al, 2007 Study Design: Prospective Cohort Study Class: B Rating: Neutral quality	Randomized cross-over 28-day feeding trial.	N=11 (four men, seven women). Age: 62±9.4 years. Insulin resistant by OGTT. Location: Spain.	Three isocaloric diets (% energy): 38% fat and 47% CHO. In two high fat diets (% energy): 23% SFA or MUFA; 20% fat; 65% CHO in the low-fat diet (replacement of SFA).	SFA vs. MUFA: ↑ HBA1c (P<0.01), ↑ fasting glucose by 9.6% (P<0.05), ↑ HOMA by 17.2% (P<0.01), ↑ fasting proinsulin by 26.1% (P<0.05), NS effects on postprandial glucose, postprandial insulin or postprandial GLP-1 SFA vs. CHO: ↑ HBA1c by 6.3% (P<0.01), ↑ fasting glucose by 9.3% (P<0.05), ↓ postprandial glucose by 51 (P<0.05), ↓ postprandial insulin by 53 (P<0.05), ↑ postprandial GLP-1 by 134.6 (P<0.05). NS effects on HOMA or fasting proinsulin. NS effects on fasting insulin or GLP1, or the 60 minutes proinsulin:insulin ratio with any diet.	None.

48

Rasmussen BM, Vessby B et al, 2006 Study Design: Randomized controlled trial; parallel, multi-center study Class: A Rating: Neutral quality	KANWU Study.	N=162 (95 men and 67 women). Healthy population. Attrition:162 because of intent to treat analysis. Three dropped out. Age: 30 to 65 years SFA/placebo group (N=42): 49.3±7.1 (mean±SD) SFA/n-3 FA group (N=41): 48.5±8.0 MUFA/placebo group (N=40): 47.0±8.8 MUFA/n-3 FA group (N=39): 49.5±7.3. Location: Denmark.	Isoenergetic diets with the same amount of macronurients consumed for three months. 37% kcal from fat was used for both the high-MUFA and the high-SFA diets. MUFA diet: 8% kcal from SFA; 23% from MUFA; 6% from PUFA. SFA diet: 17% kcal SFA; 14% from MUFA; 6% from PUFA. Randomized subgroups from the MUFA group and from the SFA group received additional fish oil capsules with 3.6g n-3 fatty acids per day (2.4g as EPA and DHA). Trained dietitians instructed all subject on preparation of their diets and met with subjects at least every other week until the end of the study. Edible fats supplied to use as spreads, for cooking and in dressings that contained neglible amounts of TFAs, n-3 FAs or olive oil.	A significant ↓ from baseline in SBP for the MUFA treated group (-2.2%; P=0.009) and for DBP (-3.8%; P=0.0001) without significant Δ for the SFA diet group. MUFA diet caused lower DBP than the SFA diet (P=0.0475). Above shows the Δ from baseline with the added covariate of < or >37% of total kcals as fat. When total fat was <37%, the MUFA diet ↓ SBP and DBP. These differences disappeared when fat intake was >37% of kcals. There was no effect of added n-3 FAs.	Double-blinding was not used. Weight, exercise and smoking habits were kept stable for the duration of the study. Compliance was checked by diet records and serum phospholipid fatty acid composition. There was a slightly ↑ dietary fiber intake and ↓ cholesterol intake by the MUFA group. There was no difference in calculated dietary intakes of Ca, Na, K and alcohol between the groups.

Tanasescu et al 2004 Study Design: Prospective Cohort Study Class: B Rating: Positive quality		N=5, 672 female nurses. Age: 30-55 years in 1976. Reported a physician's diagnosis of diabetes at age >30 years. Location: United States.	Dietary fat and cholesterol assessed by semi-quantitative FFQ. Estimated the effects of isocaloric (5% energy as fat) substitution of CHO or MUFA for SFA from the multivariate model including SFA, PUFA, MUFA, TFA, cholesterol, PRO, total calories, fiber and non-dietary covariates.	619 new cases of CVD (nonfatal MI, fatal CHD and stroke) were identified between 1980 and 1998 (57,195 person-years). The P:S ratio (PUFA to SFA) was inversely associated with risk of fatal CVD. Replacement of 5% energy from SFA with equivalent energy from MUFA was associated with 37% lower risk of CVD.	None.
Thijssen et al 2005 Study Design: Randomized Crossover Trial Class: A Rating: Positive quality	Three test diets consumed over three five-week periods. Washout period of at least one week between diets.	N=45 healthy subjects (18 men; 27 women). Mean age: 51 years (range 28-66 years). All subjects were assumed to have completed the trial. Location: The Netherlands.	Compared the effects of stearic, oleic and linoleic acids on platelet aggregation, coagulation, fibrinolysis and hematological variables. Three-test diets in random order over three five-week periods. Test diets contained ~35% energy from fat and each diet contained 7% energy as either stearic acid, oleic acid or linoleic acid. After each intervention period, there was a washout period of at least one week when participants consumed their habitual diets.	After the high linoleic acid diet, the number of erythrocytes was lower and ex vivo platelet aggregation was favorably prolonged compared to the stearic acid diet. Stearic acid consumption reduced platelet volume compared to the other two fatty acids (P<0.001). The effects on coagulation and fibrinolytic variables did not differ among the three fatty acids.	Recruitment methods for subjects are described elsewhere. Handling of withdrawals not discussed. Sponsored by the Dutch Dairy Association.

Thijssen MA and Mensink RP, 2005 Study Design: Randomized Controlled Trial Class: A Rating: Positive quality	Four to five weeks.	N=45 (18 males, 27 females). Healthy non-smoker adults, slightly hypercholesterolemic. Age: 28-66 years (mean 51 years). Location: The Netherlands.	Compare the effects of stearic, oleic and linoleic acids on platelet aggregation, coagulation, fibrinolysis and hematological variables. Each participant consumed three different diets in random order over three five-week periods. After each intervention period, there was a washout period of at least one week when participants consumed their habitual diets. Three diets, each diet contained 7% energy from stearic acid, oleic acid or linoleic acid. The diets contained ~35% energy from fat.	Ex vivo platelet aggregation time favorably prolonged (P=0.036 for diet effects) on linoleic acid diet compared with the stearic acid diet (P=0.040); no difference with oleic acid diet (P=0.198). In vitro platelet aggregation induced by collagen and ADP, and variables of coagulation and fibrinolysis did not differ between the diets. Hct values were slightly lower in men on linoleic acid diet compared to diets high in stearic acid and oleic acid. Platelet volume ↓ by 0.32fL on the stearic aid diet, compared with the oleic acid diet (P<0.001) and by 0.35fL compared with the linoleic acid diet (P<0.001).	None.

Research recommendations

Determine the benefits and risks of MUFA vs. PUFA as an isocalaoric substitute for SFA. Determine the mechanism by which dietary MUFA improve serum lipids, glucose metabolism, insulin levels, HOMA scores, inflammatory markers and blood pressure in both healthy persons and in persons with T2D.

Search plan and results

Inclusion Criteria

Health Outcomes

- Lipid and lipoprotein levels (LDL-C, HDL-C, non-HDL-C)
- Markers of inflammation
- Glucose tolerance, HbA1c values, insulin resistance.

Subjects/Population

- *Age*: Two years to adult
- *Setting*: US and international
- *Health status*: Healthy population and those with elevated chronic risk (CHD or CVD, type 2 diabetes, metabolic syndrome and obesity).

Search Criteria

- *Study design preferences*: RCT or clinical controlled studies, large non-randomized observational studies, meta-analysis and systematic reviews. Feeding period must be greater than four weeks
- *Size of study groups*: Sample size more than 10 subjects for each study group
- *Study dropout rate*: Less than 20%; preference for smaller dropout rates
- *Year range*: 2004 to October 2009
- *Languages*: Limited to articles in English
- *Other*: Article must be published in peer-reviewed journal.

Exclusion Criteria

Subjects/Population

- *Age*: Infants less than two years
- *Setting*: Inpatients
- *Health status*: None.

Search Criteria

- *Size of study groups*: Sample sizes less than 10
- *Study designs*: Cross-sectional; feeding periods less than four weeks; experimental fat must be from natural source
- *Study dropout rate*: If the dropout rate in a study is 20% or greater, the study will be rejected
- *Year range*: Prior to December 2003
- *Other*: Animal studies, abstracts or presentations.

Search Terms and Electronic Databases Used

PubMed:

"Fatty Acids, Omega-6"[Majr:NoExp] AND (triglycerides[majr] OR cholesterol[majr] OR "Diabetes Mellitus, Type 2"[mh] OR Myocardial infarction[majr] OR "Coronary Disease"[majr] "Heart Diseases"[majr] OR "Cardiovascular Diseases"[majr:NoExp]) lim eng/humans

oleic acid[mh] AND (glucose[majr] OR metabolic syndrome* OR insulin sensitivit* OR "Diabetes Mellitus, Type 2"[Mesh] OR hyperglycemia OR lipidemia OR "Body weight"[majr])

((n-6 AND (polyunsaturated OR PUFA*)) OR "Linolenic Acids"[Mesh] OR "Linoleic Acid"[Mesh] OR "Arachidonic Acid"[Mesh]) AND "Diabetes Mellitus, Type 2"[Mesh]

(n-6 AND (polyunsaturated OR PUFA*)) AND (Myocardial infarction[majr] OR "Coronary Disease"[majr] "Heart Diseases"[majr] OR "Cardiovascular Diseases"[majr:NoExp])

((n-6 AND (polyunsaturated OR PUFA*)) OR "Linolenic Acids"[Mesh] OR "Linoleic Acid"[Mesh] OR "Arachidonic Acid"[Mesh]) AND (triglycerides[majr] OR cholesterol[majr])

("Linolenic Acids"[Mesh] OR "Linoleic Acid"[Mesh] OR "Arachidonic Acid"[Mesh] OR oleic acid[mh]) AND (Myocardial infarction[mh] OR "Coronary Disease"[mh] OR "Cerebrovascular Disorders"[mh:NoExp] OR "Stroke"[mh:NoExp] OR "Heart Diseases"[mh] OR "Cardiovascular Diseases"[mh:NoExp]) 68 + 25 = 93 hits (limit to clinical trials, prospective studies, systematic reviews/meta)

oleic acid[mh] AND (Myocardial infarction[mh] OR "Coronary Disease"[majr] OR "Cerebrovascular Disorders"[majr:NoExp] OR "Stroke"[Majr:NoExp] OR "Heart Diseases"[majr] OR "Cardiovascular Diseases"[Majr:NoExp] OR "Triglycerides"[Mesh] OR "Arrhythmias, Cardiac"[Mesh] OR clotting OR Inflammation[mh] OR "Blood Pressure"[mh])

("Linolenic Acids"[Mesh] OR "Linoleic Acid"[Mesh] OR "Arachidonic Acid"[Mesh]) AND (Myocardial infarction[mh] OR "Coronary Disease"[majr] OR "Cerebrovascular Disorders"[majr:NoExp] OR "Stroke"[Majr:NoExp] OR "Heart Diseases"[majr] OR "Cardiovascular Diseases"[Majr:NoExp] OR "Triglycerides"[Mesh] OR "Arrhythmias, Cardiac"[Mesh] OR clotting OR Inflammation[mh] OR "Blood Pressure"[mh])

("Coronary Disease"[Mesh] OR "Cerebrovascular Disorders"[Mesh:NoExp] OR "Stroke"[Mesh:NoExp] OR "Heart Diseases"[Mesh] OR "Cardiovascular Diseases"[Mesh:NoExp] OR "Diabetes Mellitus, Type 2"[Mesh]) AND "Dietary Fats, Unsaturated"[Mesh] AND (Polyunsaturated OR PUFA* OR Monounsaturated OR MUFA*)

"Diabetes Mellitus, Type 2"[Mesh] AND (Polyunsaturated OR PUFA* OR Monounsaturated OR MUFA*)

Date Searched: 06/21/2009 to 08/11/2009, 10/26/2009

Summary of Articles Identified to Review

- Total hits from all electronic database searches: 871
- Total articles identified to review from electronic databases: 65
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 23
- Number of Review Articles Identified: 1
- Total Number of Articles Identified: 24
- Number of Articles Reviewed but Excluded: 41

Included Articles (References)

MUFA and Health Outcomes

What is the effect of dietary intake of MUFA when substituted for SFA on increased risk of CVD and type 2 diabetes (T2D), including intermediate markers such as lipid

53

and lipoprotein levels and inflammation?

Systematic Reviews/Meta-analysis

1. Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, Bälter K, Fraser GE, Goldbourt U, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Ascherio A. Major types of dietary fat and risk of coronary heart disease: A pooled analysis of 11 cohort studies. Am J Clin Nutr. 2009 May; 89(5): 1, 425-1, 432. Epub 2009 Feb 11. PMID: 19211817.

Primary Articles

1. Allman-Farinelli MA, Gomes K, Favaloro EJ, Petocz P. A diet rich in high-oleic-acid sunflower oil favorably alters low-density lipoprotein cholesterol, triglycerides, and factor VII coagulant activity. J Am Diet Assoc. 2005 Jul; 105(7): 1, 071-1, 079. PMID: 15983523.
2. Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER 3rd, Conlin PR, Erlinger TP, Rosner BA, Laranjo NM, Charleston J, McCarron P, Bishop LM; OmniHeart Collaborative Research Group. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: Results of the OmniHeart randomized trial. JAMA. 2005 Nov 16; 294(19): 2, 455-2, 464. PMID: 16287956.
3. Berglund L, Lefevre M, Ginsberg HN, Kris-Etherton PM, Elmer PJ, Stewart PW, Ershow A, Pearson TA, Dennis BH, Roheim PS, Ramakrishnan R, Reed R, Stewart K, Phillips KM; DELTA Investigators. Comparison of monounsaturated fat with carbohydrates as a replacement for saturated fat in subjects with a high metabolic risk profile: Studies in the fasting and postprandial states. Am J Clin Nutr. 2007 Dec; 86(6): 1, 611-1, 620. PMID: 18065577.
4. Binkoski AE, Kris-Etherton PM, Wilson TA, Mountain ML, Nicolosi RJ. Balance of unsaturated fatty acids is important to a cholesterol-lowering diet: Comparison of mid-oleic sunflower oil and olive oil on cardiovascular disease risk factors. J Am Diet Assoc. 2005 Jul; 105(7): 1, 080-1, 086. PMID: 15983524.
5. Clifton PM, Noakes M, Keogh JB. Very low-fat (12%) and high monounsaturated fat (35%) diets do not differentially affect abdominal fat loss in overweight, nondiabetic women. J Nutr. 2004 Jul; 134(7): 1, 741-1, 745. PMID: 15226463.
6. Due A, Larsen TM, Mu H, Hermansen K, Stender S, Astrup A. Comparison of 3 ad libitum diets for weight-loss maintenance, risk of cardiovascular disease, and diabetes: A six-month randomized, controlled trial. Am J Clin Nutr. 2008 Nov; 88(5): 1, 232-1, 241. PMID: 18996857.
7. Haban P, Klvanova J, Zidekova E, Nagyova A. Dietary supplementation with olive oil leads to improved lipoprotein spectrum and lower n-6 PUFAs in elderly subjects. Med Sci Monit. 2004 Apr; 10(4): PI49-PI54. PMID: 15039655.
8. Paniagua JA, de la Sacristana AG, Sánchez E, Romero I, Vidal-Puig A, Berral FJ, Escribano A, Moyano MJ, Peréz-Martinez P, López-Miranda J, Pérez-Jiménez F. A MUFA-rich diet improves posprandial glucose, lipid and GLP-1 responses in insulin-resistant subjects. J Am Coll Nutr. 2007 Oct; 26(5): 434-444. PMID: 17914131.
9. Rasmussen BM, Vessby B, Uusitupa M, Berglund L, Pedersen E, Riccardi G,

Archived from www.NEL.gov on March 21, 2017

Rivellese AA, Tapsell L, Hermansen K; KANWU Study Group. Effects of dietary saturated, monounsaturated, and n-3 fatty acids on blood pressure in healthy subjects. Am J Clin Nutr. 2006 Feb; 83(2): 221-226. PMID: 16469978.

10. Thijssen MA, Hornstra G, Mensink RP. Stearic, oleic, and linoleic acids have comparable effects on markers of thrombotic tendency in healthy human subjects. J Nutr. 2005 Dec; 135(12): 2, 805-2, 811. PMID: 163171242.

11. Thijssen MA, Mensink RP. Small differences in the effects of stearic acid, oleic acid, and linoleic acid on the serum lipoprotein profile of humans. Am J Clin Nutr. 2005 Sep; 82(3): 510-516. PMID: 16155261.

What is the effect of replacing a high carbohydrate diet with a high MUFA diet in persons with T2D?

Primary Articles

1. Brehm BJ, Lattin BL, Summer SS, Boback JA, Gilchrist GM, Handacek RJ, D'Alessio DA. One-year comparison of a high-monounsaturated fat diet with a high-carbohydrate diet in type 2 diabetes. Diabetes Care. 2009; 32: 215-220. PMID: 18957534.

2. Brunerova L, Smejkalova V. Potockova J, Andel M. A comparison of the influence of a high-fat diet enriched in monounsaturated fatty acids and conventional diet on weight loss and metabolic parameters in obese non-diabetic and Type 2 diabetic patients. Diabet Med. 2007 May; 24(5): 533-540. Epub 2007 Mar 22. PMID: 17381504.

3. Gerhard GT, Ahmann A, Meeuws K, McMurry MP, Duell PB, Connor WE. Effects of a low-fat diet compared with those of a high-monounsaturated fat diet on body weight, plasma lipids and lipoproteins, and glycemic control in type 2 diabetes. Am J Clin Nutr. 2004 Sep; 80(3): 668-673. PMID: 15321807.

4. Rodriguez-Villar C, Pérez-Heras A, Mercadé I, Casals E, Ros E. Comparison of a high-carbohydrate and a high-monounsaturated fat, olive oil-rich diet on the susceptibility of LDL to oxidative modification in subjects with Type 2 diabetes mellitus. Diabet Med. 2004 Feb; 21(2): 142-149. PMID: 14984449.

5. Shah M, Adams-Huet B, Bantle JP, Henry RR, Griver KA, Raatz SK, Brinkley LJ, Reaven GM, Garg A. Effect of a high-carbohydrate versus a high--cis-monounsaturated fat diet on blood pressure in patients with type 2 diabetes. Diabetes Care. 2005 Nov; 28(11): 2, 607-2, 612. PMID: 16249527.

N-6 PUFA and Health Outcomes

Systematic Reviews/Meta-analysis

1. Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, Bälter K, Fraser GE, Goldbourt U, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Ascherio A. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. Am J Clin Nutr. 2009 May; 89(5): 1, 425-1, 432. Epub 2009 Feb 11. PMID: 19211817.

Primary Articles

1. Hodge AM, English DR, O'Dea K, Sinclair AJ, Makrides M, Gibson RA, Giles GG. Plasma phospholipid and dietary fatty acids as predictors of type 2

      diabetes: Interpreting the role of linoleic acid. Am J Clin Nutr. 2007 Jul; 86(1): 189-197. PMID: 17616780.

2. Laaksonen DE, Nyyssönen K, Niskanen L, Rissanen TH, Salonen JT. Prediction of cardiovascular mortality in middle-aged men by dietary and serum linoleic and polyunsaturated fatty acids. Arch Intern Med. 2005 Jan 24; 165(2): 193-199. PMID: 15668366.

3. Liou YA, King DJ, Zibrik D, Innis SM. Decreasing linoleic acid with constant alpha-linolenic acid in dietary fats increases (n-3) eicosapentaenoic acid in plasma phospholipids in healthy men. J Nutr. 2007 Apr; 137(4): 945-952. PMID: 17374659.

4. Mozaffarian D, Ascherio A, Hu FB, Stampfer MJ, Willett WC, Siscovick DS, Rimm EB. Interplay between different polyunsaturated fatty acids and risk of coronary heart disease in men. Circulation. 2005 Jan 18; 111(2): 157-164. Epub 2005 Jan 3. PMID: 15630029.

5. Oh K, Hu FB, Manson JE, Stampfer MJ, Willett WC. Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the nurses' health study. Am J Epidemiol. 2005 Apr 1; 161(7): 672-679. PMID: 15781956.

6. St-Onge MP, Aban I, Bosarge A, Gower B, Hecker KD, Allison DB. Snack chips fried in corn oil alleviate cardiovascular disease risk factors when substituted for low-fat or high-fat snacks. Am J Clin Nutr. 2007 Jun; 85(6): 1, 503-1, 510. PMID: 17556685.

7. Thijssen MA, Hornstra G, Mensink RP. Stearic, oleic, and linoleic acids have comparable effects on markers of thrombotic tendency in healthy human subjects. J Nutr. 2005 Dec; 135(12): 2, 805-2, 811. PMID: 16317124.

8. Thijssen MA, Mensink RP. Small differences in the effects of stearic acid, oleic acid, and linoleic acid on the serum lipoprotein profile of humans. Am J Clin Nutr. 2005 Sep; 82(3): 510-516. PMID: 16155261.

9. Zhao G, Etherton TD, Martin KR, West SG, Gillies PJ, Kris-Etherton PM. Dietary alpha-linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women. J Nutr. 2004 Nov; 134(11): 2, 991-2, 887. PMID: 15514264.

Excluded Articles

Article	Reason for Exclusion
Berry SE, Miller GJ, Sanders TA. The solid fat content of stearic acid-rich fats determines their postprandial effects. *Am J Clin Nutr.* 2007 Jun; 85(6): 1, 486-1, 494. PMID: 17556683.	Both study arms involve high fat. Outcomes are related to commercial randomization of oils.

Bondia-Pons I, Schröder H, Covas MI, Castellote AI, Kaikkonen J, Poulsen HE, Gaddi AV, Machowetz A, Kiesewetter H, López-Sabater MC. <u>Moderate consumption of olive oil by healthy European men reduces systolic blood pressure in non-Mediterranean participants.</u> *J Nutr.* 2007 Jan; 137(1): 84-87. PMID: 17182805.	Treatment period too short (three weeks).
Carrero JJ, Baró L, Fonollá J, González-Santiago M, Martínez-Férez A, Castillo R, Jiménez J, Boza JJ, López-Huertas E. <u>Cardiovascular effects of milk enriched with omega-3 polyunsaturated fatty acids, oleic acid, folic acid, and vitamins E and B$_6$ in volunteers with mild hyperlipidemia.</u> *Nutrition.* 2004 June; 20(6): 521-527. PMID 15165614.	Does not address questions. Study involves effect of milk enrichment and does not look at the relationship of variables in question.
Carrero JJ, Fonollá J, Marti JL, Jiménez J, Boza JJ, López-Huertas E. Intake of fish oil, oleic acid, folic acid, and vitamins B$_6$ and E for 1 year decreases plasma C-reactive protein and reduces coronary heart disease risk factors in male patients in a cardiac rehabilitation program. *J Nutr.* 2007 Feb; 137(2): 384-390. PMID: 17237316.	Multiple variables supplimented at same time.
Cicero AF, Nascetti S, López-Sabater MC, Elosua R, Salonen JT, Nyyssönen K, Poulsen HE, Zunft HJ, Kiesewetter H, de la Torre K, Covas MI, Kaikkonen J, Mursu J, Koenbick C, Bäumler H, Gaddi AV; EUROLIVE Study Group. <u>Changes in LDL fatty acid composition as a response to olive oil treatment are inversely related to lipid oxidative damage: The EUROLIVE study.</u> *J Am Coll Nutr.* 2008 Apr; 27(2): 314-320. PMID: 18689564.	Intervention provided as capsule.

Covas MI, Nyyssönen K, Poulsen HE, Kaikkonen J, Zunft HJ, Kiesewetter H, Gaddi A, de la Torre R, Mursu J, Bäumler H, Nascetti S, Salonen JT, Fitó M, Virtanen J, Marrugat J, EUROLIVE Study Group. <u>The effect of polyphenols in olive oil on heart disease risk factors: a randomized trial.</u> *Ann Intern Med.* 2006 Sep 5; 145(5): 333-341. PMID: 16954359.	Does not address question. Studies effect of polyphenols in olive oil on heart disease risk factors.
Damsgaard CT, Frøkiaer H, Andersen AD, Lauritzen L. <u>Fish oil in combination with high or low intakes of linoleic acid lowers plasma triacylglycerols but does not affect other cardiovascular risk markers in healthy men.</u> *J Nutr.* 2008 Jun; 138(6): 1, 061-1, 066. PMID: 18492834.	Intervention provided as capsule. Other nutrients unaccounted for.
Djoussé L, Hunt SC, Arnett DK, Province MA, Eckfeldt JH, Ellison RC. <u>Dietary linolenic acid is inversely associated with plasma triacylglycerol: the National Heart, Lung, and Blood Institute Family Heart Study.</u> *Am J Clin Nutr.* 2003 Dec; 78(6): 1, 098-1, 1102. PMID: 14668270.	Does not meet inclusion criteria. Cross-sectional study.
Engler MM, Engler MB. <u>Omega-3 fatty acids: role in cardiovascular health and disease.</u> *J Cardiovasc Nurs.* 2006 Jan-Feb; 21(1): 17-24, quiz 25-26. Review. PMID: 16407732.	Does not address questions. Descriptive. Metabolic effects of n-3.
Erkkilä AT, Matthan NR, Herrington DM, Lichtenstein AH. <u>Higher plasma docosahexaenoic acid is associated with reduced progression of coronary atherosclerosis in women with CAD.</u> *J Lipid Res.* 2006 Dec; 47(12): 2, 814-2, 819. Epub 2006 Sep 18. PMID: 16983146.	Moved to n-3 marine and plant questions.

Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Ruiz-Gutiérrez V, Covas MI, Fiol M, Gómez-Gracia E, López-Sabater MC, Vinyoles E, Arós F, Conde M, Lahoz C, Lapetra J, Sáez G, Ros E; PREDIMED Study Investigators. Effects of a Mediterranean-style diet on cardiovascular risk factors: A randomized trial. *Ann Intern Med.* 2006 Jul 4; 145(1): 1-11. PMID: 16818923.	Does not look at relationships between variables. Examines Mediterranean Pattern, not specifically MUFA or PUFA.
Fitó M, Cladellas M, de la Torre R, Martí J, Alcántara M, Pujadas-Bastardes M, Marrugat J, Bruguera J, López-Sabater MC, Vila J, Covas MI; The members of the SOLOS Investigators. Antioxidant effect of virgin olive oil in patients with stable coronary heart disease: A randomized, crossover, controlled, clinical trial. Ath*erosclerosis.* 2005 Jul; 181(1): 149-158. Epub 2005 Feb 12. PMID:15939067.	Does not look at relationships between variables. Compares antioxidant effect of two olive oils, one with higher phenolic content.
Fitó M, Cladellas M, de la Torre R, Martí J, Muñoz D, Schröder H, Alcántara M, Pujadas-Bastardes M, Marrugat J, López-Sabater MC, Bruguera J, Covas MI; SOLOS Investigators. Anti-inflammatory effect of virgin olive oil in stable coronary disease patients: A randomized, crossover, controlled trial. *Eur J Clin Nutr.* 2008 Apr; 62(4): 570-574. Epub 2007 Mar 21. PMID: 17375118.	Does not look at relationships between variables. Compares antioxidant effect of two olive oils, one with higher phenolic content.
Freese R, Vaarala O, Turpeinen AM, Mutanen M. No difference in platelet activation or inflammation markers after diets rich or poor in vegetables, berries and apples in healthy subjects. *Eur J Nutr.* 2004 Jun; 43(3): 175-182. Epub 2004 Jan 6. PMID: 15168040.	Does not address question. Variables studied are vegetables, berries and apples.
Garg A. High-monounsaturated-fat diets for patients with diabetes mellitus: A meta-analysis. *Am J Clin Nutr.* 1998 Mar; 67(3 Suppl): 577S-582S. PMID: 9497173.	Does not meet inclusion criteria. Study conducted 1998.

59

Gaullier JM, Halse J, Høye K, Kristiansen K, Fagertun H, Vik H, Gudmundsen O. <u>Conjugated linoleic acid supplementation for one year reduces body fat mass in healthy overweight humans.</u> *Am J Clin Nutr.* 2004 Jun; 79(6): 1, 118-1, 125. PMID: 15159244.	Intervention provided as capsule.
Gradek WQ, Harris MT, Yahia N, Davis WW, Le NA, Brown WV. <u>Polyunsaturated fatty acids acutely suppress antibodies to malondialdehyde-modified lipoproteins in patients with vascular disease.</u> *Am J Cardiol.* 2004 Apr 1; 93(7): 881-885. PMID: 15050493.	Does not meet inclusion criteria for feeding period. Short-term,postprandial metabolic study.
Harper CR, Jacobson TA. <u>Usefulness of omega-3 fatty acids and the prevention of coronary heart disease.</u> *Am J Cardiol.* 2005 Dec 1; 96(11): 1, 521-1, 529. Epub 2005 Oct 21. PMID: 16310434.	Non-systematic negative review.
Harris WS. <u>Linoleic acid and coronary heart disease.</u> *Prostaglandins Leukot Essent Fatty Acids.* 2008 Sep-Nov;79(3-5):169-71. Epub 2008 Oct 31. PMID: 18951772	Narrative review
Hartweg J, Farmer AJ, Holman RR, Neil A.<u>Potential impact of omega-3 treatment on cardiovascular disease in type 2 diabetes.</u> *Curr Opin Lipidol.* 2009 Feb; 20(1): 30-38. PMID: 19133409.	Treatment uses of omega-3 fatty acids.
Hilpert KF, West SG, Kris-Etherton PM, Hecker KD, Simpson NM, Alaupovic P. <u>Postprandial effect of n-3 polyunsaturated fatty acids on apolipoprotein B-containing lipoproteins and vascular reactivity in type 2 diabetes.</u> *Am J Clin Nutr.* 2007 Feb; 85(2): 369-376. PMID: 17284731.	Does not meet feeding criteria. Feeding period less than four weeks.

60

Kabagambe EK, Baylin A, Ascherio A, Campos H. <u>The type of oil used for cooking is associated with the risk of nonfatal acute myocardial infarction in Costa Rica.</u> *J Nutr.* 2005 Nov; 135(11): 2, 674-2, 679. PMID: 16251629.	Does not meet inclusion criteria. Case control study.
Kontogianni MD, Panagiotakos DB, Chrysohoou C, Pitsavos C, Zampelas A, Stefanadis C. <u>The impact of olive oil consumption pattern on the risk of acute coronary syndromes: The CARDIO2000 case-control study.</u> *Clin Cardiol.* 2007 Mar; 30(3): 125-129. PMID: 17385704.	Does not meet inclusion criteria. Case control study.
Kris-Etherton PM, Hecker KD, Binkoski AE. <u>Polyunsaturated fatty acids and cardiovascular health.</u> *Nutr Rev.* 2004 Nov; 62(11): 414-426. Review. PMID: 15622714.	Non-systematic narrative review.
Kris-Etherton PM, Pearson TA, Wan Y, Hargrove RL, Moriarty K, Fishell V, Etherton TD. <u>High-monounsaturated fatty acid diets lower both plasma cholesterol and triacylglycerol concentrations.</u> *Am J Clin Nutr.* 1999 Dec; 70(6): 1, 009-1, 015. PMID: 10584045.	Addresses the question. Published prior to inclusion dates.
Levick SP, Loch DC, Taylor SM, Janicki JS. <u>Arachidonic acid metabolism as a potential mediator of cardiac fibrosis associated with inflammation.</u> *J Immunol.* 2007 Jan 15; 178(2): 641-646. PMID: 17202322.	Does not address questions. Narrative review.
López S, Bermúdez B, Pacheco YM, López-Lluch G, Moreda W, Villar J, Abia R, Muriana FJ. <u>Dietary oleic and palmitic acids modulate the ratio of triacylglycerols to cholesterol in postprandial triacylglycerol-rich lipoproteins in men and cell viability and cycling in human monocytes.</u> *J Nutr.* 2007 Sep; 137(9): 1, 999-2, 005. PMID: 17709433.	Postprandial study lasting three and five hours does not meeting intake criteria. Studies fatty acid ratios.

Lovegrove JA. <u>CVD risk in South Asians: The importance of defining adiposity and influence of dietary polyunsaturated fat.</u> *Proc Nutr Soc.* 2007 May; 66(2): 286-298. Review. PMID: 17466109.	Negative review. Not systematic. Restricted to a defined foreign population
Madigan C, Ryan M, Owens D, Collins P, Tomkin GH. <u>Comparison of diets high in monounsaturated versus polyunsaturated fatty acid on postprandial lipoproteins in diabetes.</u> *J Med Sci.* 2005 Jan-Mar; 174(1): 8-20. PMID: 15868884.	Does not meet inclusion criteria. Short-term, postprandial study.
Malpuech-Brugère C, Verboeket-van de Venne WP, Mensink RP, Arnal MA, Morio B, Brandolini M, Saebo A, Lassel TS, Chardigny JM, Sébédio JL, Beaufrère B. <u>Effects of two conjugated linoleic acid isomers on body fat mass in overweight humans.</u> *Obes Res.* 2004 Apr; 12(4): 591-598. PMID: 15090626.	Does not meet inclusion criteria. Study investigates isomers of CLA.
Manning PJ, Sutherland WH, McGrath MM, de Jong SA, Walker RJ, Williams MJ. <u>Postprandial cytokine concentrations and meal composition in obese and lean women.</u> *Obesity (Silver Spring).* 2008 Sep; 16(9): 2, 046-2, 052. PMID: 19186329.	Does not meet inclusion criteria for feeding period. Short-term feeding followed by postprandial tests.
Montoya MT, Porres A, Serrano S, Fruchart JC, Mata P, Gerique JA, Castro GR. <u>Fatty acid saturation of the diet and plasma lipid concentrations, lipoprotein particle concentrations, and cholesterol efflux capacity.</u> *Am J Clin Nutr.* 2002 Mar; 75(3): 484-491. PMID: 11864853.	Note: Key evidence addressing the question presents data first published in 1996. New data is limited to lipoprotein particle distribution.
Moore CS, Bryant SP, Mishra GD, Krebs JD, Browning LM, Miller GJ, Jebb SA. <u>Oily fish reduces plasma triacylglycerols: A primary prevention study in overweight men and women.</u> *Nutrition.* 2006 Oct; 22(10): 1, 012-1, 024. PMID: 17027436.	Does not meet inclusion criteria. Covers omega-3 fatty acids.

Mozaffarian D. <u>Does alpha-linolenic acid intake reduce the risk of coronary heart disease? A review of the evidence.</u> *Altern Ther Health Med.* 2005 May-Jun; 11(3): 24-30; quiz 31, 79. PMID: 15945135.	Narrative review.
Mullen A, Moloney F, Nugent AP, Doyle L, Cashman KD, Roche HM. <u>Conjugated linoleic acid supplementation reduces peripheral blood mononuclear cell interleukin-2 production in healthy middle-aged males.</u> *J Nutr Biochem.* 2007 Oct; 18(10): 658-666. Epub 2007 Mar 21. PMID: 17368881.	Intervention provided as capsules.
Njelekela M, Ikeda K, Mtabaji J, Yamori Y.<u>Dietary habits, plasma polyunsaturated fatty acids and selected coronary disease risk factors in Tanzania.</u> *East Afr Med J.* 2005 Nov; 82(11): 572-578. PMID: 16463751.	Cross-sectional population study.
Nugent AP, Roche HM, Noone EJ, Long A, Kelleher DK, Gibney MJ. <u>The effects of conjugated linoleic acid supplementation on immune function in healthy volunteers.</u> *Eur J Clin Nutr.* 2005 Jun; 59(6): 742-750. PMID: 15827560.	Intervention provided as capsules
Oda E, Hatada K, Katoh K, Kodama M, Nakamura Y, Aizawa Y. <u>A case-control pilot study on n-3 polyunsaturated fatty acid as a negative risk factor for myocardial infarction.</u> *Int Heart J.* 2005 Jul; 46(4): 583-591. PMID: 16157949.	Pilot study, small number of participants.
Oda E, Hatada K, Kimura J, Aizawa Y, Thanikachalam PV, Watanabe K. <u>Relationships between serum unsaturated fatty acids and coronary risk factors: Negative relations between nervonic acid and obesity-related risk factors.</u> *Int Heart J.* 2005 Nov; 46(6): 975-985. PMID: 16394593.	Does not address question. Correlates blood lipids with weight and height of control participants in a previous case study.

Pacheco YM, Bermúdez B, López S, Abia R, Villar J, Muriana FJ. Ratio of oleic to palmitic acid is a dietary determinant of thrombogenic and fibrinolytic factors during the postprandial state in men. *Am J Clin Nutr.* 2006 Aug; 84(2): 342-349. PMID: 16895881.	Does not look at relationships between variables asked in question. Studies effect of ratios of MUFA:PUFA.

CHAPTER 4. SPECIFIC FATS, FATTY ACIDS, AND CHOLESTEROL – REPLACING A HIGH CARBOHYDRATE DIET WITH A HIGH-MUFA DIET IN TYPE 2 DIABETICS

WHAT IS THE EFFECT OF REPLACING A HIGH-CARBOHYRDRATE DIET WITH A HIGH-MUFA DIET IN TYPE 2 DIABETICS?

Conclusion statement

Moderate evidence indicates that increased monounsaturated fatty acid (MUFA) intake, rather than high carbohydrate intake, may be beneficial for persons with type 2 diabetes. High MUFA intake, when replacing a high carbohydrate intake, results in improved biomarkers of glucose tolerance and diabetic control.

Grade

Moderate

Evidence summary overview

To determine the effects of replacing a high-carbohydrate (CHO) diet with a high-monounsaturated fat (MUFA) diet in persons with type 2 diabetes (T2D), five randomized controlled trials (RCTs) published since 2004 were reviewed. These RCTs were conducted in the US and Europe and ranged in size from 11 to 95 subjects. Two studies were methodologically strong (Brehm, 2009; Gerhard, 2004) and three were methodologically neutral (Brunerova, 2007; Rodriguez-Villar, 2004; and Shah, 2005).

In persons with T2D, a high-MUFA diet compared to high-CHO diet decreased blood low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) (Rodriguez-Villar, 2004), increased high-density lipoprotein cholesterol (HDL-C) (Brunerova, 2007), and decreased fasting blood glucose (FBG) and hemoglobin A1c (HbA1c) (Brunerova, 2007). On the other hand, when high MUFA and CHO diets were also low-calorie or weight-loss diets, the results were more difficult to interpret. Brehm et al (2008) found no significant (NS) differences in fasting glucose, insulin, HbA1c or HDL-C between the MUFA and CHO groups. Both groups improved compared to baseline due to decreased caloric intake (200 to 300kcal per day). Gerhard et al (2004) did not find any significant difference in blood lipids or glycemic control in a comparison of high MUFA vs. high CHO diets in T2D subjects; however, in this case, the two diet interventions were not isocaloric and the MUFA diet was a higher-calorie diet. Shah et al (2005) measured the effects of high MUFA vs. CHO on blood pressure (BP) in persons with T2D and found that long-term consumption of a high-CHO may modestly raise BP in persons with T2D.

Evidence summary paragraphs

Brehm et al, 2008 (positive quality) This was an RCT to investigate the effects of high monounsaturated fatty acid [MUFA, 45% energy as CHO, 15% protein (PRO) and 40% fat (20% as MUFA)] and high carbohydrate (CHO, 60% energy as CHO, 15% PRO and 25% fat) diets on body weight and glycemic control in overweight or obese men

and women (N=124, age=56.5±0.8 years, body mass index (BMI)=35.9±0.3kg/m2 and HbA1C = 7.3±0.1%) with T2D over a one-year period. Anthropometric and metabolic parameters were assessed at baseline and after four, eight and 12 months. Subjects met alternating with each of three study dietitians throughout the year for either individual counseling or a group session. Food intake was monitored by detailed three-day food records. Subjects wore pedometers and recorded pedometer readings and physical activity concurrent with their food records. Food records showed that both groups had similar energy intake but a significant difference in MUFA intake. Both groups had similar weight loss over one year (-4.0±0.8 vs. -3.8±0.6kg) and comparable improvement in body fat, waist circumference (WC), diastolic blood pressure (DBP), HDL-C, HbA1C and fasting glucose and insulin. A follow-up assessment of a subset of participants (N=36) was conducted 18 months after completion of the 52-week trial. These participants maintained their weight loss and HbA1C during the follow-up period. Authors conclude that in individuals with T2D, high-MUFA diets are an alternative to conventional lower-fat, high-CHO diets with comparable beneficial effects on body weight, body composition, cardiovascular risk factors and glycemic control.

Brunerova et al, 2007 (neutral quality) This was an RCT conducted in the Czech Republic to elucidate the impact of two types of individualized weight reduction diets on weight loss and on parameters of glucose and lipid metabolism in 31 obese, non-diabetic (mean age 53.6±3.5 years) and 27 obese, adults with T2D (mean age 54.5±3.5 years). For three months, subjects were assigned to either a conventional diet, which was a standard diabetic diet consisting of 60% CHO, 10% PRO and 30% fat (10% MUFA, 10% PUFA, 10% SFA), or an experimental diet, which was a high-fat diet enriched with MUFA, consisting of 45% CHO, 10% PRO, and 45% fat (22.5% MUFA, 11.25% PUFA, and 11.25% SFA). Both diets were individually calculated for calorie content and contained less than 300mg cholesterol per day. Subjects visited with a dietitian every two weeks for compliance monitoring through diet records, and with a physician every month. All enrolled subjects completed the trial. After three months, body weight, waist-hip ratio (WHR), total body fat, levels of C-peptide, TG and the Homeostasis Model Assessment (HOMA-IR) for insulin resistance decreased in all subjects (P<0.001). Additionally, for diabetic subjects on the MUFA-enriched diet, FBG and HbA1c values significantly decreased (P<0.01) and HDL-C significantly increased (P<0.05), but were NS different from the conventional diet group.

Gerhard et al, 2004 (positive quality) This randomized crossover trial conducted in the US compared two ad-libitum diets in patients with T2D to ascertain which diet would lead to greater weight loss and greater improvements in dyslipidemia and glycemic control. Eight women and three men (mean age 50.4±4.8 years) were enrolled in the trial. Subjects were fed either a low-fat (20% fat, 8.0% as MUFA, 65% CHO) or high-MUFA (40% fat, 25% as MUFA, 45% CHO) diet in random order for six weeks. The two diets separated by a six- to 12-week washout period. Subjects consumed significantly more (P<0.05) calories (212kcal), fat, SFA, MUFA and cholesterol while on the high-MUFA diet; they consumed significantly less (P<0.05) CHO and fiber while on that diet compared to when on the low-fat diet. Body weight decreased significantly on the low-fat diet (1.53kg, P<0.001). Plasma TC, LDL-C and HDL-C and triacylglycerol concentrations, glycemic control, and insulin sensitivity did not differ significantly between the two test diets. (Confounder: One group consumed less

66

calories, with unequal intakes of more than 250kcal per day by low-fat group.)

Rodriguez-Villar et al, 2004 (neutral quality) This was a randomized crossover trial conducted in Spain, compared the effects of a high-CHO diet (CHO, 28% energy from from fat) and a high-monounsaturated fatty acid (MUFA, olive oil) diet (40% energy from fat, less than 10% energy from CHO) on LDL oxidative resistance among 22 free-living adults (12 men and 10 women) with T2D. During a six-week pre-inclusion period, individuals consumed their usual diabetic diet, which was low in SFA and high in CHO, followed by assignment to six weeks of isocaloric test diets in crossover fashion, without any washout period between diets. Body weight, glycemic control, total TG, TC, LDL-C and HDL-C levels were similar after both diets; the high-MUFA diet lowered very-low-density lipoprotein (VLDL) cholesterol by 35% (P=0.023) and VLDL TG by 16% (P=0.016) compared with the high-CHO diet.

Shah et al, 2005 (neutral quality) This was a randomized crossover study. This study compared the effect of feeding a carefully controlled isoenergic high-CHO (H-CHO; 55% energy as CHO, 30% as fat and 10% as MUFA) and high-MUFA (H-MUFA; 45% energy as fat, 25% as MUFA and 40% as CHO) diet each on BP in 42 T2D subjects for six weeks, in the US. In phase 2 of the study, 21 subjects (N=13 on H-CHO, N=8 H-MUFA) continued the diet they received during the second phase for an additional eight weeks. Repeat-measures ANOVA showed that BP during the last three days of each phase was similar after six weeks of the H-CHO and H-MUFA diets (SBP: 128±16 vs. 127±15mmHg, P=0.9; DBP: 75±7 vs. 75±8mmHg, P=0.7). The second phase of the diet interventions did not meet inclusion criteria for analysis (less than 10 subjects in the H-MUFA diet group).

Overview table

Author, Year, Study Design, Class, Rating	Study Duration	Study Population, Demographics	Intervention	Significant Outcomes	Limitations
Brehm BJ, Lattin BL et al, 2009 Study Design: Randomized Controlled Trial Class: A Rating: Positive quality	One year.	N=95. N=52 ↑-CHO (17 men; 35 women). N=43 ↑-MUFA (17 men; 26 women). Age: 56.5±0.8 years. BMI: 35.9±0.3kg/m^2. HbA1c: 7.3±0.1% T2D (not on insulin). Attrition: 23%.	MUFA vs. CHO. Subjects assigned two diets, ~1,550 kcal per day, for 52 weeks (% energy): ↑ MUFA: 45% CHO, 15% PRO, 40% Fat (20% MUFA) ↑ CHO: 60% CHO, 15% PRO, 25% Fat. Diets contained similar amounts of PRO, SFA and cholesterol. Intent to treat.	At 52 weeks: No difference between diet groups for weight loss, BMI, Δ in body composition, BP, HbA1c and lipid profile.	None.

Brunerova et al 2007 Study Design: Randomized Controlled Trial Class: A Rating: Neutral quality	Three months.	N=58 subjects. N=31 obese, non-diabetic; mean age, 53.6±3.5 years. N=27 obese, T2D adults not on insulin; mean age 54.5±3.5 years. All enrolled subjects completed the trial. Location: Czech Republic.	MUFA vs. CHO: Conventional diet: Standard diabetic diet [60% CHO, 10% PRO, 30% Fat (10% MUFA, 10% PUFA, 10% SFA)] Experimental diet: High-fat enriched with MUFA [45% CHO, 10% PRO, 45% Fat (22.5% MUFA, 11.25% PUFA and 11.25% SFA)].	After three months: ↓ FBG and HbA1c values ↑ HDL-C (P<0.05) ↓ body weight, WHR, total body fat, levels of C-peptide ↓ TG and HOMA-R in all groups (P<0.01). Diabetic subjects on the MUFA diet: ↓ FBG and HbA1c values (P<0.01) ↑ HDL-C (P<0.05).	Metabolic effects of the macronutrient composition may be masked by weight reduction.

Gerhard et al 2004 Study Design: Randomized Crossover study Class: A Rating: Positive quality	Six-week intervention, six- to 12-week washout period.	N=11 adults (eight women; three men) with T2D. Mean age: 50.4±4.8 years. Location: United States.	MUFA vs. CHO. Two test diets fed in random order (% energy): Low-fat (20% fat, 65% CHO) High-MUFA (40% fat, 25% MUFA, 45% CHO).	High-MUFA subjects consumed more (P<0.05) calories (212kcal), fat, SFA, MUFA and cholesterol. Plasma TG, glycemic control and insulin sensitivity did not differ between the two diets. ↓ consumption of CHO and fiber on the low-fat diet (P<0.05). ↓ body weight on the low-fat diet (1.53kg, P<0.001). ↓ plasma total, LDL-C and HDL-C on both diets (NS).	Authors indicate both diets mirror diets in the real world.

Rodriguez-Villar et al 2004 Study Design: Randomized Crossover Trial Class: A Rating: Neutral quality	Six-week intervention.	N=22 (12 men; 10 women) free-living subjects with T2D. HbA1c: <8%. Mean age: 61±7 years. Attrition rate: 15%. Location: Spain.	MUFA vs. CHO: Consumed usual diabetic diet (↓ SFA and ↑ CHO) for six weeks. Followed by test diets in crossover fashion, without wash out period for an additional six weeks. Test diets (% energy): High-CHO (28% fat, % MUFA). High-MUFA diet (40% fat, 25% MUFA).	Body weight, glycemic control, total TG, TC, LDL-C and HDL-C levels were similar after both diets. ↑-MUFA vs. ↑ CHO diet: ↓ VLDL-C by 35% (P=0.023) ↓ VLDL-TG by 16% (P= 0.016).	Relatively small sample size; no washout period used between diets.

71

Shah M, Adams-Huet B et al, 2005 Study Design: Randomized Controlled Trial Class: A Rating: Neutral quality	Six-week intervention.	N=42 patients with T2D. Location: United States.	CHO vs. MUFA. Two isoenergenic diets (% energy): 1. High-CHO: 55% CHO, 30% fat, 10% MUFA. 2. High-MUFA: 45% fat, 25% MUFA, 40% CHO. Measured effect on BP.	At six weeks: No difference in BP between diet groups.	Short duration study.

Research recommendations

Determine the benefits and risks of MUFA vs. PUFA as an isocalaoric substitute for SFA. Determine the mechanism by which dietary MUFA improve serum lipids, glucose metabolism, insulin levels, HOMA scores, inflammatory markers and blood pressure in both healthy persons and in persons with T2D.

Search plan and results

Inclusion Criteria

Health Outcomes

- Lipid and lipoprotein levels (LDL-C, HDL-C, non-HDL-C)
- Markers of inflammation
- Glucose tolerance, HbA1c values, insulin resistance.

Subjects/Population

- *Age*: Two years to adult
- *Setting*: US and international
- *Health status*: Healthy population and those with elevated chronic risk (CHD or CVD, type 2 diabetes, metabolic syndrome and obesity).

Search Criteria

- *Study design preferences*: RCT or clinical controlled studies, large non-randomized observational studies, meta-analysis and systematic reviews.

72

Feeding period must be greater than four weeks
- *Size of study groups*: Sample size more than 10 subjects for each study group
- *Study dropout rate*: Less than 20%; preference for smaller dropout rates
- *Year range*: 2004 to October 2009
- *Languages*: Limited to articles in English
- *Other*: Article must be published in peer-reviewed journal.

Exclusion Criteria

Subjects/Population

- *Age*: Infants less than two years
- *Setting*: Inpatients
- *Health status*: None.

Search Criteria

- *Size of study groups*: Sample sizes less than 10
- *Study designs*: Cross-sectional; feeding periods less than four weeks; experimental fat must be from natural source
- *Study dropout rate*: If the dropout rate in a study is 20% or greater, the study will be rejected
- *Year range*: Prior to December 2003
- *Other*: Animal studies, abstracts or presentations.

Search Terms and Electronic Databases Used

PubMed:

"Fatty Acids, Omega-6"[Majr:NoExp] AND (triglycerides[majr] OR cholesterol[majr] OR "Diabetes Mellitus, Type 2"[mh] OR Myocardial infarction[majr] OR "Coronary Disease"[majr] "Heart Diseases"[majr] OR "Cardiovascular Diseases"[majr:NoExp]) lim eng/humans

oleic acid[mh] AND (glucose[majr] OR metabolic syndrome* OR insulin sensitivit* OR "Diabetes Mellitus, Type 2"[Mesh] OR hyperglycemia OR lipidemia OR "Body weight"[majr])

((n-6 AND (polyunsaturated OR PUFA*)) OR "Linolenic Acids"[Mesh] OR "Linoleic Acid"[Mesh] OR "Arachidonic Acid"[Mesh]) AND "Diabetes Mellitus, Type 2"[Mesh]

(n-6 AND (polyunsaturated OR PUFA*)) AND (Myocardial infarction[majr] OR "Coronary Disease"[majr] "Heart Diseases"[majr] OR "Cardiovascular Diseases"[majr:NoExp])

((n-6 AND (polyunsaturated OR PUFA*)) OR "Linolenic Acids"[Mesh] OR "Linoleic Acid"[Mesh] OR "Arachidonic Acid"[Mesh]) AND (triglycerides[majr] OR cholesterol[majr])

("Linolenic Acids"[Mesh] OR "Linoleic Acid"[Mesh] OR "Arachidonic Acid"[Mesh] OR oleic acid[mh]) AND (Myocardial infarction[mh] OR "Coronary Disease"[mh] OR "Cerebrovascular Disorders"[mh:NoExp] OR "Stroke"[mh:NoExp] OR "Heart Diseases"[mh] OR "Cardiovascular Diseases"[mh:NoExp]) 68 + 25 = 93 hits (limit to

73

clinical trials, prospective studies, systematic reviews/meta)

oleic acid[mh] AND (Myocardial infarction[mh] OR "Coronary Disease"[majr] OR "Cerebrovascular Disorders"[majr:NoExp] OR "Stroke"[Majr:NoExp] OR "Heart Diseases"[majr] OR "Cardiovascular Diseases"[Majr:NoExp] OR "Triglycerides"[Mesh] OR "Arrhythmias, Cardiac"[Mesh] OR clotting OR Inflammation[mh] OR "Blood Pressure"[mh])

("Linolenic Acids"[Mesh] OR "Linoleic Acid"[Mesh] OR "Arachidonic Acid"[Mesh]) AND (Myocardial infarction[mh] OR "Coronary Disease"[majr] OR "Cerebrovascular Disorders"[majr:NoExp] OR "Stroke"[Majr:NoExp] OR "Heart Diseases"[majr] OR "Cardiovascular Diseases"[Majr:NoExp] OR "Triglycerides"[Mesh] OR "Arrhythmias, Cardiac"[Mesh] OR clotting OR Inflammation[mh] OR "Blood Pressure"[mh])

("Coronary Disease"[Mesh] OR "Cerebrovascular Disorders"[Mesh:NoExp] OR "Stroke"[Mesh:NoExp] OR "Heart Diseases"[Mesh] OR "Cardiovascular Diseases"[Mesh:NoExp] OR "Diabetes Mellitus, Type 2"[Mesh]) AND "Dietary Fats, Unsaturated"[Mesh] AND (Polyunsaturated OR PUFA* OR Monounsaturated OR MUFA*)

"Diabetes Mellitus, Type 2"[Mesh] AND (Polyunsaturated OR PUFA* OR Monounsaturated OR MUFA*)

Date Searched: 06/21/2009 to 08/11/2009, 10/26/2009

Summary of Articles Identified to Review

- Total hits from all electronic database searches: 871
- Total articles identified to review from electronic databases: 65
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 23
- Number of Review Articles Identified: 1
- Total Number of Articles Identified: 24
- Number of Articles Reviewed but Excluded: 41

Included Articles (References)

MUFA and Health Outcomes

What is the effect of dietary intake of MUFA when substituted for SFA on increased risk of CVD and type 2 diabetes (T2D), including intermediate markers such as lipid and lipoprotein levels and inflammation?

Systematic Reviews/Meta-analysis

1. Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, Bälter K, Fraser GE, Goldbourt U, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Ascherio A. Major types of dietary fat and risk of coronary heart disease: A pooled analysis of 11 cohort studies. Am J Clin Nutr. 2009 May; 89(5): 1, 425-1, 432. Epub 2009 Feb 11. PMID: 19211817.

Primary Articles

1. Allman-Farinelli MA, Gomes K, Favaloro EJ, Petocz P. A diet rich in high-oleic-

74

acid sunflower oil favorably alters low-density lipoprotein cholesterol, triglycerides, and factor VII coagulant activity. J Am Diet Assoc. 2005 Jul; 105(7): 1, 071-1, 079. PMID: 15983523.

2. Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER 3rd, Conlin PR, Erlinger TP, Rosner BA, Laranjo NM, Charleston J, McCarron P, Bishop LM; OmniHeart Collaborative Research Group. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: Results of the OmniHeart randomized trial. JAMA. 2005 Nov 16; 294(19): 2, 455-2, 464. PMID: 16287956.

3. Berglund L, Lefevre M, Ginsberg HN, Kris-Etherton PM, Elmer PJ, Stewart PW, Ershow A, Pearson TA, Dennis BH, Roheim PS, Ramakrishnan R, Reed R, Stewart K, Phillips KM; DELTA Investigators. Comparison of monounsaturated fat with carbohydrates as a replacement for saturated fat in subjects with a high metabolic risk profile: Studies in the fasting and postprandial states. Am J Clin Nutr. 2007 Dec; 86(6): 1, 611-1, 620. PMID: 18065577.

4. Binkoski AE, Kris-Etherton PM, Wilson TA, Mountain ML, Nicolosi RJ. Balance of unsaturated fatty acids is important to a cholesterol-lowering diet: Comparison of mid-oleic sunflower oil and olive oil on cardiovascular disease risk factors. J Am Diet Assoc. 2005 Jul; 105(7): 1, 080-1, 086. PMID: 15983524.

5. Clifton PM, Noakes M, Keogh JB. Very low-fat (12%) and high monounsaturated fat (35%) diets do not differentially affect abdominal fat loss in overweight, nondiabetic women. J Nutr. 2004 Jul; 134(7): 1, 741-1, 745. PMID: 15226463.

6. Due A, Larsen TM, Mu H, Hermansen K, Stender S, Astrup A. Comparison of 3 ad libitum diets for weight-loss maintenance, risk of cardiovascular disease, and diabetes: A six-month randomized, controlled trial. Am J Clin Nutr. 2008 Nov; 88(5): 1, 232-1, 241. PMID: 18996857.

7. Haban P, Klvanova J, Zidekova E, Nagyova A. Dietary supplementation with olive oil leads to improved lipoprotein spectrum and lower n-6 PUFAs in elderly subjects. Med Sci Monit. 2004 Apr; 10(4): PI49-PI54. PMID: 15039655.

8. Paniagua JA, de la Sacristana AG, Sánchez E, Romero I, Vidal-Puig A, Berral FJ, Escribano A, Moyano MJ, Peréz-Martinez P, López-Miranda J, Pérez-Jiménez F. A MUFA-rich diet improves posprandial glucose, lipid and GLP-1 responses in insulin-resistant subjects. J Am Coll Nutr. 2007 Oct; 26(5): 434-444. PMID: 17914131.

9. Rasmussen BM, Vessby B, Uusitupa M, Berglund L, Pedersen E, Riccardi G, Rivellese AA, Tapsell L, Hermansen K; KANWU Study Group. Effects of dietary saturated, monounsaturated, and n-3 fatty acids on blood pressure in healthy subjects. Am J Clin Nutr. 2006 Feb; 83(2): 221-226. PMID: 16469978.

10. Thijssen MA, Hornstra G, Mensink RP. Stearic, oleic, and linoleic acids have comparable effects on markers of thrombotic tendency in healthy human subjects. J Nutr. 2005 Dec; 135(12): 2, 805-2, 811. PMID: 163171242.

11. Thijssen MA, Mensink RP. Small differences in the effects of stearic acid, oleic acid, and linoleic acid on the serum lipoprotein profile of humans. Am J Clin Nutr. 2005 Sep; 82(3): 510-516. PMID: 16155261.

What is the effect of replacing a high carbohydrate diet with a high MUFA diet in persons with T2D?

Primary Articles

1. Brehm BJ, Lattin BL, Summer SS, Boback JA, Gilchrist GM, Handacek RJ, D'Alessio DA. One-year comparison of a high-monounsaturated fat diet with a high-carbohydrate diet in type 2 diabetes. Diabetes Care. 2009; 32: 215-220. PMID: 18957534.
2. Brunerova L, Smejkalova V. Potockova J, Andel M. A comparison of the influence of a high-fat diet enriched in monounsaturated fatty acids and conventional diet on weight loss and metabolic parameters in obese non-diabetic and Type 2 diabetic patients. Diabet Med. 2007 May; 24(5): 533-540. Epub 2007 Mar 22. PMID: 17381504.
3. Gerhard GT, Ahmann A, Meeuws K, McMurry MP, Duell PB, Connor WE. Effects of a low-fat diet compared with those of a high-monounsaturated fat diet on body weight, plasma lipids and lipoproteins, and glycemic control in type 2 diabetes. Am J Clin Nutr. 2004 Sep; 80(3): 668-673. PMID: 15321807.
4. Rodriguez-Villar C, Pérez-Heras A, Mercadé I, Casals E, Ros E. Comparison of a high-carbohydrate and a high-monounsaturated fat, olive oil-rich diet on the susceptibility of LDL to oxidative modification in subjects with Type 2 diabetes mellitus. Diabet Med. 2004 Feb; 21(2): 142-149. PMID: 14984449.
5. Shah M, Adams-Huet B, Bantle JP, Henry RR, Griver KA, Raatz SK, Brinkley LJ, Reaven GM, Garg A. Effect of a high-carbohydrate versus a high--cis-monounsaturated fat diet on blood pressure in patients with type 2 diabetes. Diabetes Care. 2005 Nov; 28(11): 2, 607-2, 612. PMID: 16249527.

N-6 PUFA and Health Outcomes

Systematic Reviews/Meta-analysis

1. Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, Bälter K, Fraser GE, Goldbourt U, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Ascherio A. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. Am J Clin Nutr. 2009 May; 89(5): 1, 425-1, 432. Epub 2009 Feb 11. PMID: 19211817.

Primary Articles

1. Hodge AM, English DR, O'Dea K, Sinclair AJ, Makrides M, Gibson RA, Giles GG. Plasma phospholipid and dietary fatty acids as predictors of type 2 diabetes: Interpreting the role of linoleic acid. Am J Clin Nutr. 2007 Jul; 86(1): 189-197. PMID: 17616780.
2. Laaksonen DE, Nyyssönen K, Niskanen L, Rissanen TH, Salonen JT. Prediction of cardiovascular mortality in middle-aged men by dietary and serum linoleic and polyunsaturated fatty acids. Arch Intern Med. 2005 Jan 24; 165(2): 193-199. PMID: 15668366.
3. Liou YA, King DJ, Zibrik D, Innis SM. Decreasing linoleic acid with constant alpha-linolenic acid in dietary fats increases (n-3) eicosapentaenoic acid in plasma phospholipids in healthy men. J Nutr. 2007 Apr; 137(4): 945-952. PMID: 17374659.

76

4. Mozaffarian D, Ascherio A, Hu FB, Stampfer MJ, Willett WC, Siscovick DS, Rimm EB. Interplay between different polyunsaturated fatty acids and risk of coronary heart disease in men. Circulation. 2005 Jan 18; 111(2): 157-164. Epub 2005 Jan 3. PMID: 15630029.

5. Oh K, Hu FB, Manson JE, Stampfer MJ, Willett WC. Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the nurses' health study. Am J Epidemiol. 2005 Apr 1; 161(7): 672-679. PMID: 15781956.

6. St-Onge MP, Aban I, Bosarge A, Gower B, Hecker KD, Allison DB. Snack chips fried in corn oil alleviate cardiovascular disease risk factors when substituted for low-fat or high-fat snacks. Am J Clin Nutr. 2007 Jun; 85(6): 1, 503-1, 510. PMID: 17556685.

7. Thijssen MA, Hornstra G, Mensink RP. Stearic, oleic, and linoleic acids have comparable effects on markers of thrombotic tendency in healthy human subjects. J Nutr. 2005 Dec; 135(12): 2, 805-2, 811. PMID: 16317124.

8. Thijssen MA, Mensink RP. Small differences in the effects of stearic acid, oleic acid, and linoleic acid on the serum lipoprotein profile of humans. Am J Clin Nutr. 2005 Sep; 82(3): 510-516. PMID: 16155261.

9. Zhao G, Etherton TD, Martin KR, West SG, Gillies PJ, Kris-Etherton PM. Dietary alpha-linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women. J Nutr. 2004 Nov; 134(11): 2, 991-2, 887. PMID: 15514264.

Excluded Articles

Article	Reason for Exclusion
Berry SE, Miller GJ, Sanders TA. The solid fat content of stearic acid-rich fats determines their postprandial effects. *Am J Clin Nutr.* 2007 Jun; 85(6): 1, 486-1, 494. PMID: 17556683.	Both study arms involve high fat. Outcomes are related to commercial randomization of oils.
Bondia-Pons I, Schröder H, Covas MI, Castellote AI, Kaikkonen J, Poulsen HE, Gaddi AV, Machowetz A, Kiesewetter H, López-Sabater MC. Moderate consumption of olive oil by healthy European men reduces systolic blood pressure in non-Mediterranean participants. *J Nutr.* 2007 Jan; 137(1): 84-87. PMID: 17182805.	Treatment period too short (three weeks).

Carrero JJ, Baró L, Fonollá J, González-Santiago M, Martínez-Férez A, Castillo R, Jiménez J, Boza JJ, López-Huertas E. Cardiovascular effects of milk enriched with omega-3 polyunsaturated fatty acids, oleic acid, folic acid, and vitamins E and B$_6$ in volunteers with mild hyperlipidemia. *Nutrition.* 2004 June; 20(6): 521-527. PMID 15165614.	Does not address questions. Study involves effect of milk enrichment and does not look at the relationship of variables in question.
Carrero JJ, Fonollá J, Marti JL, Jiménez J, Boza JJ, López-Huertas E. Intake of fish oil, oleic acid, folic acid, and vitamins B$_6$ and E for 1 year decreases plasma C-reactive protein and reduces coronary heart disease risk factors in male patients in a cardiac rehabilitation program. *J Nutr.* 2007 Feb; 137(2): 384-390. PMID: 17237316.	Multiple variables supplimented at same time.
Cicero AF, Nascetti S, López-Sabater MC, Elosua R, Salonen JT, Nyyssönen K, Poulsen HE, Zunft HJ, Kiesewetter H, de la Torre K, Covas MI, Kaikkonen J, Mursu J, Koenbick C, Bäumler H, Gaddi AV; EUROLIVE Study Group. Changes in LDL fatty acid composition as a response to olive oil treatment are inversely related to lipid oxidative damage: The EUROLIVE study. *J Am Coll Nutr.* 2008 Apr; 27(2): 314-320. PMID: 18689564.	Intervention provided as capsule.
Covas MI, Nyyssönen K, Poulsen HE, Kaikkonen J, Zunft HJ, Kiesewetter H, Gaddi A, de la Torre R, Mursu J, Bäumler H, Nascetti S, Salonen JT, Fitó M, Virtanen J, Marrugat J, EUROLIVE Study Group. The effect of polyphenols in olive oil on heart disease risk factors: a randomized trial. *Ann Intern Med.* 2006 Sep 5; 145(5): 333-341. PMID: 16954359.	Does not address question. Studies effect of polyphenols in olive oil on heart disease risk factors.

Damsgaard CT, Frøkiaer H, Andersen AD, Lauritzen L. Fish oil in combination with high or low intakes of linoleic acid lowers plasma triacylglycerols but does not affect other cardiovascular risk markers in healthy men. *J Nutr.* 2008 Jun; 138(6): 1, 061-1, 066. PMID: 18492834.	Intervention provided as capsule. Other nutrients unaccounted for.
Djoussé L, Hunt SC, Arnett DK, Province MA, Eckfeldt JH, Ellison RC. Dietary linolenic acid is inversely associated with plasma triacylglycerol: the National Heart, Lung, and Blood Institute Family Heart Study. *Am J Clin Nutr.* 2003 Dec; 78(6): 1, 098-1, 1102. PMID: 14668270.	Does not meet inclusion criteria. Cross-sectional study.
Engler MM, Engler MB. Omega-3 fatty acids: role in cardiovascular health and disease. *J Cardiovasc Nurs.* 2006 Jan-Feb; 21(1): 17-24, quiz 25-26. Review. PMID: 16407732.	Does not address questions. Descriptive. Metabolic effects of n-3.
Erkkilä AT, Matthan NR, Herrington DM, Lichtenstein AH. Higher plasma docosahexaenoic acid is associated with reduced progression of coronary atherosclerosis in women with CAD. *J Lipid Res.* 2006 Dec; 47(12): 2, 814-2, 819. Epub 2006 Sep 18. PMID: 16983146.	Moved to n-3 marine and plant questions.
Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Ruiz-Gutiérrez V, Covas MI, Fiol M, Gómez-Gracia E, López-Sabater MC, Vinyoles E, Arós F, Conde M, Lahoz C, Lapetra J, Sáez G, Ros E; PREDIMED Study Investigators. Effects of a Mediterranean-style diet on cardiovascular risk factors: A randomized trial. *Ann Intern Med.* 2006 Jul 4; 145(1): 1-11. PMID: 16818923.	Does not look at relationships between variables. Examines Mediterranean Pattern, not specifically MUFA or PUFA.

Fitó M, Cladellas M, de la Torre R, Martí J, Alcántara M, Pujadas-Bastardes M, Marrugat J, Bruguera J, López-Sabater MC, Vila J, Covas MI; The members of the SOLOS Investigators. <u>Antioxidant effect of virgin olive oil in patients with stable coronary heart disease: A randomized, crossover, controlled, clinical trial.</u> Ath*erosclerosis.* 2005 Jul; 181(1): 149-158. Epub 2005 Feb 12. PMID:15939067.	Does not look at relationships between variables. Compares antioxidant effect of two olive oils, one with higher phenolic content.
Fitó M, Cladellas M, de la Torre R, Martí J, Muñoz D, Schröder H, Alcántara M, Pujadas-Bastardes M, Marrugat J, López-Sabater MC, Bruguera J, Covas MI; SOLOS Investigators. <u>Anti-inflammatory effect of virgin olive oil in stable coronary disease patients: A randomized, crossover, controlled trial.</u> *Eur J Clin Nutr.* 2008 Apr; 62(4): 570-574. Epub 2007 Mar 21. PMID: 17375118.	Does not look at relationships between variables. Compares antioxidant effect of two olive oils, one with higher phenolic content.
Freese R, Vaarala O, Turpeinen AM, Mutanen M. <u>No difference in platelet activation or inflammation markers after diets rich or poor in vegetables, berries and apples in healthy subjects.</u> *Eur J Nutr.* 2004 Jun; 43(3): 175-182. Epub 2004 Jan 6. PMID: 15168040.	Does not address question. Variables studied are vegetables, berries and apples.
Garg A. <u>High-monounsaturated-fat diets for patients with diabetes mellitus: A meta-analysis.</u> *Am J Clin Nutr.* 1998 Mar; 67(3 Suppl): 577S-582S. PMID: 9497173.	Does not meet inclusion criteria. Study conducted 1998.
Gaullier JM, Halse J, Høye K, Kristiansen K, Fagertun H, Vik H, Gudmundsen O. <u>Conjugated linoleic acid supplementation for one year reduces body fat mass in healthy overweight humans.</u> *Am J Clin Nutr.* 2004 Jun; 79(6): 1, 118-1, 125. PMID: 15159244.	Intervention provided as capsule.

80

Gradek WQ, Harris MT, Yahia N, Davis WW, Le NA, Brown WV. Polyunsaturated fatty acids acutely suppress antibodies to malondialdehyde-modified lipoproteins in patients with vascular disease. *Am J Cardiol.* 2004 Apr 1; 93(7): 881-885. PMID: 15050493.	Does not meet inclusion criteria for feeding period. Short-term,postprandial metabolic study.
Harper CR, Jacobson TA. Usefulness of omega-3 fatty acids and the prevention of coronary heart disease. *Am J Cardiol.* 2005 Dec 1; 96(11): 1, 521-1, 529. Epub 2005 Oct 21. PMID: 16310434.	Non-systematic negative review.
Harris WS. Linoleic acid and coronary heart disease. Prostaglandins Leukot Essent Fatty Acids. 2008 Sep-Nov;79(3-5):169-71. Epub 2008 Oct 31. PMID: 18951772	Narrative review
Hartweg J, Farmer AJ, Holman RR, Neil A.Potential impact of omega-3 treatment on cardiovascular disease in type 2 diabetes. *Curr Opin Lipidol.* 2009 Feb; 20(1): 30-38. PMID: 19133409.	Treatment uses of omega-3 fatty acids.
Hilpert KF, West SG, Kris-Etherton PM, Hecker KD, Simpson NM, Alaupovic P. Postprandial effect of n-3 polyunsaturated fatty acids on apolipoprotein B-containing lipoproteins and vascular reactivity in type 2 diabetes. *Am J Clin Nutr.* 2007 Feb; 85(2): 369-376. PMID: 17284731.	Does not meet feeding criteria. Feeding period less than four weeks.
Kabagambe EK, Baylin A, Ascherio A, Campos H. The type of oil used for cooking is associated with the risk of nonfatal acute myocardial infarction in Costa Rica. *J Nutr.* 2005 Nov; 135(11): 2, 674-2, 679. PMID: 16251629.	Does not meet inclusion criteria. Case control study.

Kontogianni MD, Panagiotakos DB, Chrysohoou C, Pitsavos C, Zampelas A, Stefanadis C. <u>The impact of olive oil consumption pattern on the risk of acute coronary syndromes: The CARDIO2000 case-control study.</u> *Clin Cardiol.* 2007 Mar; 30(3): 125-129. PMID: 17385704.	Does not meet inclusion criteria. Case control study.
Kris-Etherton PM, Hecker KD, Binkoski AE. <u>Polyunsaturated fatty acids and cardiovascular health.</u> *Nutr Rev.* 2004 Nov; 62(11): 414-426. Review. PMID: 15622714.	Non-systematic narrative review.
Kris-Etherton PM, Pearson TA, Wan Y, Hargrove RL, Moriarty K, Fishell V, Etherton TD. <u>High-monounsaturated fatty acid diets lower both plasma cholesterol and triacylglycerol concentrations.</u> *Am J Clin Nutr.* 1999 Dec; 70(6): 1, 009-1, 015. PMID: 10584045.	Addresses the question. Published prior to inclusion dates.
Levick SP, Loch DC, Taylor SM, Janicki JS. <u>Arachidonic acid metabolism as a potential mediator of cardiac fibrosis associated with inflammation.</u> *J Immunol.* 2007 Jan 15; 178(2): 641-646. PMID: 17202322.	Does not address questions. Narrative review.
López S, Bermúdez B, Pacheco YM, López-Lluch G, Moreda W, Villar J, Abia R, Muriana FJ. <u>Dietary oleic and palmitic acids modulate the ratio of triacylglycerols to cholesterol in postprandial triacylglycerol-rich lipoproteins in men and cell viability and cycling in human monocytes.</u> *J Nutr.* 2007 Sep; 137(9): 1, 999-2, 005. PMID: 17709433.	Postprandial study lasting three and five hours does not meeting intake criteria. Studies fatty acid ratios.
Lovegrove JA. <u>CVD risk in South Asians: The importance of defining adiposity and influence of dietary polyunsaturated fat.</u> *Proc Nutr Soc.* 2007 May; 66(2): 286-298. Review. PMID: 17466109.	Negative review. Not systematic. Restricted to a defined foreign population

Madigan C, Ryan M, Owens D, Collins P, Tomkin GH. <u>Comparison of diets high in monounsaturated versus polyunsaturated fatty acid on postprandial lipoproteins in diabetes.</u> *J Med Sci.* 2005 Jan-Mar; 174(1): 8-20. PMID: 15868884.	Does not meet inclusion criteria. Short-term, postprandial study.
Malpuech-Brugère C, Verboeket-van de Venne WP, Mensink RP, Arnal MA, Morio B, Brandolini M, Saebo A, Lassel TS, Chardigny JM, Sébédio JL, Beaufrère B. <u>Effects of two conjugated linoleic acid isomers on body fat mass in overweight humans.</u> *Obes Res.* 2004 Apr; 12(4): 591-598. PMID: 15090626.	Does not meet inclusion criteria. Study investigates isomers of CLA.
Manning PJ, Sutherland WH, McGrath MM, de Jong SA, Walker RJ, Williams MJ. <u>Postprandial cytokine concentrations and meal composition in obese and lean women.</u> *Obesity (Silver Spring).* 2008 Sep; 16(9): 2, 046-2, 052. PMID: 19186329.	Does not meet inclusion criteria for feeding period. Short-term feeding followed by postprandial tests.
Montoya MT, Porres A, Serrano S, Fruchart JC, Mata P, Gerique JA, Castro GR. <u>Fatty acid saturation of the diet and plasma lipid concentrations, lipoprotein particle concentrations, and cholesterol efflux capacity.</u> *Am J Clin Nutr.* 2002 Mar; 75(3): 484-491. PMID: 11864853.	Note: Key evidence addressing the question presents data first published in 1996. New data is limited to lipoprotein particle distribution.
Moore CS, Bryant SP, Mishra GD, Krebs JD, Browning LM, Miller GJ, Jebb SA. <u>Oily fish reduces plasma triacylglycerols: A primary prevention study in overweight men and women.</u> *Nutrition.* 2006 Oct; 22(10): 1, 012-1, 024. PMID: 17027436.	Does not meet inclusion criteria. Covers omega-3 fatty acids.
Mozaffarian D. <u>Does alpha-linolenic acid intake reduce the risk of coronary heart disease? A review of the evidence.</u> *Altern Ther Health Med.* 2005 May-Jun; 11(3): 24-30; quiz 31, 79. PMID: 15945135.	Narrative review.

Mullen A, Moloney F, Nugent AP, Doyle L, Cashman KD, Roche HM. <u>Conjugated linoleic acid supplementation reduces peripheral blood mononuclear cell interleukin-2 production in healthy middle-aged males.</u> *J Nutr Biochem.* 2007 Oct; 18(10): 658-666. Epub 2007 Mar 21. PMID: 17368881.	Intervention provided as capsules.
Njelekela M, Ikeda K, Mtabaji J, Yamori Y.<u>Dietary habits, plasma polyunsaturated fatty acids and selected coronary disease risk factors in Tanzania.</u> *East Afr Med J.* 2005 Nov; 82(11): 572-578. PMID: 16463751.	Cross-sectional population study.
Nugent AP, Roche HM, Noone EJ, Long A, Kelleher DK, Gibney MJ. <u>The effects of conjugated linoleic acid supplementation on immune function in healthy volunteers.</u> *Eur J Clin Nutr.* 2005 Jun; 59(6): 742-750. PMID: 15827560.	Intervention provided as capsules
Oda E, Hatada K, Katoh K, Kodama M, Nakamura Y, Aizawa Y. <u>A case-control pilot study on n-3 polyunsaturated fatty acid as a negative risk factor for myocardial infarction.</u> *Int Heart J.* 2005 Jul; 46(4): 583-591. PMID: 16157949.	Pilot study, small number of participants.
Oda E, Hatada K, Kimura J, Aizawa Y, Thanikachalam PV, Watanabe K. <u>Relationships between serum unsaturated fatty acids and coronary risk factors: Negative relations between nervonic acid and obesity-related risk factors.</u> *Int Heart J.* 2005 Nov; 46(6): 975-985. PMID: 16394593.	Does not address question. Correlates blood lipids with weight and height of control participants in a previous case study.

Pacheco YM, Bermúdez B, López S, Abia R, Villar J, Muriana FJ. Ratio of oleic to palmitic acid is a dietary determinant of thrombogenic and fibrinolytic factors during the postprandial state in men. *Am J Clin Nutr.* 2006 Aug; 84(2): 342-349. PMID: 16895881.	Does not look at relationships between variables asked in question. Studies effect of ratios of MUFA:PUFA.

CHAPTER 5. SPECIFIC FATS, FATTY ACIDS, AND CHOLESTEROL – MATERNAL INTAKE OF N-3 FATTY ACIDS ON BREAST MILK COMPOSITION AND INFANT HEALTH OUTCOMES

WHAT ARE THE EFFECTS OF THE MATERNAL DIETARY INTAKE OF OMEGA-3 FATTY ACIDS FROM SEAFOOD ON BREAST MILK COMPOSITION AND INFANT HEALTH OUTCOMES?

Conclusion statement

Moderate evidence indicates that increased maternal dietary intake of long chain n-3 polyunsaturated fatty acids (PUFA), in particular docosahexaenoic acid (DHA) from at least two servings of seafood per week, during pregnancy and lactation is associated with increased DHA levels in breast milk and improved infant health outcomes, such as visual acuity and cognitive development.

Grade

Moderate

Evidence summary overview

Overall, nine articles were reviewed since 2000 to determine the effect of omega-3 fatty acids (n-3 FAs) on breast milk composition and infant health outcomes. There were seven methodologically strong prospective cohort studies conducted in the US, Europe and Canada in healthy women with low-risk pregnancies, healthy mother and infant pairs or healthy children up to eight years in cohort sizes ranging from 211 to 50,276 subjects (Drouillet, 2009; Hibbeln, 2007; Innis, 2001; Oken, 2005; Oken, 2008a; Oken, 2008b; Olsen, 2006). In addition, the evidence included one methodologically strong randomized controlled trial (RCT) of 350 mother and infant pairs in the US (Colombo, 2004) and one methodologically strong meta-analysis of 65 international studies (Brenna, 2007). For the purposes of this review, the Dietary Guidelines Advisory Committee (DGAC) excluded studies with long chain n-3 polyunsaturated fatty acids (n-3 PUFA) given in "supplement" form. Also not included were breastfeeding vs. infant formula feeding studies [before docosahexaenoic acid (DHA) addition] and studies of pre-term vs. full-term infants.

The prospective cohort studies focused on maternal DHA consumption during pregnancy and, overall, the evidence for benefits from maternal DHA consumption during pregnancy was strong. Because RCTs with DHA supplements were excluded, there were fewer studies on maternal DHA intake during lactation. However, one study examined both pregnancy and duration of breastfeeding with improved infant cognitive outcomes (Oken, 2008b) and another measured breastfeeding with associated DHA biomarkers in infants with improved cognitive outcomes (Innis, 2001).

One prospective cohort study showed that low maternal fish intake was associated with increased risk of children being in the lowest quartile for verbal intelligence quotient (IQ), and increased risk of suboptimal outcomes for fine motor skills and communication/social development scores (Hibbeln, 2007). Hibbeln et al (2007)

Archived from www.NEL.gov on March 21, 2017

estimated incidence of suboptimal verbal IQ in children eight years of age as a function of maternal seafood consumption during pregnancy in 11,875 women. The study was conducted in British women and analysis controlled for 28 potentially confounding variables, such as birth weight, alcohol use during pregnancy and smoking. Children of mothers reporting the highest seafood consumption, estimated using a food frequency questionnaire (FFQ) and estimated n-3 intake, were significantly less likely to score in the lowest quartile for verbal IQ compared to women who reported no seafood consumption during pregnancy.

Evidence summary paragraphs

Brenna et al, 2007 (positive quality) This was a meta-analysis of 65 international studies representing 2,474 women, to establish the distributions of DHA and arachidonic acid (AA) concentration in mature breast milk from mothers worldwide consuming free-living or control diets. In primary analyses, the DHA concentration was 0.32±0.22% (range, 0.06% to 1.4%) and the AA concentration was 0.47±0.13% (range, 0.24 to 1.0%), indicating that the DHA concentration in breast milk is lower and more variable than that of AA. The highest DHA concentrations were found primarily in coastal populations and were associated with marine food consumption. In addition, the correlation between DHA and AA was significantly low (R=0.25, P=0.02), reflecting a high degree of variability in the ratio of DHA to AA in individual breast milk samples.

Colombo et al, 2004 (positive quality) This was an RCT conducted in the US to determine the relationship between DHA levels and the development of attention measured through visual habituation during the first year of life and on measures of attention span and distraction during the second year of life. Three hundred fifty mothers and their infants were initially enrolled in a RCT for the evaluation of DHA supplementation on pregnancy outcomes; mothers' DHA intake was manipulated by providing high-DHA (135mg DHA) or ordinary (35mg DHA) eggs during the last trimester of pregnancy. Infants were seen at four, six and eight months of age for visual habitation sessions and at 12 and 18 months of age for free-play sessions in which looking to objects was measured during a single-object session and distractibility was measured during both single- and multiple-object exploration sessions. Of the 70 infants recruited from the original 350, 50 infants provided valid data at each of the three time points for the visual habitation sessions, 58 returned for the 12-month session and 49 toddlers returned for the 18-month session. Infants whose mothers had high DHA at birth showed an accelerated decline in looking over the first year, increases in examining during single-object exploration and less distractibility in the second year. Analyses on the attention and distractibility data during toddlerhood suggest that toddlers of mothers with higher levels of DHA at birth showed more mature developmental profiles on single-object attention measures and more optimal performance on distractibility assessments than toddlers from mothers with lower DHA levels.

Drouillet et al, 2004 (positive quality) This was a prospective cohort study conducted in France to explore the relationship between seafood consumption before and during pregnancy and fetal growth, with the particular aim of assessing the possible effect of maternal overweight on this relationship. Food frequency questionnaires were completed at recruitment (before 24 weeks of gestation, concerning usual food intake

87

in the year before pregnancy), and after the first few days following delivery (concerning food intake during the last three months of pregnancy). Of 2,002 women initially recruited (mean age 29.1±4.9 years), 1,805 women were included in the analysis and 464 were overweight. In the whole sample of women, there was no association between seafood intake and fetal growth. However, for overweight women, higher consumption of seafood before pregnancy was associated with higher fetal biparietal and abdominal circumferences and anthropometric measures;from the lowest to the highest tertiles of intake, mean birthweight was 167g higher (P=0.002).

Hibbeln et al, 2007 (positive quality) This was an observational cohort study conducted in the United Kingdom to assess neurodevelopmental outcomes in childhood based on different levels of maternal seafood intake during pregnancy in participants of the Avon Longitudinal Study of Parents and Children (ALSPAC). Maternal seafood consumption was measured by a self-completed, non-quantitative FFQ obtained at 32 weeks of gestation. Gross motor, fine motor, communication and social skills scales were derived from the Denver Developmental Screening Test and completed by mothers at age six, 18, 30 and 42 months. The Strengths and Difficulties Questionnaire, which included pro-social, hyperactivity, emotional symptoms, conduct problems and peer problems subscales, was completed by mothers at age 81 months. Intelligence quotient was estimated with an abbreviated version of the WISC-III, and given to children at age eight through standardized testing procedures. Of 14,541 pregnancies in the ALSPAC cohort, 13,988 children survived for at least 12 months. 8,946 infants were included at baseline, 8,801 children were included at 81 months and 5,449 children were included at eight years. After adjustment for potential confounders, maternal seafood intake during pregnancy of less than 340g per week was associated with increased risk of children being in the lowest quartile for verbal intelligence quotient, compared with mothers who consumed more than 340g per week (P=0.004). Low maternal seafood intake was also associated with increased risk of suboptimum outcomes for pro-social behavior, fine motor, communication and social development scores.

Innis et al, 2001 (positive quality) This was a prospective cohort study conducted in Canada to determine whether DHA levels in breastfed infants correlated with visual and neural development. Enrolled infants were exclusively breastfed for three months. Visual acuity was measured at two, four, six and 12 months, speech perception and object search task was measured at nine months, Bayley's mental development index and psychomotor development index was measured at six and 12 months, and novelty preference was measured at six and nine months. 83 infants were enrolled (39 male and 44 female); however, only 75 infants were exclusively breastfed for three months. Infant red blood cell (RBC) phosphatidylethanolamine DHA was significantly related to visual acuity at both two (R=0.32, P=0.01) and 12 (R=0.30, P=0.03) months of age. In addition, the ability to discriminate non-native retroflex and phonetic contrasts at nine months of age was related to the plasma phospholipid DHA (R=0.48, P<0.02) and RBC phosphatidyl-ethanolamine DHA (R=0.26, P=0.02) at two months of age.

Oken et al, 2005 (positive quality) This was a prospective cohort study conducted in the US to examine the associations of maternal fish and seafood intake and maternal hair mercury with six-month infant cognition in participants of Project Viva. Participants

completed a semi-quantitative FFQ at 26 to 28 weeks of gestation, and maternal hair samples were collected during the hospitalization for the delivery. The FFQ was previously calibrated against blood levels of long-chain n-3 FAs and distinguished four categories of seafood consumption (canned tuna, shellfish/mollusk, dark/fatty fish, and lean/other fish). Infants underwent cognitive testing at approximately six months of age using the percent novelty preference on visual recognition memory testing. Of 211 mothers consenting to the hair sample,135 mother-infant pairs were included in the analysis. Mothers consumed an average of 1.2 fish servings per week during the second trimester and mean hair mercury was 0.55ppm, with 10% of samples having greater than 1.2ppm. Higher fish consumption in pregnancy was associated with better infant cognition, but higher mercury levels were associated with lower cognition; mean visual recognition memory score was 59.8 (range 10.9 to 92.5) and scores were highest among infants of women who consumed more than two weekly fish servings but had mercury levels less than 1.2ppm.

Oken et al, Am J Epidemiol 2008 (positive quality) This was a prospective cohort study conducted in the US to study associations between maternal fish intake, blood mercury levels and child cognition in participants of Project Viva. Participants completed a semi-quantitative FFQ at 26 to 28 weeks of gestation, and blood samples were analyzed during the second trimester visit. Children completed the Peabody Picture Vocabulary Test (PPVT) and the Wide Range Assessment of Visual Motor Abilities (WRAVMA) at three years of age. Three hundred forty-one mother-child pairs were included in the analysis. Mean maternal fish intake varied from 0 to 7.5 servings, with a mean intake of 1.5 servings per week. Higher fish intake was associated with better child cognitive test performance, and higher mercury levels with poorer test scores. Effect estimates for more than two weekly servings of fish intake vs. no intake were 2.2 (95% CI: -2.6 to 7.0) for the PPVT and 6.4 (95% CI interval: 2.0 to 10.8) for the WRAVMA, and for mercury in the top decile, the effect estimates were -4.5 (95% CI: -8.5 to -0.4) for the PPVT and -4.6 (95% CI: -8.3 to -0.9) for the WRAVMA. There was no benefit associated with fish consumption of less than two servings per week.

Oken et al, Am J Clin Nutr 2008 (positive quality) This was a prospective cohort study conducted in Denmark to examine associations of maternal fish consumption during pregnancy and the duration of infant breastfeeding with attainment of child developmental milestones in participants from the Danish National Birth Cohort. Enrolled women completed semi-quantitative FFQ at gestation week 25, and were instructed to complete computer-assisted telephone interviews at gestation weeks 12 and 30, and at six and 18 months after delivery. Of 50,276 women completing the initial interview and FFQ, 35,557 women completed the six-month postpartum interview and 25,446 women completed the 18-month postpartum interview. Higher maternal fish intake and greater duration of breastfeeding were associated with higher child developmental scores at 18 months (OR=1.29, 95% CI: 1.20 to 1.38 for the highest vs. lowest quintile of fish intake and OR=1.28, 95% CI: 1.18 to 1.38 for breastfeeding more than 10 months compared to breastfeeding less than one month); these associations were similar for development at six months.

Olsen et al, 2006 (positive quality) This was a prospective cohort study conducted in Denmark to examine the association between seafood intake and risks of pre-term and

post-term delivery. Women completed questionnaires regarding fish consumption during gestation weeks 16 and 30. 8,729 pregnant women were included in the analysis. When fish intake was based solely on intake reported during the first trimester, mean gestation length was shorter by 3.91 days (95% CI: 2.24 to 5.58) and odds of pre-term delivery were increased 2.38 times (95% CI: 1.23 to 4.61) in those who never consumed fish compared with those who consumed fish as a main meal and fish in sandwiches at least once per week. These measures were similar when fish intake was based on intake reported during the second trimester. In women reporting the same fish intake in both trimesters, those who never consumed fish had 8.57 days (95% CI: 5.46 to 11.7) shorter mean gestation and 19.6 times (95% CI: 2.32 to 165) increased odds of pre-term delivery compared to high fish consumers. However, odds of elective and post-term delivery were reduced by a factor of 0.33 and 0.34, respectively, in women who never consumed fish.

Overview table

Author, Year, Study Design, Class, Rating	Study Description/ Duration	Study Population, Demographics	Intervention	Significant Outcomes	Limitations
Brenna JT, Varamini B et al, 2007 Study Design: Meta-analysis. Class: M Rating: Positive quality		65 international studies. N=2,474women.	Determined concentration of DHA and AA in breast milk from mothers consuming free-living diets.	In primary analyses, DHA=0.32 ±0.22% (range, 0.06% to 1.4%) and AA=0.47±0.13% (range, 0.24% to 1.0%), indicating DHA in breast milk is lower and more variable than AA. Highest DHA found in coastal populations with high seafood consumption. The correlation between DHA and AA was low (R=0.25, P=0.02), indicating a ↑ degree of variability in DHA:AA in breast milk samples.	Studies varied in sample sizes and infant ages.

Colombo et al 2004 Study Design: Randomized Controlled Trial Class: A Rating: Positive quality	DHA during pregnancy. 18-month follow-up.	350 mothers and infants enrolled to evaluate DHA supplement during last trimester on pregnancy outcomes. Of 70 infants recruited from the original 350, 50 provided valid data at each of three time points for visual habituation; 58 returned for a 12-month session and 49 returned for a 18-month session. Location: United States.	To determine relation ship between DHA and development of attention measured through visual habitation in first year and during second year. Mothers were fed high-DHA eggs (135mg per day) or low-DHA eggs (35mg DHA per day) during last trimester. Infants were seen at four, six and eight months for visual habitation and 12 and 18 months for free-play and distractibility.	Infants of ↑-DHA mothers showed an accelerated ↓ in looking (more rapid encoding) over the first year, ↑ examining and less distractibility in second year. Analyses of attention and distractibility during toddlerhood showed toddlers of ↑-DHA mothers had more mature single-object attention measures and optimal performance on distractibility assessments.	Relatively small sample size. DHA supplement did not affect maternal DHA levels in previous trial.

Drouillet et al 2009 Study Design: Prospective Cohort Study Class: B Rating: Positive quality		2,002 women recruited; 1,805 women included in analysis; 464 overweight. Mean age: 29.1±4.9 years. Food intake assessed at 24weeks and delivery. Location: France.	Studied on relationship between seafood consumption and fetal growth and potential effect of maternal overweight on relationship. FFQs completed at recruitment, <24 weeks, on intake in year before pregnancy and after delivery on intake in last trimester.	No association between seafood intake and fetal growth. For overweight women, ↑ consumption of seafood before pregnancy was associated with ↑ fetal biparietal and abdominal circumferences and anthropometric measures; from lowest to highest tertiles of intake, mean birthweight was 167g higher (P=0.002).	Study was not based on represent-ative sample.

Hibbeln et al 2007 Study Design: Prospective Cohort Study Class: B Rating: Positive quality	Avon Longitudinal Study of Parents and Children (ALSPAC). Eight-year follow-up.	Of 14,541pregnancies in the ALSPAC cohort, 13,988 children survived for atleast 12 months. 8,946 infants were included at baseline, 8,801 children were included at 81 months and 5,449 children were included at eight years. Location: United Kingdom.	Tested association between maternal seafood intake during pregnancy and neurodevelop-mental outcomes in childhood. Maternal seafood consumption measured by self-completed, non-quantitative FFQ at 32 weeks. Gross and fine motor, communication and social skills scales derived from Denver Development Screening Test and completed by mothers at six, 18, 30 and 42 months. Strengths and Difficulties Questionnaire at 81 months. Intelligence quotient with abbreviated WISC-III at eight years.	After adjustment for confounders, maternalseafood intake during pregnancy of <340g per week was associated with ↑ risk of children being in lowest quartile for verbal intelligence, compared with mothers who consumed >340g per week (P=0.004). ↓ maternal seafood intake was associated with ↑ risk of suboptimal outcomes for pro-social behavior, fine motor skills, communication and social development scores.	Maternal report of child develop-ment and behavior are prone to reporting bias.

Innis et al 2001 Study Design: Prospective Cohort Study Class: B Rating: Positive quality	12-month follow-up.	83 infants enrolled (39 male and 44 female). Only 75 infants were exclusively breastfed for three months. Location: Canada.	To determine whether DHA is related to visual and neural development in term breast-fed infants. Infants exclusively breastfed for three months. Visual acuity was measured at two, four, six and 12 months, speech perception and object search measured at nine months, Bayley's mental dev index and psychomotor index measured at six and 12 months, and novelty preference measured at six and nine months.	Infant RBC phosphatidylethanolamine DHA was significantly related to visual acuity at two (R=0.32, P=0.01) and 12 (R=0.30, P=0.03) months. Ability to discriminate phonetic contrasts at nine months was related to plasma phospholipid DHA. (R=0.48, P<0.02) and RBC phosphatidyl-ethanolamine DHA (R= 0.26, P=0.02) at two months.	None.

Oken et al 2005 Study Design: Prospective Cohort Study Class: B Rating: Positive quality	Six-month follow-up.	Participants of Project Viva. Of 211 mothers consenting to hair sample, 135 mother-infant pairs were included. Location: United States.	Examined associations of maternal seafood intake and maternal hair mercury with six-month infant cognition. Subjects completed semi-quantitative FFQ at 26-28 weeks and maternal hair samples taken at delivery. Infants underwent cognitive testing at six months using percent novelty preference on visual recognition memory testing.	Mothers consumed an average 1.2 fish servings a week in second trimester and mean hair mercury was 0.55ppm. ↑ fish consumption was associated with better infant cognition, but ↑ mercury levels were associated with ↓ cognition; mean visual memory score was 59.8 (range, 10.9 to 92.5) and scores were highest among infants of women who consumed >two fish servings per week, but had mercury levels <1.2ppm.	↑ proportion of women who were educated, white and from a ↑ socioeconomic class.

| Oken et al 2008

Study Design: Prospective Cohort Study

Class: B

Rating:

Positive quality | Three-year follow-up. | N=341 mother-child pairs.

Participants of Project Viva.

Location: United States. | Maternal fish intake, blood mercury and child cognition

Studied the association between maternal fish intake, blood mercury levels and child cognition.

Participants completed a semi-quantitative FFQ at 26 to 28 weeks and blood samples analyzed during second trimester visit.

Children completed Peabody Picture Vocabulary Test (PPVT) and WRAVMA at three years. | Mean maternal fish intake varied from 0 to 7.5 servings, with a mean intake of 1.5 servings a week.

↑ fish intake was associated with better child cognitive performance, and ↑ mercury with poorer test scores.

Effect estimates for >two fish servings a week vs. no intake were 2.2 (95% CI: -2.6 to 7.0) for PPVT and 6.4 (95% CI: 2.0 to 10.8) for WRAVMA.

For mercury in top decile, the effect estimates were -4.5 (95% CI: -8.5 to -0.4) for PPVT and -4.6 (95%CI: -8.3 to -0.9) for WRAVMA.

No benefit associated with <two fish servings a week. | Study population contained a high proportion of women who were educated, white and from a higher socioeconomic class. |

Oken et al 2008 Am J Clin Nutr Study Design: Prospective Cohort Study Class: B Rating: Positive quality	Participants from Danish National Birth Cohort. 18-month follow-up.	Of 50,276women completing the initial interview and FFQ, 35,557 women completed the six-month postpartum interview and 25,446 women completed 18-month postpartum interview.	Studied associations of maternal fish consumption during pregnancy and duration of breastfeeding with child development. Women completed semi-quantitative FFQ at 25 weeks and completed interviews at 12 and 30 weeks and at six and 18 months postpartum.	↑ maternal fish intake and greater duration of breastfeeding were associated with ↑ child developmental scores at18 months: OR=1.29, 95% CI: 1.20 to 1.38 for highest vs. lowest quintile of fish intake, and OR=1.28, 95%CI: 1.18 to 1.38 for breastfeeding >10 months compared to breastfeeding <one month. These associations were similar for development at six months.	Subjects were not a represent-ative sample; women included in data analysis differed from those not included with respect to breast-feeding duration, marital status and smoking during pregnancy.

| Olsen et al 2006

Study Design: Prospective Cohort Study

Class: B

Rating:

Positive quality | Length of pregnancy. | 8,729 pregnant women.

Location: Denmark. | Studied association between seafood intake in first and second trimesters and risks of pre-term and post-term delivery.

Women completed questionnaires on fish consumption from weeks 16 and 30. Test diets: ~35% E from fat. | In first trimester, mean gestation length was shorter by 3.91 days (95% CI: 2.24 to 5.58) and odds of pre-term delivery ↑ 2.38-fold (95% CI:1.23 to 4.61) in those who never consumed fish, compared to those who consumed one serving a week.

Measures similar in second trimester.

In women reporting the same fish intake in both trimesters, those who never consumed fish had 8.57 days (95% CI: 5.46 to 11.7) shorter mean gestation and 19.6-fold (95% CI: 2.32 to 165) ↑ odds of pre-term delivery compared to high fish consumers.

Odds of elective and post-term delivery were ↓ by a factor of 0.33 and 0.34, respectively, in women who never consumed fish. | Sample of pregnant women were not described in detail. |
|---|---|---|---|---|---|

Research recommendations

Investigate high vs. low DHA-consuming mothers and infants and the long-term effects on intelligence and other cognitive outcomes.

Search plan and results

Inclusion Criteria

Subjects/Population

- *Age/Life stage:* Pregnant or lactating women and infants
- *Health status:* Healthy pregnant or lactating women and term infants
- *Nutrition related problem/Condition:* Dietary intake of DHA.

Search Criteria

- *Study design preferences:* RCT or clinical controlled studies, large non-randomized observational studies, meta-analysis and systematic reviews. Feeding period must be greater than four weeks
- *Size of study groups:* The sample size must be more than 10 subjects for each study group. For example, this would include 10 patients in the intervention group and 10 patients in the control or comparison group
- *Study drop out rate:* Less than 20%; preference for smaller dropout rates
- *Year range:* 2000 to present
- *Languages:* Limited to articles in English
- *Other:* Article must be published in peer-reviewed journal.

Exclusion Criteria

Subjects/Population

- *Age*: Non-pregnant or lactating adults, children and adolescents
- *Setting*: Inpatients
- *Health status*: Medical treatment, therapy, diseased subjects, malnourished or third-world populations
- *Nutrition related problem/condition*: Supplemental DHA
- *Size of study groups*: Sample sizes less than 10
- *Study designs*: Cross-sectional; feeding periods less than four weeks
- *Study dropout rate*: If the dropout rate in a study is 20% or greater
- *Year range*: Prior to January 2000
- *Authorship*: Studies by same author with similar in content and health outcome measurements
- *Languages*: Articles not in English
- *Other*: Animal studies; abstracts or presentations.

Search Terms and Electronic Databases Used

PubMed:

"DHA" OR "FISH OIL" OR "N-3 LONG CHAIN POLYUNSATURATED FATTY ACID (LCPUFA)" AND "PREGNANCY" AND "HEALTH OUTCOMES" AND "INFANT"

100

"DHA" OR "FISH OIL" OR "N-3 LONG CHAIN POLYUNSATURATED FATTY ACID (LCPUFA)" AND "PREGNANCY" AND "DURATION"

"DHA" OR "FISH OIL" OR "N-3 LONG CHAIN POLYUNSATURATED FATTY ACID (LCPUFA)" AND "PREGNANCY" AND "PREMATURE BIRTH"

"DHA" OR "FISH OIL" OR "N-3 LONG CHAIN POLYUNSATURATED FATTY ACID (LCPUFA)" AND "PREGNANCY" AND "INTRAUTERINE GROWTH RETARDATION"

"DHA" OR "FISH OIL" OR "N-3 LONG CHAIN POLYUNSATURATED FATTY ACID (LCPUFA)" AND "PREGNANCY" AND "INFANT" AND "NEUROLOGICAL"

"DHA" OR "FISH OIL" OR "N-3 LONG CHAIN POLYUNSATURATED FATTY ACID (LCPUFA)" AND "PREGNANCY" AND "INFANT" AND "COGNITIVE"

"DHA" OR "FISH OIL" OR "N-3 LONG CHAIN POLYUNSATURATED FATTY ACID (LCPUFA)" AND "PREGNANCY" AND "INFANT" AND "VISION"

"DHA" OR "FISH OIL" OR "N-3 LONG CHAIN POLYUNSATURATED FATTY ACID (LCPUFA)" AND "LACTATION" OR "BREASTFEEDING" AND "INFANT" AND "NEUROLOGICAL"

"DHA" OR "FISH OIL" OR "N-3 LONG CHAIN POLYUNSATURATED FATTY ACID (LCPUFA)" AND "LACTATION" OR "BREASTFEEDING" AND "INFANT" AND "COGNITIVE"

"DHA" OR "FISH OIL" OR "N-3 LONG CHAIN POLYUNSATURATED FATTY ACID (LCPUFA)" AND "LACTATION" OR "BREASTFEEDING" AND "INFANT" AND "VISION"

"DHA" OR "FISH OIL" OR "N-3 LONG CHAIN POLYUNSATURATED FATTY ACID (LCPUFA)" AND "INFANT FORMULA" AND "INFANT" AND "NEUROLOGICAL"

"DHA" OR "FISH OIL" OR "N-3 LONG CHAIN POLYUNSATURATED FATTY ACID (LCPUFA)" AND "INFANT FORMULA" AND "INFANT" AND "COGNITIVE"

"DHA" OR "FISH OIL" OR "N-3 LONG CHAIN POLYUNSATURATED FATTY ACID (LCPUFA)" AND "INFANT FORMULA" AND "INFANT" AND "VISION"

Date Searched: 08/20/2009; 08/24/2009; 10/08/2009

Summary of Articles Identified to Review

- Total hits from all electronic database searches: 198
- Total articles identified to review from electronic databases: 50
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 8
- Number of Review Articles Identified: 1
- Total Number of Articles Identified: 9
- Number of Articles Reviewed but Excluded: 41

Included Articles (References)

Systematic Reviews/Meta-Analysis

1. Brenna JT, B. Varamini, R.G. Jensen, D.A. Diersen-Schade, J.A. Boettcher and L.M. Arterburn. Docosahexaenoic and arachidonic acid concentrations in human breast milk worldwide. Am J Clin Nutr. 2007; 85: 1, 457–1, 464. View Record in Scopus

Primary Articles

1. Colombo J, Kannass KN, Shaddy DJ, Kundurthi S, Maikranz JM, Anderson CJ, Blaga OM, Carlson SE. Maternal DHA and the development of attention in infancy and toddlerhood. Child Dev. 2004 Jul-Aug; 75(4): 1, 254-1, 267. PMID: 15260876.

2. Drouillet P, Kaminski M, De Lauzon-Guillain B, Forhan A, Ducimetière P, Schweitzer M, Magnin G, Goua V, Thiébaugeorges O, Charles MA. Association between maternal seafood consumption before pregnancy and fetal growth: Evidence for an association in overweight women. The EDEN mother-child cohort. Paediatr Perinat Epidemiol. 2009 Jan; 23(1): 76-86. PMID: 19228317.

3. Hibbeln JR, Davis JM, Steer C, Emmett P, Rogers I, Williams C, Golding J. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): An observational cohort study. Lancet. 2007 Feb 17; 369(9561): 578-585. PMID: 17307104.

4. Innis SM, Gilley J, Werker J. Are human milk long-chain polyunsaturated fatty acids related to visual and neural development in breast-fed term infants? J Pediatr. 2001 Oct; 139(4): 532-538.

5. Oken E, Radesky JS, Wright RO, Bellinger DC, Amarasiriwardena CJ, Kleinman KP, Hu H, Gillman MW. Maternal fish intake during pregnancy, blood mercury levels, and child cognition at age 3 years in a US cohort. Am J Epidemiol. 2008 May 15; 167(10): 1, 171-1, 181. Epub 2008 Mar 18. PMID: 18353804.

6. Oken E, Østerdal ML, Gillman MW, Knudsen VK, Halldorsson TI, Strøm M, Bellinger DC, Hadders-Algra M, Michaelsen KF, Olsen SF. Associations of maternal fish intake during pregnancy and breastfeeding duration with attainment of developmental milestones in early childhood: a study from the Danish National Birth Cohort. Am J Clin Nutr. 2008 Sep; 88(3): 789-796. PMID: 18779297.

7. Oken E, Wright RO, Kleinman KP, Bellinger D, Amarasiriwardena CJ, Hu H, Rich-Edwards JW, Gillman MW. Maternal fish consumption, hair mercury, and infant cognition in a U.S. Cohort. Environ Health Perspect. 2005 Oct; 113(10): 1, 376-1, 380. PMID: 16203250.

8. Olsen SF, Østerdal ML, Salvig JD, Kesmodel U, Henriksen TB, Hedegaard M, Secher NJ. Duration of pregnancy in relation to seafood intake during early and mid pregnancy: Prospective cohort. Eur J Epidemiol. 2006; 21(10): 749-758. Epub 2006 Nov 17. PMID: 17111251.

Excluded Articles

Article	Reason for Exclusion
Asserhøj M, Nehammer S, Matthiessen J, Michaelsen KF, Lauritzen L. <u>Maternal fish oil supplementation during lactation may adversely affect long-term blood pressure, energy intake, and physical activity of 7-year-old boys.</u> *J Nutr.* 2009 Feb; 139(2): 298-304. Epub 2008 Dec 17. PMID: 19091800.	Fish oil with 600<u>mg</u> <u>EPA</u> per day and 800mg <u>DHA</u> per day.
Auestad N, Halter R, Hall RT, Blatter M, Bogle ML, Burks W, Erickson JR, Fitzgerald KM, Dobson V, Innis SM, Singer LT, Montalto MB, Jacobs JR, Qiu W, Bornstein MH. <u>Growth and development in term infants fed long-chain polyunsaturated fatty acids: a double-masked, randomized, parallel, prospective, multivariate study</u>. *Pediatrics.* 2001 Aug; 108(2): 372-381. PMID: 11483802.	Infant formula.
Birch EE, Garfield S, Castañeda Y, Hughbanks-Wheaton D, Uauy R, Hoffman D. <u>Visual acuity and cognitive outcomes at four years of age in a double-blind, randomized trial of long-chain polyunsaturated fatty acid-supplemented infant formula.</u> *Early Hum Dev.* 2007 May; 83(5): 279-284. Epub 2007 Jan 18. PMID: 17240089.	Infant formula.
Cheruku SR, Montgomery-Downs HE, Farkas SL, Thoman EB, Lammi-Keefe CJ. <u>Higher maternal plasma docosahexaenoic acid during pregnancy is associated with more mature neonatal sleep-state patterning.</u> *Am J Clin Nutr.* 2002 Sep; 76(3): 608-613. Erratum in: *Am J Clin Nutr.* 2003 Dec; 78(6): 1,227. PMID: 12198007.	Dietary DHA was not assessed, nor was supplement given (low subject number).
Daniels JL, Longnecker MP, Rowland AS, Golding J; ALSPAC Study Team. University of Bristol Institute of Child Health. <u>Fish intake during pregnancy and early cognitive development of offspring.</u> *Epidemiology.* 2004 Jul; 15(4): 394-402. PMID: 15232398.	No information on DHA.

Dunstan JA, Mitoulas LR, Dixon G, Doherty DA, Hartmann PE, Simmer K, Prescott SL. The effects of fish oil supplementation in pregnancy on breast milk fatty acid composition over the course of lactation: A randomized controlled trial. *Pediatr Res.* 2007 Dec; 62(6): 689-694. PMID: 17957152.	2.2g per day DHA and 1.1g per day EPA; started at 20 weeks gestation.
Dunstan JA, Simmer K, Dixon G, Prescott SL. Cognitive assessment of children at age 2 1/2 years after maternal fish oil supplementation in pregnancy: A randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed.* 2008 Jan; 93(1): F45-F50. Epub 2006 Dec 21. PMID: 17185423.	2.2g per day DHA and 1.1g per day EPA; started at 20 weeks gestation.
Eilander A, Hundscheid DC, Osendarp SJ, Transler C, Zock PL. Effects of n-3 long chain polyunsaturated fatty acid supplementation on visual and cognitive development throughout childhood: A review of human studies. *Prostaglandins Leukot Essent Fatty Acids.* 2007 Apr; 76(4): 189-203. PMID: 17376662.	Supplemental DHA.
Gibson RA, Chen W, Makrides M. Randomized trials with polyunsaturated fatty acid interventions in preterm and term infants: Functional and clinical outcomes. *Lipids.* 2001 Sep; 36(9): 873-883. PMID: 11724459.	Infant formula.
Helland IB, Saugstad OD, Saarem K, Van Houwelingen AC, Nylander G, Drevon CA. Supplementation of n-3 fatty acids during pregnancy and lactation reduces maternal plasma lipid levels and provides DHA to the infants. *J Matern Fetal Neonatal Med.* 2006 Jul; 19(7): 397-406. PMID: 16923694.	10ml cod liver oil or corn oil per day; cod liver oil = 1,183mg per 10ml DHA, 803mg per 10ml EPA; total 2,494mg per 10ml n-3 PUFAs started 18 weeks gestation; term infants.
Helland IB, Saugstad OD, Smith L, Saarem K, Solvoll K, Ganes T, Drevon CA. Similar effects on infants of n-3 and n-6 fatty acids supplementation to pregnant and lactating women. *Pediatrics.* 2001 Nov; 108(5): E82. PMID: 11694666.	10ml cod liver oil or corn oil per day; cod liver oil = 1,183mg per 10ml DHA, 803mg per 10ml EPA; total 2,494mg per 10ml n-3 PUFAs started 18 weeks gestation; term infants.

Archived from www.NEL.gov on March 21, 2017

Helland IB, Smith L, Blomén B, Saarem K, Saugstad OD, Drevon CA. Effect of supplementing pregnant and lactating mothers with n-3 very-long-chain fatty acids on children's IQ and body mass index at 7 years of age. *Pediatrics.* 2008 Aug; 122(2): e472-e479. PMID: 18676533.	10ml cod liver oil or corn oil per day; cod liver oil = 1,183mg per 10ml DHA, 803mg per 10ml EPA; total 2,494mg per 10ml n-3 PUFAs started 18 weeks gestation; term infants.
Helland IB, Smith L, Saarem K, Saugstad OD, Drevon CA. Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics.* 2003 Jan;111(1):e39-44. PMID: 12509593	10ml cod liver oil or corn oil per day; cod liver oil = 1,183mg per 10ml DHA, 803mg per 10ml EPA; total 2,494mg per 10ml n-3 PUFAs started 18 weeks gestation; term infants.
Hoffman DR, Boettcher, JA Diersen-Schade DA. Toward optimizing vision and cognition in term infants by dietary docosahexaenoic and arachidonic acid supplementation: A review of randomized controlled trials. *Prostaglandins, Leukotrienes and Essential Fatty Acids.* 2009; doi:10.1016/j.plefa.2009.05.003.	Infant formula.
Horvath A, Koletzko B, Szajewska H. Effect of supplementation of women in high-risk pregnancies with long-chain polyunsaturated fatty acids on pregnancy outcomes and growth measures at birth: A meta-analysis of randomized controlled trials, *Br. J. Nutr.* 2007; 98 253–259.	Supplemental DHA.
Innis SM, Adamkin DH, Hall RT, Kalhan SC, Lair C, Lim M, Stevens DC, Twist PF, Diersen-Schade DA, Harris CL, Merkel KL, Hansen JW. Docosahexaenoic acid and arachidonic acid enhance growth with no adverse effects in preterm infants fed formula. *J Pediatr.* 2002 May; 140(5): 547-554. PMID: 12032520.	Infant formula.
Innis SM, Friesen RW. Essential n-3 fatty acids in pregnant women and early visual acuity maturation in term infants. *Am J Clin Nutr.* 2008 Mar; 87(3): 548-557. PMID: 18326591.	400mg per day (Algal oil capsule/Martek); started at 16 weeks gestation; term infants.

Jensen CL, Maude M, Anderson RE, Heird WC. Effect of docosahexaenoic acid supplementation of lactating women on the fatty acid composition of breast milk lipids and maternal and infant plasma phospholipids. *Am J Clin Nutr.* 2000 Jan; 71(1 Suppl): 292S-299S. PMID: 10617985.	Algae-produced TG with high DHA (less than 230mg DHA per day) or two eggs with high DHA (170mg per day), low EPA or high DHA fish oil (260mg DHA per day) or two regular eggs.
Jensen CL, Voigt RG, Prager TC, Zou YL, Fraley JK, Rozelle JC, Turcich MR, Llorente AM, Anderson RE, Heird WC. Effects of maternal docosahexaenoic acid intake on visual function and neurodevelopment in breastfed term infants. *Am J Clin Nutr.* 2005 Jul; 82(1): 125-132.PMID: 16002810.	Algal oil capsule, 200mg DHA per day (Martek).
Judge MP, Harel O, Lammi-Keefe CJ. A docosahexaenoic acid-functional food during pregnancy benefits infant visual acuity at four but not six months of age. *Lipids.* 2007 Mar; 42(2): 117-122. Epub 2007 Jan 19. PMID: 17393217.	300mg DHA functional food cereal bar per day; started at 24 weeks gestation (N=16 DHA; N=14 placebo).
Judge MP, Harel O, Lammi-Keefe CJ. Maternal consumption of a docosahexaenoic acid-containing functional food during pregnancy: benefit for infant performance on problem-solving but not on recognition memory tasks at age 9 mo. *Am J Clin Nutr.* 2007 Jun; 85(6): 1,572-1,577. PMID: 17556695	300mg DHA functional food cereal bar per day; started at 24 weeks gestation (N=16 DHA; N=14 placebo).
Krauss-Etschmann S, Hartl D, Rzehak P, Heinrich J, Shadid R, Del Carmen Ramírez-Tortosa M, Campoy C, Pardillo S, Schendel DJ, Decsi T, Demmelmair H, Koletzko BV; Nutraceuticals for Healthier Life Study Group.Decreased cord blood IL-4, IL-13, and CCR4 and increased TGF-beta levels after fish oil supplementation of pregnant women. *J Allergy Clin Immunol.* 2008 Feb; 121(2): 464-470.e6. Epub 2007 Nov 5. PMID: 1798041.	Related to allergies.
Larnkjaer A, Christensen JH, Michaelsen KF, Lauritzen L. Maternal fish oil supplementation during lactation does not affect blood pressure, pulse wave velocity, or heart rate variability in 2.5-year-old children. *J Nutr.* 2006 Jun; 136(6): 1,539-1,544. PMID: 16702318.	1g DHA per 0.5g EPA.

Lauritzen L, Christensen JH, Damsgaard CT, Michaelsen KF. <u>The effect of fish oil supplementation on heart rate in healthy Danish infants.</u> *Pediatr Res.* 2004 Dec; 64(6): 610-614.PMID: 18679165.	Supplementation in late infancy
Lauritzen L, Jørgensen MH, Mikkelsen TB, Skovgaard M, Straarup EM, Olsen SF, Høy CE, Michaelsen KF. <u>Maternal fish oil supplementation in lactation: Effect on visual acuity and n-3 fatty acid content of infant erythrocytes.</u> *Lipids.* 2004 Mar; 39(3): 195-206. PMID: 15233397.	1g DHA per 0.5g EPA.
Lauritzen L, Jørgensen MH, Olsen SF, Straarup EM, Michaelsen KF. <u>Maternal fish oil supplementation in lactation: Effect on developmental outcome in breast-fed infants.</u> *Reprod Nutr Dev.* 2005 Sep-Oct; 45(5): 535-547. PMID: 16188206.	1g DHA per 0.5g EPA.
Makrides M, Duley L, Olsen SF. Marine oil, and other prostaglandin precursor, supplementation for pregnancy uncomplicated by pre-eclampsia or intrauterine growth restriction, *Cochrane Database Syst Rev 3.* 2006; CD003402.	Supplemental DHA.
Makrides M, Gibson RA, McPhee AJ, Collins CT, Davis FG, Doyle LW, Simmer K, Colditz PB, Morris S, Smithers SG, Willson K, Ryan P. Neurodevelopmental outcomes of preterm infants fed high-dose docosahexaenoic acid: a randomized controlled trial, *JAMA.* 2009; 301(2): 175–182.	Infant formula.
Malcolm CA, McCulloch DL, Montgomery C, Shepherd A, Weaver LT. <u>Maternal docosahexaenoic acid supplementation during pregnancy and visual evoked potential development in term infants: a double blind, prospective, randomised trial.</u> *Arch Dis Child Fetal Neonatal Ed.* 2003 Sep; 88(5): F383-F390. PMID: 12937042.	200mg per day in fish oil capsules; started at 15 weeks of gestation; only term infants.

McCann JC, Ames BN. <u>Is docosahexaenoic acid, an n-3 long-chain polyunsaturated fatty acid, required for development of normal brain function? An overview of evidence from cognitive and behavioral tests in humans and animals.</u> *Am J Clin Nutr.* 2005 Aug; 82(2): 281-95. Review. PMID: 16087970.	Includes animal studies.
Myers GJ, Davidson PW, Cox C, Shamlaye CF, Palumbo D, Cernichiari E, Sloane-Reeves J, Wilding GE, Kost J, Huang LS, Clarkson TW. <u>Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study.</u> *Lancet.* 2003 May 17; 361(9,370): 1,686-1,692. PMID: 12767734.	No information on DHA.
Olsen SF, Østerdal ML, Salvig JD, Mortensen LM, Rytter D, Secher NJ, Henriksen TB. <u>Fish oil intake compared with olive oil intake in late pregnancy and asthma in the offspring: 16 years of registry-based follow-up from a randomized controlled trial.</u> *Am J Clin Nutr.* 2008 Jul; 88(1): 167-175. PMID: 18614738.	Health outcome: Asthma.
Simmer K, Patole SK, Rao SC. <u>Longchain polyunsaturated fatty acid supplementation in infants born at term.</u> *Cochrane Database Syst Rev.* 2008 Jan 23;(1): CD000376. Review. PMID: 18253974.	Infant formula.
Simmer K, Schulzke SM, Patole S. <u>Longchain polyunsaturated fatty acid supplementation in preterm infants.</u> *Cochrane Database Syst Rev.* 2008 Jan 23;(1): CD000375. Review. PMID: 18253973.	Infant formula.
Smit EN, Muskiet FA, Boersma ER. <u>Docosahexaenoic acid (DHA) status of breastfed malnourished infants and their mothers in North Pakistan.</u> *Adv Exp Med Biol.* 2000; 478: 395-396. PMID: 11065099.	Malnourished infants.
Smit EN, Oelen EA, Seerat E, Boersma ER, Muskiet FA. <u>Fish oil supplementation improves docosahexaenoic acid status of malnourished infants.</u> *Arch Dis Child.* 2000 May; 82(5): 366-369. PMID: 10799425.	Supplementation during childhood.

108

Smithers LG, Gibson RA, McPhee A, Makrides M. <u>Higher dose of docosahexaenoic acid in the neonatal period improves visual acuity of preterm infants: Results of a randomized controlled trial.</u> *Am J Clin Nutr.* 2008 Oct; 88(4): 1,049-1,056. PMID: 18842793.	Infant formula.
Smuts CM, Borod E, Peeples JM, Carlson SE. <u>High-DHA eggs: Feasibility as a means to enhance circulating DHA in mother and infant.</u> *Lipids.* 2003 Apr; 38(4): 407-414. PMID: 12848286.	135mg DHA per egg.
Smuts CM, Huang M, Mundy D, Plasse T, Major S, Carlson SE. <u>A randomized trial of docosahexaenoic acid supplementation during the third trimester of pregnancy.</u> *Obstet Gynecol.* 2003 Mar; 101(3): 469-479. PMID: 12636950.	33 or 133mg DHA from eggs; started from 24th to 28th week of gestation.
Szajewska H, Horvath A, Koletzko B. <u>Effect of n-3 long-chain polyunsaturated fatty acid supplementation of women with low-risk pregnancies on pregnancy outcomes and growth measures at birth: A meta-analysis of randomized controlled trials.</u> *Am J Clin Nutr.* 2006 Jun; 83(6): 1,337-1,344. Review. PMID: 16762945.	Supplemental DHA.
Tofail F, Kabir I, Hamadani JD, Chowdhury F, Yesmin S, Mehreen F, Huda SN. <u>Supplementation of fish-oil and soy-oil during pregnancy and psychomotor development of infants.</u> *J Health Popul Nutr.* 2006 Mar; 24(1): 48-56. PMID: 16796150.	Fish oil vs. soy oil; 4g per day; during last trimester.

CHAPTER 6. SPECIFIC FATS, FATTY ACIDS, AND CHOLESTEROL – PLANT N-3 FATTY ACIDS AND RISK OF CARDIOVASCULAR DISEASE

WHAT IS THE RELATIONSHIP BETWEEN CONSUMPTION OF PLANT N-3 FATTY ACIDS AND RISK OF CARDIOVASCULAR DISEASE?

Conclusion statement

Alpha-linolenic acid (ALA) intake of 0.6-1.2 percent of total calories will meet current recommendations and may lower cardiovascular disease (CVD) risk, but new evidence is insufficient to warrant greater intake beyond this level. Limited, but supportive evidence suggests that higher intake of n-3 from plant sources may reduce mortality among persons with existing CVD.

Grade

Limited

Evidence summary overview

The Nutrition Evidence Library (NEL) conducted an evidence review to determine the relationship between consuming plant-derived omega-3 polunsaturated fatty acids (n-3 PUFA) and the risk of cardiovascular disease (CVD) events. This review relied upon an evidence-based review conducted by the American Dietetic Association (ADA) on the relationship between n-3 fatty acids (n-3 FAs) and CVD, covering the literature from 2004 to 2007 (ADA, 2008). Overall, five studies were reviewed by ADA that addressed this question. These included two methodologically strong case-control studies (Lemaitre, 2003; Rastogi, 2004), and three prospective cohort studies (two were methodologically strong [Albert, 2005; Mozaffarian, 2005] and one was methodologically neutral [Folsom and Demissie, 2005]). In addition, the NEL reviewed three studies since 2008, including one methodologically strong case-control study conducted in the US (Lemaitre, 2009), one methodologically strong prospective cohort study covering 2,682 men in Finland (Virtanen, 2009), and one methodologically strong systematic review of 14 randomized controlled trials (RCTs), 25 prospective cohort studies and seven case-control studies (Wang, 2006).

Two studies of persons with CVD were part of the 2008 ADA review. One methodologically neutral RCT (Baylin, 2003) and one methodologically neutral case-control study (De Lorgeril, 1999) found a diet high in plant-derived n-3 FAs protective against recurrence of myocardial infarction (MI).

Evidence summary paragraphs

Systematic reviews/Meta-analyses

Wang et al, 2006 (positive quality). This was a systematic review that investigated the effects of n-3 FAs, consumed as fish or fish oils rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) or as alpha-linolenic acid (ALA), on CVD outcomes. Studies that were of less than or equal to one year in duration and that reported estimates of fish or n-3 FA intakes and CVD outcomes were included. Fourteen RCTs

110

(11 fish oil supplement trials, five diet or diet advice trials) and one prospective cohort study addressed secondary prevention. One RCT assessing ALA supplementation, 25 prospective cohort studies and seven case-control studies reported on the association of n-3 FAs with primary prevention of CVD. Most cohort studies reported that fish consumption was associated with lower rates of all-cause mortality and adverse cardiac outcomes. Three studies assessed the effects of increased intakes of ALA, which were estimated to be between 1.8 and 6.3g per day (Singh RB et al, 2002 and Bemelmans et al, 2002). No firm conclusions regarding the effects of either ALA or the marine n-3 FA could are reached from these trials. Two of the ALA dietary trials reported significant reductions or trends toward lower rates of all-cause mortality, cardiac and sudden death, or non-fatal MI (Singh RB et al, 2002 and de Lorgeril et al, 1999), whereas the third trial reported a non-significant (NS) increase in the risk of all-cause mortality (Bemelmans et al, 2002), which was very low in both groups. Evidence suggests that increased consumption of n-3 FAs from fish or fish-oil supplements, but not of ALA, reduces the rates of all-cause mortality, cardiac and sudden death.

Primary Articles

Albert et al, 2005 (positive quality) cohort study (N=76,763 females, 50.8±7.1 years of age), found in an age-adjusted analysis, a trend toward a lower risk of sudden cardiac death with greater ALA intake (ALA source not specified). This relationship became significant (P=0.02) in the fourth quintile of intake, a median absolute intake of 1.16g per day. For every 0.1% increase in energy intake from ALA, the associated hazard ratio was 0.88 (95% CI: 0.80 to 0.98). Women in the two highest quintiles of ALA intake had a 38% to 40% lower sudden cardiac death risk. Intake of ALA was NS related to other non-sudden fatal coronary heart disease (CHD) events or to non-fatal MI.

Baylin et al, 2003 (neutral quality) case-control study, found an inverse relationship (P<0.0001) in 482 cases and controls, between adipose tissue ALA and risk of non-fatal acute MI. The greatest protection was found in those individuals who also had low total trans fatty acids (TFA) in adipose tissue (P<0.05). Subjects in the top quintiles of adipose tissue ALA (0.72% of fatty acids) had a lower risk of MI than those in the lowest quintile (0.35% of fatty acids) (P<0.0001). The difference in adipose tissue ALA corresponds to approximately 0.3g per day of dietary intake.

De Lorgeril et al, 1999 (neutral quality) RCT, reported a decreased rate of cardiac death and non-fatal MI in 423 subjects following a Mediterranean diet vs. a Western diet (1.24 vs. 4.07 per hundred patients per year) for 46 months. The experimental group had a significantly lower intake of total lipids (P=0.02), saturated fats (P=0.0001) and increased intake of oleic, linoleic and ALA fatty acids (P=0.0001). The plasma concentration of 18:3 (ω-3) and 22:6 (ω-3) tended to be inversely associated with recurrence of MI (P=0.11 and P=0.16, respectively).

Folsom and Demissie, 2005 (neutral quality), prospective cohort study, assessed the effect of fish or marine n-3 FA intake on CVD and CHD mortality over a 10-year period in 41,836 postmenopausal women aged 55-69 years, initially free of heart disease and cancer (4,653 deaths over 442,965 person-years). A food frequency questionnaire (FFQ) was used to determine if intake may decrease risk of total and CHD death.

Among women initially free of heart disease and cancer there was an inverse age- and energy-adjusted association between total mortality and fish intake, with a relative risk (RR) of 0.82 (95% CI: 0.74, 0.91) for the highest vs. lowest quintile. Age- and energy-adjusted associations also were inverse (P for trend<0.05), although not entirely monotonic, for cardiovascular, CHD and cancer mortality. Adjustment for multiple other risk factors attenuated all associations to statistically NS levels. Estimated marine n-3 FA intake also was not associated with total or cause-specific mortality. In comparison, plant-derived ALA was inversely associated with mortality after multivariable adjustment.

Lemaitre et al, 2009 (positive quality), case-control study in which the researchers investigated the association of red blood cell RBC) membrane ALA with sudden cardiac arrest risk in 265 cases, aged 25 to 74 years, who were out-of-hospital sudden cardiac arrest patients attended by paramedics and were free of prior clinically diagnosed heart disease. The study was conducted in the US (Seattle). Controls (N=415) were randomly identified from the community, and matched to cases by age, sex and calendar year. Blood was obtained at the time of cardiac arrest (cases) or at the time of an interview (controls) and analysis of the samples showed that higher membrane ALA acid was associated with a higher risk of sudden cardiac arrest. Alpha-linolenic acid levels were positively associated with RBC membrane levels of linoleic acid (r=0.39), trans-18:2 (r=0.22) and eicosapentaenoic acid (EPA) (r=0.16), but not with docosahexaenoic acid (DHA) (r=0.04). After adjustment for matching factors, smoking, diabetes, hypertension (HTN), education, physical activity, weight, height and total fat intake, the odds ratios (OR) corresponding to increasing quartiles of ALA were 1.7 (95% CI, 1.0-3.0), 1.9 (95% CI, 1.1-3.3) and 2.5 (95% CI, 1.3-4.8) compared with the lowest quartile. An increase in ALA corresponding to one standard deviation (SD) was associated with 32% higher risk of sudden cardiac arrest (OR=1.32, 95% CI: 1.07-1.63) after adjustment for confounding variables. The association was independent of red blood cell levels of long-chain n-3 FAs, TFAs, and linoleic acid. Authors concluded that higher membrane levels of ALA are associated with higher risk of sudden cardiac arrest.

Lemaitre et al, 2003 (positive quality), case-control study (N=179 pairs) nested in the Cardiovascular Health Study cohort, found free-living older adults (over 65 years of age), after adjustment for risk factors, a higher concentration of combined plasma DHA and EPA was associated with a lower risk of fatal ischemic heart disease (IHD). Based on data from 54 cases of fatal IHD, 125 cases of non-fatal MI and 179 matched controls, for a one-SD increase in plasma phospholipids DHA and EPA, there was an associated 70% lower risk of fatal IHD (OR: 0.30; 95% CI: 0.12, 0.76; P=0.01) and for a one-SD increase in ALA, there was an associated 50% lower risk of fatal IHD (OR: 0.48; 95% CI: 0.24, 0.96; P=0.04). The first controlled for coronary risk factors, updated prior report of CVD, alcohol intake, aspirin, vitamin supplements and postmenopausal hormone use. The second included the covariates in model one and additionally controlled for intake of other fatty acids that resulted in a change of more than 10% in the parameter estimate for ALA intake.

Mozaffarian et al 2005 (positive quality) 14-year prospective cohort study, examined the interplay between intermediate and long chain n-3 FA and n-6 FA intake on the

112

incidence of CHD in 45,722 male health professionals. Dietary n-3 FA and n-6 FA intake were assessed by administration of a self-administered validated FFQ at multiple time-points and development of CHD assessed by a biennial health history questionnaire. Relative risk of non-fatal MI was lower in those with high intakes of ALA (RR=0.58; 95% CI 0.23 to 0.75). The effect of ALA on total CHD and non-fatal MI occurred mostly in men with low intakes of EPA plus DHA. Long-chain and intermediate-chain n-3 FA intakes were associated with lower CHD risk, without modification by n-6 FA intake when adjusted for age; body mass index (BMI); smoking; physical activity; history of diabetes, HTN or hypercholesterolemia; aspirin use; alcohol use; and intake of protein, saturated fat (SFA) dietary fiber, monounsaturated fat (MUFA), trans fatty acids (TFA), total calories and ALA. High intake of EPA plus DHA (more than 250mg per day or equivalent to one or two fish meals per week) compared to low intake (less than 250mg per day) was associated with a 35% lower risk of sudden death (RR=0.65; 95% CI; 0.47 to 0.88). High intake of EPA plus DHA was associated with reduced sudden death regardless of ALA level.

Rastogi et al, 2004 (positive quality), case-control study (N=350 cases and 700 controls), found a lower relative risk of IHD in those using mustard oil, which is rich in ALA, for cooking (RR=0.49; 95% CI: 0.24, 0.99) vs. those who used sunflower oil. The risk was further reduced when the mustard oil was used for frying (RR=0.29; 95% CI: 0.13, 0.64). Individuals using vanaspati, a hydrogenated vegetable oil, were at a slightly, but not significantly, higher risk of IHD than those not using it (RR: 1.81; 95% CI: 0.99, 3.31).

Virtanen et al 2009, positive quality prospective population-based cohort study, examined the relationship between serum concentrations of long-chain n-3 PUFAs, EPA, docosapentaenoic acid (DPA) and DHA, which also serve as a marker of fish or fish oil consumption, and risk of atrial fibrillation (AF) in middle-aged or older men, 42-60 years old and free of AF at baseline (1984-1989) in Eastern Finland. During 17.7 years of follow-up, 240 men from the total cohort of 2,174 men experienced an AF event that required hospitalization. Men in the highest quartile of serum EPA+DPA+DHA had a 35% lower risk of AF compared with men in the lowest quartile. Of the individual fatty acids, only serum DHA was associated with the risk, with a 38% lower risk in the highest quartile. No association with the risk was found with serum intermediate chain-length n-3 PUFA, ALA, not even when the serum EPA+DPA+DHA concentration was low. Authors conclude that long-chain n-3 PUFAs, and especially DHA, may be effective in reducing the risk of AF.

Overview table

Author, Year, Study Design, Class, Rating	Study Population/ Location	Intervention Protocol/ Exposure levels	Significant Results	Limitations
Albert et al 2005 Study Design: Prospective Cohort Study Class: B Rating: Positive quality	N=76,763 women. Age: 50 years (SD 7.1). Participating in Nurses' Health Study (97,423). Completed the baseline FFQ. Location: United States.	ALA intake SCD. Five semi-quantitative FFQ between 1984 and 1998. Follow-up questionnaires for exposure information and new medical illnesses.	ALA-predominant n-3 fatty acid consumed: Mean absolute intake: 0.66g per day in the lowest and 1.39g per day in the highest quintile. Greater ALA intake was associated with a trend toward a lower risk of sudden cardiac death: For every 0.1% ↑ in energy intake from ALA, the associated HR=0.88. Women in the two highest quintiles of ALA intake had a 38-40% ↓ SCD risk. ALA intake related to other non-sudden fatal CHD events or to non-fatal MI.	As do other similar studies, this cannot prove causality, since association between ALA consumption and SCD could, at least in part, have been caused by residual confounders Information on coronary risk and diet was ascertained by self-reporting, potentially leading to some misclassific-tion.
Baylin A, Kabagambe EK, et al 2003 (Circulation) Study Design: Case control. Class: C Rating: Neutral quality	482 case patients with first nonfatal acute MI and 482 matched controls. Location: Costa Rica.	Subcutaneous adipose tissue biopsy to assess ALA content. FFQ (ALA content of diet not assessed).	Cases had lower adipose tissue ALA levels (P=<0.001). An inverse relationship between adipose tissue ALA and the risk of non-fatal acute MI. Subjects in the top quintiles of adipose tissue ALA (0.72%) had a ↓ risk of MI than those in the lowest quintile (0.35%). The difference between the two groups corresponded to ~0.3g per day of intake.	Biomarkers are prone to misclassification because of laboratory error.

114

De Lorgeril M, Salen P, et.al. 1999 Study Design: Randomized controlled trial. Class: A Rating: Neutral quality	N=423 (204 controls and 219 experimental). Survivors of MI. Age: <70 years. Location: France.	Mediterranean-type diet vs. prudent diet. Investigator designed mediterranean style diet vs. prudent diet from private physician.	All-cause and cardiovascular mortality (P=0.01) and the combination of recurrent MI and cardiac death (P=0.0001) were ↓ with the Mediterranean diet The experimental group had a significantly ↓ intake of total lipids (P=0.02), SFA (P=0.0001) and ↑ intake of oleic, linoleic and ALA fatty acids (P=0.0001). Plasma concentration of 18:3 (ω-3) and 22:6(ω-3) tended to be inversely associated with recurrence of MI (P=0.11 and 0.16, respectively).	The Lyon Diet Heart Study had been previously published; not all of the details of the study were included in this paper.
Folsom and Demissie, 2004 Study Design: Cohort study. Class: B Rating: Neutral quality	N=41,836 post menopausal women without initial history of heart disease from Iowa. Locatin: United States.	Fish or marine n-3 FA intake and cause of death (CVD or CHD). Baseline dietary intake assessed in 1986 using a FFQ with four fish and seafood questions. Mean respective intakes of EPA, DHA and total marine n-3 FAs were 53mg, 135mg and 188mg per day. The mean intake of ALA was 1.09g per day.	Plant-derived ALA was inversely associated with mortality after multivariable adjustment. No independent association of fish intake with CVD, CHD or stroke mortality.	Self-reported a prior history of MI, angina or other heart disease. Causes of death not verified. Single self-reported of usual fish intake may result in errors of recall.

Lemaitre et al 2009 Study Design: Case-Control Study Class: C Rating: Postive quality	N=265 married residents of King. N=415 controls randomly identified from and matched to cases by age, sex and calendar year. Age: 25-74 years. Location: United States.	Serum EPA+DHA+DPA+ALA and SCA No intervention. Out-of-hospital SCA subjects in Seattle Washington, between 1988 and 2005. SCAis a sudden pulse-less condition in the absence of evidence of a non-cardiac cause of cardiac arrest. Identified from EM incident reports, incident reports, death certificates, medical examiner reports, and autopsy reports to exclude patients with cardiac arrest due to a non-cardiac cause. Administered a FFQ to 81 controls. For each food item, controls were asked to estimate usual serving size and frequency of consumption of 120 line items during the prior month Nutrient intake estimated from the questionnaire database that is derived from the University of Minnesota Nutrition Coding Center nutrient database.	Subset of control: Average total fat intake=36.0% of total energy (7.8% energy from PUFA); and mean dietary intake of ALA was 1.9g per day. RBC membrane ALA levels modestly related to the estimate of ALA intake adjusted for total caloric intake (r=0.21, P=0.06). The RBC membrane levels of ALA were not related to total caloric intake (r=0.04) and to SFA intake (r= -0.01. Mean RBC ALA levels ↑ in Cases than Controls. ALA positively associated with RBC membrane levels of LA (r=0.39), levels of trans-18:2 (r=0.22), and levels of EPA (r=0.16), but not with levels of DHA (r=0.04). RBC membrane levels of ALA associated with ↑ risk of SCA. An ↑ in ALA corresponding to one STD associated with 32% ↑ risk of SCA (OR, 1.32; 95% CI, 1.07-1.63).	Measured dietary ALA in a small subset of controls, and could not contrast the associations of diet and membrane levels. ALA with SCA within this study population. Could result in residual confounding such incompletely adjusted for SFA intake. Use of surrogate respondents inevitably introduced some misclassification in assessment of potential confounders. Participation rate in the control=60%, and the OR associated with higher levels of ALA could be overestimated if controls who declined participation in the study ate more ALA-containing foods than the controls who participated.

Lemaitre RN, King IB et al, 2003 Study Design: Prospective nested case-control Class: C Rating: Positive quality	54 cases of fatal IHD, 125 cases of non-fatal MI and 179 matched controls of free living adults. Age: >65 years.	Serum EPA+DHA+ALA and IHD No intervention. Plasma phospholipids concentrations of DHA, EPA and ALA taken two years before the event were used as a biomarker for intake. Fish oil supplement users excluded from the study.	Higher concentration of combined DHA and EPA was associated with a ↓ risk of fatal IHD (OR: 0.30 (95% CI: 0.12, 0.76; P=0.01). No association with non-fatal MI.	None.
Mozaffarian D, Ascherio A et al, 2005 Study Design: Prospective 14-year follow-up study of dietary n-3 and n-6 intake assessed by administration of a self-administered validated FFQ at multiple time points and development of CHD assessed by biennial health history questionnaire. Class: B Rating: Positive quality	N=45,722 male health professionals from the US. Prospective 14-year follow-up study of dietary n-3 and n-6 intake assessed by administration of a self-questionnaire. Location: United States.	Dietary n-3 and n-6 intake: Assessed by a self-administered validated FFQ at baseline and every four years. Development of CHD assessed by biennial health history questionnaire.	High intake of EPA+DHA intake (>100mg per day) compared to low intake (<100mg per day): Associated with a 35% ↓risk of sudden death (HR=0.65; 95% CI=0.47 to 0.88) High intake of EPA+DHA associated with ↓ sudden death, regardless of ALA level.	Relatively small number of incident fatal IHD events and the indirect assessment of dietary PUFAs.

117

Rastogi, Reddy et al, 2004 Study Design: Case-control. Class: C Rating: Positive quality	N=350 cases of first MI. N=700 controls (12% female) eastern Indian individuals. Location: India.	Mustard oil (high in ALA) vs. Sunflower oil and IHD Food Frequency and Activity questionnaires.	Suggestive trend of ↓ risk with fish intake (RR=0.69; 95% CI: 0.46, 1.03), but not with vegetarianism Use for Cooking: Mustard oil (high ALA): Compared to sunflower oil - RR=0.49 (95% CI: 0.24, 0.99) for IHD. Use for Frying: Mustard oil=RR of 0.29 (95% CI: 0.13, 0.64) in multivariate analysis. Adding vanaspati (hydrogenated vegetable oil) to foods slightly, but NS ↑ risk of IHD over those who did not (RR=1.81; 95% CI: 0.99, 3.31).	Potential sources study includes the selection of controls and a differential recall among cases and controls. No companion nutrient database was available for FFQ; hence total energy intake could not be computed. Differential recall of dietary intake from different sites could be a potential concern. Study controls were more educated.

Virtanen et al 2008 Study Design: Prospective Cohort Study Class: B Rating: Positive quality	Health professionals aged 40-75 years. Health Professionals Follow-up Study. 18 years of follow-up. Location: United States.	Fish and n-3 fatty acid intake and total major chronic disease. Multiple validated FFQ over time used to compute cumulative averages of dietary intake. Fish intake based on 131-item food FFQ. Intake and amounts of four different seafood items: Canned tuna fish, dark meat fish (mackerel, salmon, sardines, bluefish and swordfish), other fish (not specified) and shrimp, lobster or scallops as a main dish Fish intake in categories: One to three servings per month, one serving per week Two to four servings per week, >five servings per week.	During 18 years of follow-up, 9,715 (24.1%) major chronic disease events occurred: 3,639 CVD events 4,690 cancers 1,386 deaths other causes. Baseline, mean (±SD) EPA+DHA intake was 0.3±0.2g per day and fish intake per day, was 0.3±0.3g per day compared to men with ↓ fish intake: Men with ↑ fish intake more likely to be physically active, have hypercholesterol-emia and HTN, use aspirin and multivitamin supplements, drink more alcohol and smoke. Men with higher fish intake consumption: Have ↑ intakes of energy, protein, EPA+DHA, PUFA, fiber, fruit and vegetables and ↓ intakes of SFA, MUFA and TFA. Age-adjusted analyses: Fish intake inversely associated with risk of major chronic disease (P for trend=0.02). Multivariable adjustment: Neither fish nor dietary n-3 FA intake was significantly associated with risk of total major chronic disease. Compared with fish consumption of Fish intake more than five servings per week not associated with lower risk. Higher or lower n-6 FA intake: NS modification of the results (P for interaction >0.10).	Databases used may not reflect rapid changes in the use of different types of vegetable oils in the food supply. Did not evaluate the potential effects of fish or EPA+DHA intake on other specific disease outcomes, such as heart failure, atrial fibrillation, that may be improved by fish intake.

119

Wang et al 2006 Study Design: Systematic Review Class: M Rating: Positive quality	N=46 articles identified: 14 RCTs 25 prospective cohort Seven case-control. Secondary prevention trials (11 RCTs): Total subjects: N=19,403 One prospective cohort study: Total N=415. Primary prevention trials: One RCT 25 cohort (N>340,000) Seven case-control. Three estimated ALA intakes. Studies that were of ≥ one year in duration. Location: United States, Europe, China, Japan.	Fish, Fish oil and ALA intake and CVD Comprehensive search 1966 to July 2005. n-3 FAs, consumed as fish or fish oils rich in EPA and DHA or as ALA, on CVD outcomes. Secondary prevention studies: Investigated 14 RCTs (11 fish oil supplement trials, five diet or diet advice trials) One prospective cohort study. Primary-prevention studies: 11 RCT assessing ALA supplements 25 prospective cohort studies and seven case-control studies reported on the association of n-3 FAs with CVD.	After controlling for age, randomization to aspirin and β-carotene and coronary risk factors: Dietary fish intake was associated with a ↓ risk of sudden death, with an apparent threshold effect at a consumption level of one fish meal per week. (P for trend=0.03).	No meta-analysis conducted.

Research recommendations

Conduct randomized controlled trials and prospective observational studies in persons with and without CVD on plant compared to marine n-3 fatty acids. Examine diets rich in plant n-3 fatty acids in subjects with and without adequate intake of n-3 fatty acids from marine sources. Examine the mechanism of action of marine vs. plant n-3 fatty acids for synergies and/or inhibition.

Search plan and results

Inclusion Criteria

Subjects/Population

- *Age*: Adults (19 years +)

120

- *Setting*: Any, except ICU, Burn Unit or Emergency Care, US and International
- *Health Status*:
  - Healthy
  - Dyslipidemia, Hyperlipidemia* or Hypercholesterolemia, CHD, CVD

*According to ATP III (2004), hyperlipidemia is defined as a TC greater than 200 and/or LDL-C greater than 130 without CVD; LDL-C greater than 100 with CVD; and LDL-C greater than 70 for patients with a CHD event, stroke, TIA, peripheral vascular disease AND ONE OF THE FOLLOWING:1) acute coronary syndrome, 2) type 2 diabetes mellitus, 3) metabolic syndrome, 4) a SINGLE POORLY CONTROLLED risk factor, 5) 3 risk factors irrespective of how well controlled.

Note: in ATP III, diabetes is regarded as a CHD risk equivalent.

Nutrition Related Problem/Condition:

- Cardiac Events: MI, arythmia, angioplasty, stent, death

Search Criteria

- *Study design preferences*: Meta-analysis and Systematic reviews, RCT or Clinical Controlled Studies, Large nonrandomized observational studies, Prospective Cohort, large case-control studies, Cross Sectional Studies (last resort), Feeding period must be greater than 4 weeks.
- *Size of study groups*: Sample size must equal 10 subjects for each study group. For example, this would include 10 subjects in the intervention group and 10 subjects in the control or comparison group.Study dropout rate: Less than 20%; preference for smaller dropout rates
- *Year Range*: March 2004 –Dec 2007 (covered by ADA) July 2007 to Aug 2009 (covered by USDA)
- *Authorship*: If an author is included on more than one Review Article or primary research article that is similar in content, the most recent review or article will be accepted and earlier versions will be rejected. If an author is included on more than one Review Article or primary research article and the content is different, then both reviews may be accepted.
- *Languages*: Limited to articles in English
- Other: Article must be published in peer-reviewed journal

Exclusion Criteria

Subjects/Population

- *Age*: Infants, Children and adolescents <19 years
- *Setting*: ICU, Burn Unit, Emergency Care
- *Health Status*: Presence of diabetes, TC less than or equal to 200 and/or LDL-C less than or equal to 130. Also, see inclusion criteria
- *Nutrition Related Problem/Condition*: (i.e., eating disorders)
- *Cardiac Events*: stroke, triglyceride, lipids, inflammatory markers
- *Size of study groups*: Sample sizes < 10
- *Study Designs*: Small case studies, Cross sectional Studies
- Feeding periods <4 weeks.

121

- Experimental fat must be from natural sources
- *Study Dropout rate*: Dropout rate in a study is 20% or greater
- *Year Range*: Prior to July 2007 included in ADA analysis
- *Authorship*: Studies by same author similar in content
- *Languages*: Articles not in English
- *Other*: Animal studies; Abstracts or presentations

Search Terms and Electronic Databases Used:

PubMed:

(arrhythmia* OR "Arrhythmias, Cardiac"[Mesh] OR "Arrhythmia, Sinus"[Mesh]) AND ("Fatty Acids, Omega-3"[Mesh] OR "Docosahexaenoic Acids"[mh] OR "alpha-Linolenic Acid"[Mesh] OR "SR 3 linolenic acid "[Substance Name] OR "8, 11, 14-Eicosatrienoic Acid"[Mesh] OR "Fish Oils"[Mesh] OR "Plant Oils")

("Fatty Acids, Omega-3"[Mesh] OR "Fish Oils"[Mesh] OR "alpha-Linolenic Acid"[Mesh] OR "SR 3 linolenic acid "[Substance Name] OR "8, 11, 14-Eicosatrienoic Acid"[Mesh]) AND ("Death, Sudden, Cardiac"[Mesh OR "Biological Markers"[Mesh] OR "Coronary Disease"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Cardiovascular Diseases"[Mesh])

("Fatty Acids, Omega-3"[Mesh] OR "Docosahexaenoic Acids" "alpha-Linolenic Acid"[Mesh] OR "SR 3 linolenic acid "[Substance Name] OR "8, 11, 14-Eicosatrienoic Acid"[Mesh]) AND ("Fish Oils"[Mesh] OR "Plant Oils") AND ("Biological Markers"[Mesh] OR "Coronary Disease"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Cardiovascular Diseases"[Mesh:NoExp] OR "blood pressure"[mh] OR hypertension[mh])**Date Searched:** 08/21/2009

Summary of Articles Identified to Review

- Total hits from all electronic database searches: 371
- Total articles identified to review from electronic databases: 60
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 21
- Number of Review Articles Identified: 4
- Total Number of Articles Identified: 22
- Number of Articles Reviewed but Excluded: 32

Included articles (References)

What is the relationship between consumption of plant n-3 fatty acids and risk of cardiovascular disease?

1. Albert CM, Oh K, Whang W, Manson JE, Chae CU, Stampfer MJ, Willett WC, Hu FB. Dietary alpha-linolenic acid intake and risk of sudden cardiac death and coronary heart disease. Circulation. 2005 Nov 22;112(21):3232-8. PMID: 16301356 (ADA).
2. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study.Circulation. 1999 Feb 16;99(6):779-85. PMID: 9989963. (ADA).

122

3. Folsom AR, Demissie Z. Fish intake, marine omega-3 fatty acids, and mortality in a cohort of postmenopausal women. Am J Epidemiol. 2004 Nov 15;160(10):1005-10. PMID: 15522857

4. Lemaitre RN, King IB, Sotoodehnia N, Rea TD, Raghunathan TE, Rice KM, Lumley TS, Knopp RH, Cobb LA, Copass MK, Siscovick DS. Red blood cell membrane alpha-linolenic acid and the risk of sudden cardiac arrest. Metabolism. 2009 Apr;58(4):534-40. PMID: 19303975.

5. Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS. n-3 Polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. Am J Clin Nutr. 2003 Feb; 77 (2): 319-325. PubMed ID: 12540389 (ADA).

6. Mozaffarian D, Ascherio A, Hu FB, Stampfer MJ, Willett WC, Siscovick DS, Rimm EB. Interplay between different polyunsaturated fatty acids and risk of coronary heart disease in men. Circulation. 2005 Jan 18;111(2):157-64. Epub 2005 Jan 3. PMID: 15630029

7. Rastogi T, Reddy KS, Vaz M, Spiegelman D, Prabhakaran D, Willett WC, Stampfer MJ, Ascherio A. Diet and risk of ischemic heart disease in India. Am J Clin Nutr. 2004 Apr; 79(4): 582-592. PMID: 15051601.

8. Virtanen JK, Mursu J, Voutilainen S, Tuomainen TP. Serum long-chain n-3 polyunsaturated fatty acids and risk of hospital diagnosis of atrial fibrillation in men. Circulation. 2009 Dec 8;120(23):2315-21. Epub 2009 Nov 23.PMID: 19933935

Excluded Articles

Articles	Reasons for Exclusion
Aarsetoey H, Pönitz V, Grundt H, Staines H, Harris WS, Nilsen DW.(n-3) Fatty acid content of red blood cells does not predict risk of future cardiovascular events following an acute coronary syndrome.J Nutr. 2009 Mar;139(3):507-13. Epub 2009 Jan 21. PMID: 19158216.	Measures omega-3 index of admitted ACS patients No intervention. Cross sectional Study.
Astorg P, Bertrais S, Laporte F, Arnault N, Estaquio C, Galan P, Favier A, Hercberg S.Plasma n-6 and n-3 polyunsaturated fatty acids as biomarkers of their dietary intakes: a cross-sectional study within a cohort of middle-aged French men and women.Eur J Clin Nutr. 2008 Oct;62(10):1155-61. Epub 2007 Jul 11. PMID: 17622261.	Cross Sectional Study. Uses plasma fatty acid concentrations as marker to dietary n-3 fatty acids determined by FFQ.
Barceló-Coblijn G, Murphy EJ, Othman R, Moghadasian MH, Kashour T, Friel JK.Flaxseed oil and fish-oil capsule consumption alters human red blood cell n-3 fatty acid composition: a multiple-dosing trial comparing 2 sources of n-3 fatty acid.Am J Clin Nutr. 2008 Sep;88 (3):801-9. PMID: 18779299.	Intervention provided as capsules

123

Baylin A, Kabagambe EK, Ascherio A, Spiegelman D, Campos H.Adipose tissue alpha-linolenic acid and nonfatal acute myocardial infarction in Costa Rica.Circulation. 2003 Apr; 107(12): 1,586-1,591.	No dietary intervention.
Beydoun MA, Kaufman JS, Sloane PD, Heiss G, Ibrahim J.n-3 Fatty acids, hypertension and risk of cognitive decline among older adults in the Atherosclerosis Risk in Communities (ARIC) study. Public Health Nutr. 2008 Jan;11(1):17-29. Epub 2007 Jul 12. PMID: 17625029.	Outcomes measured involved inhibition of cognitive decline in hypertension
Bloedon LT, Balikai S, Chittams J, Cunnane SC, Berlin JA, Rader DJ, Szapary PO.Flaxseed and cardiovascular risk factors: results from a double blind, randomized, controlled clinical trial.J Am Coll Nutr. 2008 Feb;27(1):65-74. PMID: 18460483.	Intervention provided as capsules
Cazzola R, Russo-Volpe S, Miles EA, Rees D, Banerjee T, Roynette CE, Wells SJ, Goua M, Wahle KW, Calder PC, Cestaro B.Age- and dose-dependent effects of an eicosapentaenoic acid-rich oil on cardiovascular risk factors in healthy male subjects.Atherosclerosis. 2007 Jul;193(1):159-67. Epub 2006 Aug 1. PMID: 16879829	Intervention provided as capsules
Chilton FH, Rudel LL, Parks JS, Arm JP, Seeds MC.Mechanisms by which botanical lipids affect inflammatory disorders.Am J Clin Nutr. 2008 Feb;87(2):498S-503S. Review. PMID: 18258646.	Narrative review
Chung H, Nettleton JA, Lemaitre RN, Barr RG, Tsai MY, Tracy RP, Siscovick DS.Frequency and type of seafood consumed influence plasma (n-3) fatty acid concentrations.J Nutr. 2008 Dec;138(12):2422-7. PMID: 19022967.	Studies frequency, processing and type of fish consumption on plasma fatty acids.
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):1385-91.PMID: 17490977.	Intermediate outcome, not CVD event s
Damsgaard CT, Frøkiaer H, Andersen AD, Lauritzen L.Fish oil in combination with high or low intakes of linoleic acid lowers plasma triacylglycerols but does not affect other cardiovascular risk markers in healthy men.J Nutr. 2008 Jun;138(6):1061	Intermediate outcomes, not CVD event

124

Archived from www.NEL.gov on March 21, 2017

Damsgaard CT, Frøkiaer H, Lauritzen L.The effects of fish oil and high or low linoleic acid intake on fatty acid composition of human peripheral blood mononuclear cells.Br J Nutr. 2008 Jan;99(1):147-54. Epub 2007 Jul 30. PMID: 17663804.	Reported outcomes limited to FA composition of mononuclear cells
DeGiorgio CM, Miller P, Meymandi S, Gornbein JA.n-3 fatty acids (fish oil) for epilepsy, cardiac risk factors, and risk of SUDEP: clues from a pilot, double-blind, exploratory study.Epilepsy Behav. 2008 Nov;13(4):681-4. Epub 2008 Sep 7. PMID: 18721899.	Intervention provided as capsules
Delgado-Lista J, Lopez-Miranda J, Cortés B, Perez-Martinez P, Lozano A, Gomez-Luna R, Gomez P, Gomez MJ, Criado J, Fuentes F, Perez-Jimenez F.Chronic dietary fat intake modifies the postprandial response of hemostatic markers to a single fatty test meal. Am J Clin Nutr. 2008 Feb;87(2):317-22. PMID: 18258620	Intervention does not meet criteria. Single test meal.
De Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean Diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction, final report of the Lyon Diet Heart Study. Circulation. 1999; 99: 779-785. PubMed ID**:**9989963.	Intervention provided as dietary advice
Din JN, Harding SA, Valerio CJ, Sarma J, Lyall K, Riemersma RA, Newby DE, Flapan AD.Dietary intervention with oil rich fish reduces platelet-monocyte aggregation in man.Atherosclerosis. 2008 Mar;197(1):290-6. Epub 2007 Jun 18. PMID: 17575985. Djoussé L, Rautaharju PM, Hopkins PN, Whitsel EA, Arnett DK, Eckfeldt JH, Province MA, Ellison RC; Investigators of the NHLBI Family Heart Study.Dietary linolenic acid and adjusted QT and JT intervals in the National Heart, Lung, and Blood Institute Family Heart study. J Am Coll Cardiol. 2005 May 17;45(10):1716-22. PMID: 15893192.	Intermediate outcome not CVD event s Intermediate outcome Qtrr measurments, not CVD events
Dodin S, Cunnane SC, Mâsse B, Lemay A, Jacques H, Asselin G, Tremblay-Mercier J, Marc I, Lamarche B, Légaré F, Forest JC.Flaxseed on cardiovascular disease markers in healthy menopausal women: a randomized, double-blind, placebo-controlled trial. Nutrition. 2008 Jan;24(1):23-30. Epub 2007 Nov 5. PMID: 17981439.	Intermediate outcomes, not CVD event

125

Ebbesson SO, Roman MJ, Devereux RB, Kaufman D, Fabsitz RR, Maccluer JW, Dyke B, Laston S, Wenger CR, Comuzzie AG, Romenesko T, Ebbesson LO, Nobmann ED, Howard BV.Consumption of omega-3 fatty acids is not associated with a reduction in carotid atherosclerosis: the Genetics of Coronary Artery Disease in Alaska Natives study.Atherosclerosis. 2008 Aug;199(2):346-53. Epub 2007 Dec 4. PMID: 18054937.	Intermediate outcome not CVD event s
Egert S, Kannenberg F, Somoza V, Erbersdobler HF, Wahrburg U. Dietary alpha-linolenic acid, EPA, and DHA have differential effects on LDL fatty acid composition but similar effects on serum lipid profiles in normolipidemic humans.J Nutr. 2009 May;139(5):861-8. Epub 2009 Mar 4. PMID: 19261730	Intermediate outcome Qtrr measurments, not CVD events
Fekete K, Marosvölgyi T, Jakobik V, Decsi T.Methods of assessment of n-3 long-chain polyunsaturated fatty acid status in humans: a systematic review.Am J Clin Nutr. 2009 Jun;89(6):2070S-2084S. Epub 2009 May 6.PMID: 19420097.	Study involves Markers ofn–3 LCPUFA. Does not address question
Freund-Levi Y, Hjorth E, Lindberg C, Cederholm T, Faxen-Irving G, Vedin I, Palmblad J, Wahlund LO, Schultzberg M, Basun H, Eriksdotter Jönhagen M.Effects of omega-3 fatty acids on inflammatory markers in cerebrospinal fluid and plasma in Alzheimer's disease: the OmegAD study.Dement Geriatr Cogn Disord. 2009;27(5):481-90. Epub 2009 May 12. PMID: 19439966..	Intervention provided as capsules
Fuentes F, López-Miranda J, Pérez-Martínez P, Jiménez Y, Marín C, Gómez P, Fernández JM, Caballero J, Delgado-Lista J, Pérez-Jiménez F.Chronic effects of a high-fat diet enriched with virgin olive oil and a low-fat diet enriched with alpha-linolenic acid on postprandial endothelial function in healthy men.Br J Nutr. 2008 Jul;100(1):159-65. Epub 2008 Feb 14. PMID: 18275619.	Intermediate outcomes, not CVD event
Galli C, Risé P.Fish consumption, omega 3 fatty acids and cardiovascular disease. The science and the clinical trials.Nutr Health. 2009;20(1):11-20. PMID: 19326716.	Narrative Review

Gissi-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G.Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial.Lancet. 2008 Oct 4;372(9645):1223-30. Epub 2008 Aug 29. PMID: 18757090..	Subjects had chronic heart failure.
Goyens PL, Mensink RP. Effects of alpha-linolenic acid versus those of EPA/DHA on cardiovascular risk markers in healthy elderly subjects. Eur J Clin Nutr. 2006 Aug;60(8):978-84. Epub 2006 Feb 15. PMID: 16482073	Intermediate outcome Qtrr measurments, not CVD events
Guebre-Egziabher F, Rabasa-Lhoret R, Bonnet F, Bastard JP, Desage M, Skilton MR, Vidal H, Laville M.Nutritional intervention to reduce the n-6/n-3 fatty acid ratio increases adiponectin concentration and fatty acid oxidation in healthy subjects.Eur J Clin Nutr. 2008 Nov;62(11):1287-93. Epub 2007 Aug 15. PMID: 17700650.	Study involves n-3/n-6 ratio. Not variables that address the question.
Harris WS.The omega-3 index as a risk factor for coronary heart disease.Am J Clin Nutr. 2008 Jun;87(6):1997S-2002S. PMID: 18541601.	Narrative review
Hartweg J, Perera R, Montori V, Dinneen S, Neil HA, Farmer A.Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus.Cochrane Database Syst Rev. 2008 Jan 23;(1):CD003205. Review. PMID: 18254017	Reviewed outcomes did not distinguish supplements from dietary
He K, Liu K, Daviglus ML, Jenny NS, Mayer-Davis E, Jiang R, Steffen L, Siscovick D, Tsai M, Herrington D.Associations of dietary long-chain n-3 polyunsaturated fatty acids and fish with biomarkers of inflammation and endothelial activation (from the Multi-Ethnic Study of Atherosclerosis [MESA]).Am J Cardiol. 2009 May 1;103(9):1238-43. Epub 2009 Mar 4. PMID: 19406265.	Intermediate outcome not CVD events
He K, Liu K, Daviglus ML, Mayer-Davis E, Jenny NS, Jiang R, Ouyang P, Steffen LM, Siscovick D, Wu C, Barr RG, Tsai M, Burke GL.Intakes of long-chain n-3 polyunsaturated fatty acids and fish in relation to measurements of subclinical atherosclerosis.Am J Clin Nutr. 2008 Oct;88(4):1111-8. PMID: 18842801.	Intermediate outcome not CVD events

Hoyos C, Almqvist C, Garden F, Xuan W, Oddy WH, Marks GB, Webb KL.Effect of omega 3 and omega 6 fatty acid intakes from diet and supplements on plasma fatty acid levels in the first 3 years of life.Asia Pac J Clin Nutr. 2008;17(4):552-7. PMID: 19114389.	Reported outcomes limited to FA composition of plasma based on diet

CHAPTER 7. SPECIFIC FATS, FATTY ACIDS, AND CHOLESTEROL – SEAFOOD N-3 FATTY ACIDS AND RISK OF CARDIOVASCULAR DISEASE

WHAT IS THE RELATIONSHIP BETWEEN CONSUMPTION OF SEAFOOD N-3 FATTY ACIDS AND RISK OF CARDIOVASCULAR DISEASE?

Conclusion statement

Moderate evidence shows that consumption of two servings of seafood per week (4oz per serving), which provide an average of 250mg per day of long-chain n-3 fatty acids, is associated with reduced cardiac mortality from coronary heart disease (CHD) or sudden death in persons with cardiovascular disease (CVD).

Grade

Moderate

Evidence summary overview

The 2010 Dietary Guidelines Advisory Committee (DGAC) conducted a full Nutrion Evidence Library (NEL) search of the literature from 2004 to evaluate the association of seafood consumption and cardiovascular disease (CVD) risk. Results of this review were supplemented by an earlier evidence review of the literature from 2004 to 2007 conducted by the American Dietetic Association (ADA) on health benefits related to consumption of fish or fish-derived omega-3 fatty acids (n-3 FAs) in subjects without or with CVD. Taken together, the NEL and ADA evidence reviews identified 28 studies published since 2004 assessing the health benefits of seafood consumption in persons without CVD. These included seven systematic reviews and meta-analyses, including four methodologically strong reviews with meta-analyses of randomized controlled trials (RCTs) and prospective cohort studies (He, 2004; Konig, 2005; Mozaffarian, 2008; Mozaffarian and Rimm, 2006), one methodologically strong systematic review of 14 RCTs, 25 prospective cohort studies and seven case-control studies (Wang, 2006) and one methodologically neutral meta-analysis of 14 cohort and five case-control studies (Whelton, 2004). These also included four RCTs ranging in size from 33 to 48 subjects conducted in the US and Finland, including two methodologically strong studies (Lara, 2007; Seierstad, 2005) and two methodologically neutral studies (Lindqvist, 2009; Lankinen, 2009). Lastly, this included 15 prospective cohort studies conducted in the US, Europe, Japan and China, ranging in size from 300 to 57,972 subjects, including eight methodologically strong (Brouwer, 2006; Frost and Vestergaard, 2005; Iso, 2006 ; Järvinen, 2006; Mozaffarian, 2004; Mozaffarian, 2005; Virtanen, 2008; Virtanen, 2009) and seven methodologically neutral studies (Albert, 2002; Folsom and Demissie, 2005; Levitan, 2009; Pangiotakos, 2007; Streppel, 2008; Turunen, 2008; Yamagishi, 2008).

Three of the systematic reviews assessed both fish and long-chain n-3 FAs (Mozaffarian, 2008; Mozaffarian and Rimm, 2007; Wang, 2006) and three meta-analyses covered only fish (Konig, 2005; Whelton, 2004; and He, 2004). The

Archived from www.NEL.gov on March 21, 2017

systematic reviews and meta-analyses were consistent in showing that fatty fish consumption at about two servings per week [about 250mg eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) per day] decreases risk of CVD events. Intakes above this level appeared to result in no significant (NS) additional decreases in risk CVD.

The RCT evidence showed an inverse protective association between fish intake and intermediate markers of CVD risk and CVD health outcomes. The interventions were fish-specific and included the following:

- One study that showed herring significantly increased serum high-density lipoprotein cholesterol (HDL-C) levels (Lindqvist, 2009)
- Two studies on salmon that showed salmon vs. no fish intake improved serum lipids and blood pressure (BP) (Lara, 2006) and intake of salmon with different levels of EPA + DHA showed the high EPA+DHA salmon improved serum lipids and markers of inflammation (Seierstad, 2005)
- One study comparing fatty vs. lean fish showed that fatty fish consumption improved serum lipid profiles and markers of insulin resistance and inflammation (Lankinen, 2006).

Evidence from prospective cohort studies was substantial and focused on primary CVD prevention in healthy adults. Ten prospective cohort studies examined the association between fatty fish and CVD outcomes and found a positive association between seafood and seafood-derived n-3 fatty acid consumption and decreased CVD incidence or risk (Levitan, 2009; Virtanen, 2008; Yamagishi, 2008; Streppel, 2008; Turunen, 2008; Järvinen, 2006; Iso, 2006; Mozaffarian, 2005; Lemaitre, 2003; Albert, 2002). Three prospective cohort studies examined fish and fish-derived fatty acid consumption and atrial fibrillation and found either no association between fish n-3 fatty acid intake and reduced risk of atrial fibrillation (Brouwer, 2006; Frost and Vestergaard, 2005) or a inverse association between consumption of tuna or other broiled or baked fish (but not fried fish) and incidence of atrial fibrillation (Mozaffarian, 2004). Virtanen et al, (2009) reported n-3 fatty acids (especially DHA) to be effective in reducing atrial fibrillation in men.

One prospective cohort study examined the association between fatty fish intake and intermediate markers of CVD risk and found moderate intake of fatty fish was inversely associated with serum lipids and BP (Panagiotakos, 2007). One prospective cohort study assessed fish n-3 FA intake on CVD and coronary heart disease (CHD) mortality and found no independent association with CHD or stroke mortality (Folsom and Demissie, 2005). One prospective cohort study found a positive association between fish intake and increased incidence of T2D (Kaushik, 2009). This is the only observational evidence regarding risk of T2D, but the RCT on fatty vs. lean fish by Lankinen et al, (2009) examined markers of insulin resistance and can be added to the evidence regarding T2D.

The 2005 DGAC indicated there was sufficient evidence to suggest that n-3 PUFA consumption provided protection for persons with existing CVD. For the current 2010 review, conclusions related to persons with CVD relied on the ADA evidence-based review referred to above, as a NEL search did not yield additional studies that met the

130

inclusion criteria. Four studies were reviewed by the ADA that addressed the relationship between consumption of fish-derived n-3 fatty acids and risk of CVD events in persons with CVD. One was a methodologically strong meta-analysis covering 11 RCTs (Bucher, 2002) and three studies were methodologically strong prospective cohort studies conducted in the US with cohort size ranging from 228 to 415 subjects (Erkkila, 2003, 2004, 2006).

Evidence summary paragraphs

Systematic reviews/Meta-analyses

Bucher et al, 2002 (positive-quality) meta-analysis, assessed the effects of dietary and non-dietary (supplemental) intake of N-3 PUFA on CHD. Eleven studies were included: Two dietary intervention trials (intervention group N=57, control group N=58) and nine supplementation trials with N-3 PUFAs (N=7,894 in intervention groups, N=7,797 in control groups). No description of fish intake was provided. For non-fatal myocardial infarction (MI), the risk ratio in two trials of dietary intervention compared with controls was 0.8 (95% CI: 0.5 to 1.2; P=0.16, heterogeneity P=0.01). Among these patients, the risk ratio was 0.7 (95% CI: 0.6 to 0.8, P<0.001; heterogeneity P>0.20) for fatal MI, 0.7 (95% CI: 0.6 to 0.9, P<0.01; heterogeneity P>0.20) for sudden death (N=5 trials) and 0.8 (95% CI: 0.7 to 0.9, P<0.001; heterogeneity P>0.20) for overall death.

He et al, 2004 (positive quality) This was a meta-analysis of cohort studies on the association between fish intake and CHD mortality. Eligible studies provided a relative risk (RR) and corresponding 95% confidence interval (CI) for CHD mortality in relation to fish consumption and the frequency of fish intake. A database was developed on the basis of 11 eligible studies and 13 cohorts, including 222,364 individuals with an average 11.8 years of follow-up. Six cohorts were from the US, six from Europe and one from China. Pooled RR and 95% CI for CHD mortality were calculated by using fixed-effect and random-effect models. Linear regression analysis of the log RR weighted by the inverse of variance was performed to assess the possible dose-response relation.

Compared with those who never consumed fish or ate fish less than once per month, individuals with a higher intake of fish had lower CHD mortality. The pooled multivariate RRs for CHD mortality were 0.89 (95% CI, 0.79 to 1.01) for fish intake one to three times per month, 0.85 (95% CI, 0.76 to 0.96) for once per week, 0.77 (95% CI, 0.66 to 0.89) for two to four times per week and 0.62 (95% CI, 0.46 to 0.82) for five or more times per week. The observed inverse association existed in a dose-response manner. Each 20g per day increase in fish intake was related to a 7% lower risk of CHD mortality (P for trend=0.03). The effects of fish consumption on CHD mortality were not appreciably modified by sex, but were more evident among those studies with a follow-up of 12 years or longer. The authors conclude that fish consumption is inversely associated with fatal CHD and mortality from CHD may be reduced by eating fish one time per week or more.

Konig et al, 2005 (positive quality) This was a quantitative analysis of the effect of fish consumption on CHD mortality and nonfatal MI. This analysis identified studies that were appropriate for development of a dose-response relationship. Studies had to

131

satisfy quality criteria, quantify fish intake and report the precision of the relative risk estimates. Eight studies were identified (29 exposure groups). The analysis estimated that consuming small quantities of fish is associated with a 17% reduction in CHD mortality risk, with each additional serving per week associated with a further reduction in this risk of 3.9%. Small quantities of fish consumption were associated with risk reductions in non-fatal MI risk by 27%, but additional fish consumption conferred no incremental benefits.

Mozaffarian et al, 2008 (positive quality) This was a pooled analysis of both RCTs and prospective cohort studies on the effects of fish and n-3 fatty acid consumption on fatal CHD and sudden cardiac death (SCD), events that share a final common pathway of fatal ventricular arrhythmia. Randomized controlled trials and prospective cohort studies, provide concordant evidence that modest consumption of fish or fish oil (one to two servings per week of oily fish or approximately 250mg per day of EPA+DHA) reduces risk of CHD death and SCD. Pooled analysis of prospective cohort studies and RCTs showed that the magnitude and dose-response of this effect to be 36% lower risk of CHD death comparing zero and 250mg per day of EPA+DHA consumption (P<0.001). There is little additional benefit with higher fish or fish oil intakes. Reductions in risk are even larger in observational studies utilizing tissue biomarkers of n-3 FA that more accurately measure dietary consumption. Results indicate that effects of fish or fish oil on CHD death and SCD do not vary with presence or absence of prior CHD. The authors indicate that the consistency of the evidence and the magnitude of the effects strongly support modest consumption of fish or fish oil as a first-line treatment for prevention of CHD death and SCD.

Mozaffarian and Rimm, 2006 (positive quality) This was a risk/benefit analysis including pooled and meta-analysis regarding fish consumption and health outcomes. The authors investigated

1. Intake of fish or fish oil and cardiovascular risk
2. Effects of methylmercury and fish oil on early neurodevelopment
3. Risks of Methylmercury for cardiovascular and neurologic outcomes in adults
4. Health risks of dioxins and polychlorinated biphenyls in fish, using both RCTs and prospective cohort studies.

When possible, meta-analyses were done to characterize benefits and risks most accurately. Modest consumption of fish (one to two servings per week), especially species higher in EPA and DHA, reduced risk of coronary death by 36% (95% CI, 20%-50%; P<0.001) and total mortality by 17% (95% CI, 0%-32%; P=0.046). Intake of 250mg per day of EPA and DHA was sufficient for primary prevention. Docosahexaenoic acid appears beneficial for, and low-level Methylmercury may adversely affect, early neurodevelopment in infants. Women of childbearing age and lactating women should consume two seafood servings per week, limiting intake to selected fish species that are high in EPA+DHA and low in methylmercury. Methylmercury may modestly counteract the cardiovascular benefits of EPA+DHA in fish. The authors conclude that based on the strength of the evidence and the potential magnitudes of effect, the benefits of fish intake exceed the potential risks. For women of childbearing age, benefits of modest fish intake, excepting a few selected species high in Methlymercury, also outweigh risks.

Wang et al, 2006 (positive quality) This was a systematic review that investigated the effects of n-3 FAs, consumed as fish or fish oils rich in EPA and DHA or as ALA, on CVD outcomes. Studies that were of at least one year in duration and that reported estimates of fish or n-3 FA intakes and CVD outcomes were included. Fourteen RCTs (11 fish oil supplement trials, five diet or diet advice trials) and one prospective cohort study addressed secondary prevention. One RCT assessing ALA supplementation, 25 prospective cohort studies and seven case-control studies reported on the association of n-3 FAs with primary prevention of CVD. Most cohort studies reported that fish consumption was associated with lower rates of all-cause mortality and adverse cardiac outcomes. Evidence suggests that increased consumption of n-3 FAs from fish or fish-oil supplements, but not of ALA, reduces the rates of all-cause mortality, cardiac and sudden death.

Whelton et al, 2004 (neutral quality), meta-analysis of observational studies, determined if fish consumption is associated with lower fatal and total CHD. This analysis included 19 observational studies (14 cohort and five case-control) in which there was a group that consumed fish on a regular basis and a comparison group that consumed little or no fish. With a standardized protocol and data extraction form, information on study design, sample size, participant characteristics, duration of follow-up, assessment of end points and consumption of fish was abstracted. Using a random effects model, the authors pooled data from each study. Fish consumption vs. little to no fish consumption was associated with a RR of 0.83 (95% CI, 0.76-0.90; P<0.005) for fatal CHD and a RR of 0.86 (95% CI, 0.81-0.92; P<0.005) for total CHD. The results indicate that fish consumption is associated with a significantly lower risk of fatal and total CHD.

Primary Articles

Albert et al, 2002 (neutral quality) prospective case control study, assessed whether blood levels of long-chain n-3 FA were associated with reduced risk of sudden death in 94 male physicians with no history of CVD as compared to 184 case controls matched for age and smoking status. Baseline blood level of long-chain n-3 FA was significantly correlated with fish intake at 12 months ($R2=0.24$, P=0.001). The mean level of total long-chain n-3 FA was significantly lower among the men who died suddenly than among the controls (4.82 ± 1.31 vs. $5.24\%\pm1.32\%$ of total fatty acids, P=0.01). Baseline blood levels of long-chain n-3 FA were inversely related to the risk of sudden death both before adjustment for age and smoking status (P=0.004) and after such adjustment (P=0.007). As compared with men whose blood levels of long-chain n-3 FA were in the lowest quartile (3.58% total fatty acids), the adjusted risk of sudden death was significantly lower among men with levels in the third quartile (AHR, 0.28; 95% CI 0.09-0.87) and the fourth quartile (6.87% total fatty acids) (AHR, 0.19; 95% CI: 0.05-0.71).

Brouwer et al, 2006 (positive quality) This was a prospective cohort study that examined the association between consumption of very long-chain n-3 FA EPA plus DHA from fish and risk of incident atrial fibrillation using data from the Rotterdam Study, involving 5,184 subjects free from atrial fibrillation and whose dietary intake data were available. Dietary intake was assessed using a semi-quantitative food-frequency questionnaire (FFQ) and incidence of atrial fibrillation was continuously

133

monitored during follow-up. Three hundred twelve subjects developed atrial fibrillation. Intake of EPA and DHA in the third textile compared with first was not associated with risk of atrial fibrillation (RR 1.18, 95% CI 0.88-1.57). No association was observed with intake of >20g per day fish compared with no fish intake (RR: 1.17, 95% CI 0.87-1.57). After a mean follow-up period of 6.4±1.6 years, intake of EPA and DHA and fish consumption were not associated with a reduced risk of atrial fibrillation. The findings do not support the anti-arrhythmic effect of n-3 FAs.

Erkkila et al, 2003 (positive-quality) prospective cohort study, in 415 free-living adults with established coronary artery disease (CAD), found that proportions of ALA, EPA and DHA in serum cholesterylesters were associated with a reduction in the risk of death (P for trend=0.063, 0.056 and 0.026, respectively). The associations of n-3 FAs with combined fatal and non-fatal cardiovascular events were NS. Compared with no consumption, consumption of fish tended to be associated with a lower risk of death [1g to 57g per day, RR=0.50 (0.20, 1.28); >57g per day, RR=0.37 (0.14, 1.00); P for trend=0.059].

Erkkila et al, 2004 (positive-quality) prospective cohort study, examined the association between fish intake and the progression of coronary artery atherosclerosis over a three-year period in 229 postmenopausal women. Women who ate two or more servings of fish per week had significantly fewer new lesions (P=0.03). Women who ate at least one serving of tuna or dark fish per week had a smaller change in minimum coronary artery diameter (P=0.02). Among the 42% of women who were diabetic, compared with lower fish intakes, consumption of at least two servings of fish or at least one serving of tuna or dark fish per week was associated with smaller increases in the percentage of stenosis after adjustments for age, CVD risk factors and dietary intakes of fatty acids, cholesterol, fiber and alcohol. This relationship was only significant in non-diabetic women when adjustment was made for dietary factors, which suggests an independent effect of tuna and dark fish (P=0.02). In the same cohort of patients, Erkkila et al, 2006, reported women with plasma phospholipids (PL) DHA levels above the median, compared with below, exhibited less atherosclerosis progression, as expressed by decline in minimum coronary artery diameter (-0.04±0.02 and -0.10±0.02mm, respectively; P=0.007) or increase in percentage stenosis (1.34±0.76% and 3.75±0.74%, respectively; P=0.006) and had fewer new lesions [2.0% (0.5% to 3.5%) of measured segments (95% CI) and 4.2% (2.8% to 5.6%), respectively; P=0.009] after adjustments for cardiovascular risk factors.

Folsom and Demissie, 2004 (neutral quality) prospective cohort study, assessed the effect of fish or marine n-3 FA intake on CVD and CHD mortality over a 10-year period in 41,836 postmenopausal women aged 55-69 years, initially free of heart disease and cancer (4,653 deaths over 442,965 person-years). A FFQ was used to determine if intake may decrease risk of total and CHD death. Among women initially free of heart disease and cancer there was an inverse age- and energy-adjusted association between total mortality and fish intake, with a RR of 0.82 (95% CI: 0.74, 0.91) for the highest vs. lowest quintile. Age- and energy-adjusted associations also were inverse (P for trend<0.05), although not entirely monotonic, for cardiovascular, CHD and cancer mortality. Adjustment for multiple other risk factors attenuated all associations to statistically NS levels. Estimated marine n-3 fatty acid intake also was not

134

associated with total or cause-specific mortality. In comparison, plant-derived ALA was inversely associated with mortality after multivariable adjustment. There was no independent association of fish intake with CHD or stroke mortality.

Frost and Vestergaard, 2005 (positive quality) This was a prospective cohort study that examined the association between consumption of n-3 FAs from fish and risk of atrial fibrillation or flutter in a prospective cohort study of 47,949 participants (mean age: 56 years) in the Danish Diet, Cancer, and Health Study, using a detailed semi-quantitative FFQ and risk of atrial fibrillation or flutter. The subjects were followed-up in the Danish National Registry of Patients for the occurrence of atrial fibrillation or flutter and in the Danish Civil Registration System (vital status and emigration). The consumption of n-3 FAs from fish was analyzed as sex-specific quintiles with the use of Cox proportional hazards models. During the mean follow-up of 5.7 years atrial fibrillation or flutter developed in 556 subjects (374 men and 182 women). When the lowest quintile of n-3 FAs consumed from fish was used as a reference, the unadjusted hazard rate ratios (HR) in quintiles two, three, four and five were 0.93, 1.11, 1.10, and 1.44, respectively (P for trend=0.001). The corresponding adjusted HR were 0.86, 1.08, 1.01, and 1.34 (P for trend=0.006). Inclusion of information on the frequency of fatty fish consumption did not alter these associations. Consumption of n-3 FAs from fish was not associated with a reduction in risk of atrial fibrillation or flutter.

Iso et al, 2006 (positive quality) prospective cohort study, examined the association between high intake of fish and n-3 PUFA and the risk of CHD in 41,578 Japanese men and women aged 40 to 59 years, free of prior diagnosis of CVD and cancer and who completed a FFQ and were followed up from 1990-1992 to 2001. After 477,325 person-years of follow-up, 258 incident cases of CHD (198 definite and 23 probable MI and 37 SCD) were documented, comprising 196 non-fatal and 62 fatal coronary events. Strong inverse associations existed between dietary intake of n-3 FAs and risk of definite MI (HR=0.35 [0.18 to 0.66]) and nonfatal coronary events [hazard ratios (HR)=0.33 (0.17 to 0.63)]. For men, the multivariable HR (95% CI) in the highest vs. lowest quintiles of n-3 PUFAs were 0.54 (0.30 to 0.96), for total CHD 0.41 (0.21 to 0.80) for total MI, 0.35 (0.17 to 0.73) for definite MI, 0.33 (0.16 to 0.69) for non-fatal coronary events, 0.99 (0.27 to 3.62) for SCD and 1.06 (0.37 to 2.99) for fatal coronary events. The multivariable HRs and 95% CI in the highest (eight times per week, or median intake=180g per day) vs. lowest (once a week, or median intake=23g per day) quintiles of fish intake were 0.63 (0.38 to 1.04) for total CHD, 0.44 (0.24 to 0.81) for definite MI and 1.14 (0.36 to 3.63) for SCD. The reduced risk was primarily observed for nonfatal coronary events (HR=0.43 [0.23 to 0.81]), but not for fatal coronary events (HR=1.08 [0.42 to 2.76]). Authors conclude that compared with a modest fish intake of once a week or 20g per day, a higher intake was associated with substantially reduced risk of CHD, primarily non-fatal cardiac events, among middle-aged persons.

Järvinen et al, 2006 (positive quality) prospective cohort study, investigating the relationship between consumption of fish and long-chain n-3 FA and the risk of coronary heart mortality in 2,775 men and 2,445 women aged from 30 to 79 years who were free of CHD and had participated in a health examination survey from 1967 to 1972. In total, 335 men and 163 women died of CHD during a follow-up until the end of 1992. A dietary history interview method provided data on habitual consumption of fish

135

and other foods over the preceding year at baseline. The intakes of long-chain n-3 FAs were calculated on the basis of food composition values of Finnish foods. Higher consumption of fish was associated with a decreased risk of CHD among women, whereas NS association was seen among men. The RR between the highest and the lowest quintile for fish consumption was 1.00 (95% CI 0.70, 1.43; P for trend 0.83) for men and 0.59 (95 % CI 0.36, 0.99; P for trend 0.02) for women in analysis adjusting for age, energy intake, geographical area, body mass index (BMI), serum cholesterol, BP, smoking, occupation and diabetes; however, after adjustment for dietary confounders this association was no longer significant. The intake of n-3 FAs was NS associated with the risk of CHD in either men or women. In conclusion, our results for women are in line with the suggested protective effect of fish consumption against CHD but a similar association was not, however, found in men.

Lankinen et al, 2009 (neutral quality) RCT, examined how dietary fatty fish or lean fish affect serum lipidemic profiles in subjects with CHD. The study included 33 subjects with MI or unstable ischemic attack in an eight-week parallel controlled intervention trial. The subjects were randomized to either fatty fish (N=11), lean fish (N=12) or control (N=10) groups. Subjects in the fish groups had four fish meals per week and subjects in the control group consumed lean beef, pork and chicken. Lipidomics analyses were performed using ultra performance liquid chromatography coupled to electrospray ionization mass spectrometry and gas chromatography. Multiple bioactive lipid species, including ceramides, lysophosphatidylcholines and diacylglycerols, decreased significantly in the fatty fish group, whereas in the lean fish group cholesterol esters and specific long-chain triacylglycerol increased significantly. The authors conclude that the eight-week consumption of fatty fish decreased lipids which are potential mediators of lipid-induced insulin resistance and inflammation and may be related to the protective effects of fatty fish on the progression of atherosclerosis or insulin resistance.

Lara et al, 2007 (positive quality) RCT, examined the effect of fish intake in 48 non-obese, healthy adults aged 20-55, who consumed 125g per day of salmon for a four-week period followed by a four-week period with no-fish (41 completers). Blood pressure, anthropometric, body composition, blood lipids and dietary information were assessed. Compared to no-fish, eating salmon significantly decreased systolic BP (SBP) diastolic BP (DBP) and mean arterial pressure (MAP) by 4%, TG by 15%, LDL-C by 7% and significantly increased HDL-C by 5% (P<0.05). The authors state that the changes in BP and lipids alone with salmon intake predict approximately 25% reduction in CHD risk based on the PROCAM risk calculator. The authors conclude that daily consumption of salmon improves risk predictors of CHD in non-obese subjects.

Lemaitre et al, 2003 (positive quality) case-control study, (N=179 pairs) nested in the Cardiovascular Health Study cohort, found free-living older adults (over age 65), after adjustment for risk factors, a higher concentration of combined plasma DHA and EPA was associated with a lower risk of fatal ischemic heart disease (IHD). Based on data from 54 cases of fatal IHD, 125 cases of non-fatal MI and 179 matched controls, for a one-SD increase in plasma phospholipids DHA and EPA, there was an associated 70% lower risk of fatal IHD (OR: 0.30; 95% CI: 0.12, 0.76; P=0.01) and for a one-SD

136

increase in ALA, there was an associated 50% lower risk of fatal IHD (OR: 0.48; 95% CI: 0.24, 0.96; P=0.04). The first controlled for coronary risk factors, updated prior report of CVD, alcohol intake, aspirin, vitamin supplements and postmenopausal hormone use. The second included the covariates in model one and additionally controlled for intake of other fatty acids that resulted in a change of more than 10% in the parameter estimate for ALA intake.

Lindqvist et al, 2009 (neutral quality) This was an RCT to evaluate the effects of a diet rich in specified, pre-made herring meals on CVD risk factors in healthy over weight men. The design was a cross-over intervention on the effect of a six week herring diet compared with a reference diet on CVD risk factors. Thirty-five healthy, but overweight, men (mean BMI 28.3kg/m2) were randomized to a six-week herring diet (150g baked herring fillets per day, five days per week) or a reference diet (150g baked lean pork and chicken fillets per day, five days per week) with a 12-week washout period. Plasma TC, triacylglycerols (TAG), HDL, HDL2, HDL3, LDL, C-reactive protein (CRP), IL-6, IL-18, intercellular adhesion molecule-1, oxidized LDL, oxygen radical absorbance capacity using perchloric acid (ORACPCA), whole-blood fatty acids, bleeding time and BP were measured at the beginning and end of each dietary period. High-density lipoprotein was significantly higher after the herring diet period compared with after the reference diet period: 1.04 vs. 0.99mmol per L. Triacylglycerols decreased after both diets, with NS difference between the two diets. ORACPCA values did not indicate lower concentrations of non-protein plasma antioxidants and oxidized LDL was not higher after the herring diet than after the reference diet. The authors conclude that a six week herring-rich diet significantly raised HDL. No adverse effects on in vivo oxidation or serum antioxidants were found after herring intake.

Mozaffarian et al, 2005 (positive quality), prospective study, examined the interplay between intermediate and long chain n-3 FA and n-6 FA intake on the incidence of CHD in 45,722 male health professionals. Dietary n-3 FA and n-6 FA intake were assessed by administration of a self-administered validated FFQ at multiple time points and development of CHD assessed by a biennial health history questionnaire. Over 14 years of follow-up, participants experienced 218 sudden deaths, 1,521 non-fatal MIs, and 2,306 total CHD events (combined sudden death, other CHD deaths and non-fatal MI). Relative risk of non-fatal MI was lower in those with high intakes of ALA (RR=0.58; 95% CI 0.23 to 0.75). This effect of ALA on total CHD and non-fatal MI occurred mostly among men with low intakes of EPA plus DHA. Long-chain and intermediate-chain n-3 FA intakes were associated with lower CHD risk, without modification by n-6 FA intake when adjusted for age; BMI; smoking; physical activity; history of diabetes, hypertension (HTN) or hypercholesterolemia; aspirin use; alcohol use; and intake of protein, SFA, dietary fiber, MUFA, TFA, total calories and ALA. High intake of EPA plus DHA (more than 250mg per day or equivalent to one or two fish meals per week) compared to low intake (less than 250mg per day) was associated with a 35% lower risk of sudden death (RR=0.65; 95% CI; 0.47 to 0.88). High intake of EPA plus DHA was associated with reduced sudden death regardless of ALA level.

Mozaffarian et al, 2004 (positive quality) This was a prospective cohort study of 4,815 adults at least 65 years old, with dietary intake assessed at baseline in 1989 and 1990.

137

Consumption of tuna and other broiled or baked fish correlated with plasma phospholipids long-chain n-3 FAs, whereas consumption of fried fish or fish sandwiches (fish burgers) did not. Atrial fibrillation (AF) incidence was prospectively ascertained on the basis of hospital discharge records and annual electrocardiograms. During 12-year follow-up, 980 cases of incident AF were diagnosed. In multivariate analyses, consumption of tuna or other broiled or baked fish was inversely associated with incidence of AF, with 28% lower risk with intake one to four times per week (HR=0.72, 95% CI=0.58 to 0.91, P=0.005), and 31% lower risk with intake at least five times per week (HR=0.69, 95% CI=0.52 to 0.91, P=0.008), compared with less than one time per month (P trend=0.004). Results were not different after adjustment for preceding MI or congestive heart failure (CHF). In similar analyses, fried fish/fish sandwich consumption was not associated with lower risk of AF. The authors conclude that among elderly adults, consumption of tuna or other broiled or baked fish, but not fried fish or fish sandwiches, is associated with lower incidence of AF.

Panagiotakos et al, 2007 (neutral quality) This was a prospective cohort study of 542 subjects (men: 234; women: 308), from Cyprus (aged 65 to 100 years). Dietary habits (including fish consumption) were assessed with FFQs. Sixty-one percent of the participants reported that they had consumed fish approximately once a week (mean intake: 1.9±1.2 servings per week) for a mean period of 30 years. After adjusting for confounders, fish intake was inversely associated with SBP (P=0.026), fasting glucose (P<0.001), total serum cholesterol (P=0.012) and TG levels (P=0.024). Multinomial logistic regression revealed that a decrease of 100g per week in fish intake was associated with a 19% (95%CI: 1-41) higher likelihood of having one additional cardiovascular risk factor (i.e., HTN, hypercholesterolemia, diabetes, obesity). The authors conclude that long-term fish intake is associated with reduced levels of the most common CVD risk markers in a cohort of elderly people.

Seierstad et al, 2005 (positive quality) This was a double-blinded RCT. Sixty patients with CHD were randomly allocated to three groups consuming approximately 700g per week for six weeks of differently fed Atlantic salmon: 100% fish oil (FO), 100% rapeseed oil (RO) or 50% of each (FO/RO), resulting in fillets with high, intermediate and low levels of long-chain n-3 PUFA (EPA+DHA). The serum fatty acid profiles of subjects after the intervention reflected those of the corresponding salmon fillets and the respective salmon feeds. Significant differences between the groups were obtained, especially for the levels of total n-3 PUFAs and the n-3/n-6 FA ratio, which were markedly increased in the FO group in contrast to the two other groups (P<0.02 for all). In response to these changes there were significant reductions of serum TG and inflammation markers including vascular cell adhesion molecule-1 and interleukin-6 in subjects receiving the FO diet when compared with the two other groups (P<0.05 for all). The authors conclude that the FA differences in salmon fillets, in particular those very high in EPA+DHA result in favorable changes in subjects with CHD when compared with ingestion of fillets with intermediate and low levels of marine n-3 PUFAs.

Streppel et al, 2008 (neutral quality) This was a prospective cohort study conducted in the Netherlands. The study investigated the relationship between fish consumption or EPA + DHA intake from fish, and (sudden) coronary death (SCD) in the Zutphen

138

Study, a cohort of 1,373 men born between 1900 and 1920, and examined repeatedly between 1960 and 2000. Hazard ratios (HR) were obtained from time-dependent Cox regression models. The associations between long-term fish consumption, EPA+DHA intake, and SCD were stronger than those of recent consumption. Long-term fish consumption was inversely associated (borderline significant) with CHD death; however, the strength of the association decreased from age 50 [HR: 0.32 (95% CI: 0.13-0.80)] until age 80 [HR: 1.34 (0.58-3.12)]. For men with a daily EPA+DHA intake from fish below 250mg compared with no intake, CHD death risk was reduced to the same extent as for men with a daily intake above 250mg (P-value for trend=0.27). Long-term fatty-fish consumption lowered the risk of SCD [HR: 0.46 (0.27-0.78)]. The authors concluded that the strength of the association between long-term fish consumption and CHD death decreased with increasing age. Fatty-fish consumption lowered sudden coronary death risk with no clear dose-response relationship between EPA+DHA intake and SCD.

Turunen et al, 2008 (neutral quality) This was a cohort study conducted in Finland, assessed the cause-specific mortality of professional fishermen and their wives. Fish consumption was measured using a self-administered semi-quantitative FFQ, and fasting blood samples were also taken. 4,487 fishermen and their wives were followed from 1980 to 2005 and mortality rates were recorded. The average fish consumption and serum concentrations of fish-derived fatty acids and environmental contaminants were higher among the fishermen and their wives than among the general population from the same region. Fishermen and their wives exhibited a lower mortality for all causes [standard mortality ratio (SMR)=0.78, 95% CI: 0.73-0.82 for fishermen, SMR=0.84, 95% CI: 0.76-0.93 for wives] as well as IHD) SMR=0.73, 95% CI: 0.65-0.81 for fishermen, SMR=0.65, 95% CI=0.50-0.83 for wives) than the general population. Mortality from cerebrovascular diseases and malignant neoplasm was decreased among fishermen (SMR=0.67, 95% CI: 0.52-0.85, SMR=0.90, 95% CI: 0.80-1.01, respectively, for fishermen only), but not their wives.

Virtanen et al, 2009 (positive quality) prospective population-based cohort study, examined the relationship between serum concentrations of long-chain n-3 PUFA, EPA, docosapentaenoic acid (DPA) and DHA, which also serve as a marker of fish or fish oil consumption, and risk of atrial fibrillation (AF) in middle-aged or older men, 42-60 years old and free of AF at baseline (1984-1989) in Eastern Finland. During 17.7 years of follow-up, 240 men from the total cohort of 2,174 men experienced an AF event that required hospitalization. Men in the highest quartile of serum EPA+DPA+DHA had a 35% lower risk of AF compared with men in the lowest quartile. Of the individual fatty acids, only serum DHA was associated with the risk, with a 38% lower risk in the highest quartile. No association with the risk was found with serum intermediate chain-length n-3 PUFA, ALA, not even when the serum EPA+DPA+DHA concentration was low. Authors conclude that long-chain n-3 PUFAs, and especially DHA, may be effective in reducing the risk of AF in men.

Virtanen et al, 2008 (positive quality) prospective cohort study conducted in the US. The study investigated the associations of fish and n-3 fatty acid consumption with risk of total major chronic disease (CVD, cancer, and death) and to determine whether a high n-6 intake modifies the associations. Lifestyle and other risk factors were

139

assessed every two years and diet every four years (using a validated FFQ) in 40,230 US male health professionals aged 40-75 years and free of major chronic disease at baseline in 1986. During 18 years of follow-up, 9,715 major chronic disease events occurred, including 3,639 CVD events, 4,690 cancers and 1,386 deaths from other causes. After multivariable adjustment, neither fish nor dietary n-3 fatty acid consumption was significantly associated with risk of total major chronic disease. Compared with fish consumption of less than one serving per month, intake of one serving per week and of two to four servings per week was associated with a lower risk of total CVD of approximately 15%. The RR in the highest quintile was 0.97 (95% CI: 0.90, 1.04; P for trend=0.37) for major chronic disease, and 0.97 (95% CI: 0.87, 1.09; P for trend=0.93) for CVD after multivariate adjustments. Fish or EPA+DHA consumption and n-6 FA intake were not strongly correlated (r= -0.09 and -0.11, respectively). No significant effect modification by n-6 FA intake was seen (P for interactions>0.10) based on multivariate-adjusted RRs for major chronic disease, total CVD and total cancer according to both fish and n-6 FA intakes. Higher or lower n-6 FA intake did not significantly modify the results (P for interaction>0.10). The authors concluded that modest fish consumption was associated with a lower risk of total CVD, consistent with cardiac mortality benefits and that intake EPA+DHA and fish was not associated with the overall incidence of major chronic disease in generally healthy men.

Yamagishi et al, 2008 (neutral quality) This was a prospective cohort study conducted in a nationwide community-based cohort of 57,972 Japanese men and women who were part of the JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) Study. The study investigated the hypothesis that fish or n-3 PUFA intake is inversely associated with risks of mortality from IHD, cardiac arrest, heart failure, stroke and total CVD. Dietary intakes of fish and n-3 PUFA were determined by FFQ and participants were followed up for 12.7 years. Hazard ratios (HR) and 95% CI were calculated according to quintiles of fish or n-3 PUFA intake. The study documented 419 deaths due to IHD (including 329 MI), 107 due to cardiac arrest, 307 due to heart failure and 972 due to stroke (including 223 intraparenchymal hemorrhages, 153 subarachnoid hemorrhages, and 319 ischemic strokes); there were 2,045 total cardiovascular deaths and 7,008 total deaths. Inverse associations of fish and n-3 PUFA intakes with risks of mortality from heart failure (multivariable HR [95% CI] for highest vs. lowest quintiles=0.76 [0.53 to 1.09] for fish and 0.58 [0.36 to 0.93] for n-3 PUFA) were observed. Associations with IHD or MI were relatively weak and statistically NS after adjustment for potential risk factors. Neither fish nor n-3 PUFA dietary intake was associated with mortality from total stroke, its subtypes or cardiac arrest. For mortality from total CVD, intakes of fish and n-3 PUFA were associated with 18% to 19% lower risk. The authors conclude that an inverse association between fish and n-3 PUFA dietary intakes and cardiovascular mortality, especially for heart failure, suggesting a protective effect of fish intake on CVD.

Overview table

Author, Year, Study Design, Class, Rating	Study Description/ Duration	Study Population/ Location	Intervention Protocol/ Exposure levels	Significant Results	Limitations
Albert CM, Campos H et al, 2002 Study Design: Prospective nested case control Class: C Rating: Neutral quality		Male Physicians' Health Study. Age: 40-84 years old in 1982. Healthy men: N=94 in whom sudden death occurred as first symptom of CVD. N=184 controls matched for age and smoking status Location: United States.	n-3 fatty acids and CVD. Baseline: Questionnaire on health status/CVD risk factors, blood samples. 12 months: Dietary intake of fish ascertained in shortened FFQ. Six months: CVD information updated. One year and annually for 17 years: CVD information updated.	Mean level of total long-chain n-3 FAs significantly ↓ among men who died suddenly than among controls. Baseline blood levels of long-chain n-3 FAs were inversely related to risk of sudden death both before adjustment for age and smoking status and after adjustment.	Analyses on a single base-line measurement and may not accurately reflect levels of long-chain n-3 FAs over long periods. Use of whole blood combines two different pools of long-chain n-3 FAs, the plasma and the stored red-cell pools. Authors tried to control these confounders.

Brouwer IA, Heeringa J et al, 2006 Study Design: Prospective cohort study. Class: B Rating: Positive quality	Mean follow-up: 6.4 years (±1.6 years).	N=5,184 subjects (2,105 men and 3,079 women). Mean age: 67.4±7.7 years. Location: The Netherlands	EPA+DHA and Atrial fibrillation Data on health status, medical history, smoking, BMI and BP obtained at baseline. Dietary assessment was obtained using a self-administered FFQ and interview with a trained dietitian. Outcome measure: Atrial fibrillation.	Intake of EPA+DHA and fish consumption were not associated with a ↓ risk of atrial fibrillation.	None.
Bucher HC, Hengstler P et al 2002 Study Design: Meta-analysis. Class: M Rating: Positive quality		N=7,951 subjects with intake of n-3 PUFA and 7,855 control subjects. 11 RCTs were included in which n-3 PUFA from diet or supplement with placebo in patients with existing CHD as evidenced by previous MI or angina for six months or more. Excluded studies had patients with coronary bypass or transplantation surgery.	Dietary and non-dietary n-3 PUFA and CHD In trials of supplementation with n-3 PUFAs, the dose for EPA varied from 0.3 to 6.0g, whereas the dose for DHA ranged from 0.6 to 3.7g. Mean follow up: 20 months (range six to 46 months).	For non-fatal MI, the risk ratio in two trials of dietary intervention compared with controls was 0.8 (95% CI: 0.5 to 1.2; P=0.16, heterogeneity P=0.01). Among these subjects, the risk ratio was 0.7 (95% CI: 0.6 to 0.8, P<0.001; heterogeneity P>0.20) for fatal MI, 0.7 (95% CI: 0.6 to 0.9, P<0.01; heterogeneity P>0.20) for sudden death (N=5 trials) and 0.8 (95% CI: 0.7 to 0.9, P<0.001; heterogeneity P>0.20) for overall death. Supplementation with n-3 PUFA ↓ mortality due to MI (RR 0.7 with 95% CI 0.6-0.8; P<0.001) and sudden death (RR 0.7; 95% CI 0.6-0.9; P<0.01) in subjects with CHD.	No description of fish intake was provided.

142

Erkkila AT, Lehto S et al, 2003 Study Design: Cohort Class: B Rating: Positive quality		N=415 free living adults with established CAD. Location: Finland.	Fish intake and CVD events Three categories: No fish (0g per day) Above the median intake (57g per day) Below median intake.	Proportions of ALA, EPA and DHA in serum cholesterylesters associated with a ↓ in the risk of death (P for trend=0.063, 0.056 and 0.026, respectively). Associations of n-3 FA with combined fatal and non-fatal CV events NS. Compared with no consumption, intake of fish tended to be associated with ↓ risk of death [1g-57g per day, RR=0.50 (0.20, 1.28); >57g per day, RR=0.37 (0.14, 1.00); P for trend=0.059].	Type of fish consumed not reported.
Erkkilä, Lichtenstein et al 2004 Study Design: Cohort study. Class: B Rating: Positive quality	Three-year follow-up coronary angiography as part of a RCT of hormone replacement therapy (HRT).	N=229 postmenopausal women with coronary stenosis. 30% or greater of the luminal diameter. Age: ~65 years (~85%). 12% African American. Location: United States.	n-3 intake and progression of CAD FFQ: Frequency of fish consumption by summing the frequency of intake of (per serving): Tuna (84g to 112g) Dark fish (84g to 140g) Other fish (84g to 140g). Tuna and dark fish intake calculated by summing the two intakes alone.	Intake of ≥two servings of fish per week had significantly fewer new lesions (P=0.03). Intake of ≥one serving of tuna or dark fish per week had a smaller Δ in minimum coronary artery. Among diabetics (42%): Δ in minimum coronary artery diameter was significantly smaller in women who eat ≥two servings of fish per week (P=0.02). Mean baseline percentage stenosis also greater, with a smaller Δ (P=<0.001).	Authors note: Three-year follow-up may have been too short to full address association between CAD progression and all n-3 FAs.

143

Erkkilä, Matthan et al, 2006 Study Design: Cohort Class: B Rating: Positive quality	Follow-up: Three years.	N=228 women. Postmenopausal with established CAD. Location: United States.	N-3 intake and CAD progression. Measurements of coronary artery diameter. Percent stenosis and new lesion formation. Assessment of plasma n3 FA: ALA, EPA and DHA with habitual fish intake with no supplements. Median values are: In PL: ALA, 0.17; EPA, 0.49; DHA, 2.50.	↑ levels of DHA in plasma PL and TG significantly associated with the ↓ progression of coronary atherosclerosis.	Authors note: Three-year follow-up may have been too short to fully address association between CAD progression and all n-3 FAs.
Folsom and Demissie, 2004 Study Design: Cohort study. Class: B Rating: Neutral quality		N=41,836 postmenopausal women without initial history of heart disease from Iowa. Location: United States.	Fish or marine omega-3 FA intake and cause of death (CVD or CHD). Baseline dietary intake assessed in 1986 using a FFQ with four fish and seafood questions. Mean respective intakes of EPA, DHA and total marine N-3 FAs were 53mg, 135mg and 188mg per day. The mean intake of ALA was 1.09g per day.	No independent association of fish intake with CVD, CHD or stroke mortality.	None.

Frost L and Vestergaard P, 2005 Study Design: Retrospective cohort study Class: B Rating: Positive quality	Mean follow-up: 5.7 years.	N=47,949 (22,528 men; 25,421 women). Mean age: 56 years 374 men and 182 women had incident of atrial fibrillation or flutter. Location: Denmark.	Marine n-3 FA and atrial fibrillation Subjects completed a FFQ and a questionnaire about fish consumption and 3,818 subjects completed a 24-hour recall. Mean consumption of marine n-3 FA in the top quintile was >1g per day in men and women. Correlation coefficient between reported dietary intake and relative fat tissue composition of EPA and DHA was 0.47 and 0.41, respectively.	During a follow-up of 5.7 years (mean) atrial fibrillation or flutter had developed in 556 subjects Consumption of n-3 FAs from fish was not associated with a reduction in risk of these events.	None.

| He K, Song Y et al, 2004

Study Design: Meta-analysis or Systematic Review

Class: M

Rating:

Positive quality | Follow-up: 6 to 30 years (11.8 years average). | N=222,364 participants (only males in eight cohorts).

Range (N)=852-84,688 participants.

13 cohorts from 11 independent studies:

United States: Six

Europe: Six

China: One. | Fish intake and CHD.

Self-administered FFQ.

Amount of fish intake=frequency of intake (servings per day) x portion size (g per serving)

Five categories of fish intake intervals:

Never or

One to three times per month

One time per week

Two to four times per week

≥ five times per week.

Five studies provided data on non-fatal MI. | Fish intake one time per week: Significantly ↓ CHD mortality rates (pooled multivariate RR, 0.85; 95% CI, 0.76 to 0.96) vs. Never consumed fish or ate fish

Fish intake ≥five times per week: Percent CHD mortality by 38% (RR, 0.62; 95% CI, 0.46 to 0.82).

Dose relation: For each 20g per day number in fish intake, the pooled RR estimated to be 0.93 (95% CI, 0.87 to 0.99; P for trend=0.03.

Non-fatal MI: Pooled RR across five categories of fish intake: 1.0; 0.88 (95% CI, 0.70 to 1.10); 0.95 (95% CI, 0.75 to 1.22); 0.86 (95% CI, 0.67 to 1.09) and 0.79 (95% CI, 0.64 to 0.99; P for trend=0.40). | Dietary assessment, number of exposure categories and the reference group varied across individual studies

Results likely affected by misclassification of fish intake |

Iso H, Kobayashi M et al, 2006 Study Design: Prospective cohort study Class: B Rating: Positive quality	Follow-up: 11 years.	N=41,578 (19,985 men and 21,593 women) free from CHD. Age: 40-52 years. Location: Japan.	↑ intake of fish and n-3 FA and the risk of CHD. Two FFQ assessed fish intake; how often in past month (1990 FFQ) or year (1995 FFQ) subject consumed fish. A portion size for each food was specified in the 1995 FFQ, but not in the 1990 FFQ. Researchers multiply frequency score of each food with each portion size. For intake of n-3 FAs, researchers assigned grams per serving fish in 1990 and specific values for each of the fish and fish products in 1995. Death certificates and medical records reviewed to assess coronary events.	HR (95% CIs) for energy-adjusted intake of n-3 FAs, in the highest (eight times per week, median intake of 180g per day) vs. lowest (one time per week or median intake of 23g per day) quintiles of intake were: 0.61 (0.38 to 0.97) for total CHD, 0.44 (0.26 to 0.75) for MI, 0.33 (0.18 to 0.61) for definite MI, 0.32 (0.17 to 0.61) for non-fatal coronary events, 2.52 (0.75 to 8.48) for SCD and 1.92 (0.79 to 4.66) for fatal coronary events. When adjusted for age, gender, smoking, alcohol intake, BMI, histories of HTN and DM, medication use for hypercholesterolemia, education level, sports at leisure time, quintiles of dietary intake of fruits, vegetables, SFA, MUFA, n-6 PUFA, cholesterol, total energy and Public Health Clinic.	Participants who had a ↑ intake of fish and n-3 PUFA were at lower risk of CHD because of other health habits and behaviors. Measurement errors in assessing nutrient intake were inevitable. Since the baseline FFQ underestimated fish intake by one third, whereas the five-year follow-up questionnaire did so only by 16% in men and 1% in women.

147

Jarvinen R, Knekt P et al, 2006 Study Design: Prospective Cohort Study Class: B Rating: Positive quality		N=2,775 men; 2,445 women; free from CHD. Age: 30-79 years. Location: Finland.	Consumption of fish and long-chain n-3 FA and coronary heart mortality. Dietary history interview method provided data on consumption of fish and other foods over the preceding year at baseline. Intakes of long-chain n-3 FA were calculated on the basis of food composition values of Finnish foods.	↑ consumption of fish associated with ↓ risk of CHD among women. NS association was seen among men. RR between highest and lowest quintile for fish consumption was 1.00 (95 % CI 0.70, 1.43; P for trend 0.83) for men and 0.59 (95 % CI 0.36, 0.99; P for trend 0.02) for women. Analysis adjusted for age, energy, geographical area, BMI, serum cholesterol, BP, smoking, occupation and diabetes. However, after adjustment for dietary confounders this association was NS. Intake of n-3 FAs NS associated with risk of CHD in men or women.	None.
Konig A, Bouzan C et al, 2005 Study Design: Meta-analysis or Systematic Review Class: M Rating: Positive quality	Quantitative risk analysis.	Eight studies identified, including 29 exposure groups. Updated Wang et al, 2002. Results combined into a single data set. Combines the RR values from included studies, weighted by their statistical precision and regressed against fish consumption (servings per week).	Analysis of Fish Consumption and CHD Mortality Fish consumption assessed by conversion of consumption rates expressed as ranges (e.g., one to three fish servings per month) into point estimates expressed as average fish consumption servings per week.	Estimated consumption of small quantities of fish (~one serving per week) was associated with a 17% ↓ in CHD mortality risk; each additional serving per week associated with a further ↓ in risk of 3.9%. Small quantities of fish were associated with a ↓ risk of non-fatal MI by 27%, but additional fish consumption conferred no further benefit.	Detail characteristics of study populations in pooled analysis not provided. Insufficient number of RCT included to make meaningful inferences and not clear how Δ in the type of fish consumed affects risk.

148

Lankinen et al 2009 Study Design: Randomiz-ed Controlled Trial Class: A Rating: Neutral quality	Duration: 8 weeks.	N=33 subjects. Age: <70 years. Subjects with prior MI or unstable ischemic attack. Location: Finland. Trial Registration: ClinicalTrials. gov NCT00720655.	Fatty fish and blood lipids Subjects randomized to fatty fish (N=11), lean fish (N=12) or control (N=10) groups. Subjects in oily fish groups had four fish meals per week [salmon, trout, herring, etc] and in the lean fish group [pike, perch, saithe, cod]; subjects in control group consumed lean beef, pork and chicken. Lipidomic approach: measured multiple bioactive lipids, including ceramides, lyso-phosphatidylcholines and diacylglycerols.	Eight-week consumption of fatty fish ↓ lipids that are mediators of insulin resistance and inflammation. In fatty fish group, ceramides, lysophosphatidylcholines and diacylglycerols were significantly ↓. In lean fish group, cholesterol esters and long chain FA TG ↑ significantly. Concluded that fatty fish may have protective effects on atherosclerosis progression or insulin resistance.	Subjects had to use beta-blockers. Subjects all on statins.

Lara JJ, Economou M et al, 2007 Study Design: Randomized Controlled Trial Class: A Rating: Positive quality	Eight weeks (four plus four weeks with or without fish).	48 non-obese, healthy adults. Age: 20-55 years. Attrition: 8.5%	Fish Intake and lipid profile: Consumed 125g per day of salmon for four weeks. No fish for another four weeks. No washout period.	Compared to no-fish: Salmon intake ↓ SBP, DBP and MAP by 4% (P<0.05) ↓ TG by 15% (P<0.05) ↓ LDL-C by 7% (P<0.05) ↑ HDL-C by 5% (P<0.05).	None.
Lemaitre RN, King IB et al, 2003 Study Design: Prospective nested case-control Class: C Rating: Positive quality		N=54 cases of fatal IHD; N=125 cases of non-fatal MI and 179 matched controls of free-living adults. Recruited from CV health Study Cohort (N=5,201), non-institutionalized; 1989. 687 additional African Americans. Age: >65 years. Location: United States.	Plasma EPA+DHA and IHD Case-control study nested in a CV health study; No intervention. Plasma phospholipids concentration of DHA, EPA and ALA taken two years before the event were used as a biomarker for intake. Fish oil supplement users excluded from study.	Traditional IHD more prevalent in cases than in controls. Participants who experienced an incident fatal IHD event had significantly ↓ baseline plasma PL concentrations of DHA and EPA than did matched controls (P=0.02). ↑ concentration of combined DHA and EPA was associated with a ↓ risk of fatal IHD (OR: 0.30 (95% CI: 0.12, 0.76; P=0.01). No association with non-fatal MI.	Dietary intake data not reported.

Lindqvist et al 2009 Study Design: Randomized Crossover Trial Class: A Rating: Neutral quality		N=35 healthy, but overweight men. Mean BMI: 28.3kg/m^2.	Subjects randomized to a six-week herring diet (150g baked herring fillets per day, five days per week) or reference diet (150g baked lean pork and chicken fillets per day, five days per week) with a 12-week washout period.	HDL was significantly ↑ with herring diet compared with reference diet: 1.04 vs. 0.99mmol per L. TAG ↓ after both diets, with NS difference between the two diets. ORACPCA values did not indicate ↓ concentrations of non-protein plasma antioxidants and oxidized LDL was not ↑ after the herring diet than after the reference diet.	None.
Mozaffarian 2008 Study Design: Systematic Review Class: M Rating: Positive quality	Pooled analysis of RCTs and prospective cohort studies.	Four RCTs: 2,033 English men with prior MI 11,323 Italian subjects with recent MI 3,114 Welsh men with chronic angina 18,645 Japanese men and women with hypercholesterolemia. 15 prospective cohorts examined association between fish or n-3 FA intake and CHD death.	RCTs: Two servings per week oily fish or fish oil from one to 3g per day. Prospective cohorts: One to two oily fish servings per week or ~250-500mg EPA+DHA.	RCTs and prospective cohort studies provide concordant evidence that modest consumption of fish or fish oil (one to two servings per week oily fish or ~250mg per day EPA+DHA) substantially ↓ risk of CHD death and SCD. Pooled analysis of RCTs and prospective cohort studies shows the magnitude and dose-response of the effect: 36% ↓ risk of CHD death comparing zero and 250mg per day EPA+DHA consumption (P<0.001). Little additional benefit with higher fish intake.	None.

Mozaffarian D, Ascherio A et al, 2005 Study Design: Prospective 14-year follow-up study of dietary n-3 and n-6 intake assessed by administration of a self-administer-ed validated FFQ at multiple time points and develop-ment of CHD assessed by biennial health history questionnaire. Class: B Rating: Positive quality	Prospective 14-year follow-up study of dietary n-3 and n-6 intake assessed by administration of a self-FFQ.	N=45,722 male health professionals from the US. Location: United States.	Dietary n-3 and n-6 intake: Assessed by administration of a self-administered validated FFQ at baseline and every four years. Development of CHD assessed by biennial health history questionnaire.	↑ intake of EPA+DHA intake (>100mg per day) compared to ↓ intake (<100mg per day): Associated with a 35% ↓ risk of sudden death (HR=0.65; 95% CI=0.47 to 0.88) ↑ intake of EPA+DHA is associated with ↓ sudden death regardless of ALA level.	None.

Mozaffarian D, Psaty BM et al, 2004 Study Design: Prospective, population-based cohort study. Class: B Rating: Positive quality	Follow up: 12-years.	N=4,815 adults. Age: ±65 years. Dietary intake assessed 1989 and 1990.	Consumption of tuna and other broiled or baked fish correlated with plasma phospholipid long-chain n-3 FAs, whereas consumption of fried fish or fish sandwiches (fish burgers) did not. Atrial fibrillation (AF) incidence prospectively ascertained on basis of hospital discharge records and annual electro-cardiograms. During 12-year follow-up, 980 cases of incident AF were diagnosed.	In multivariate analyses, consumption of tuna or other broiled or baked fish was inversely associated with incidence of AF, with 28% ↓ risk with intake one to four times per week (HR=0.72, 95% CI=0.58 to 0.91, P=0.005) and 31% ↓ risk with intake±5 times per week (HR=0.69, 95% CI=0.52 to 0.91, P=0.008) compared with <one time per month (P trend=0.004). Results not different after adjustment for preceding MI or CHF. Fried fish or fish sandwich consumption was not associated with lower risk of AF.	

Mozaffarian D, Rimm EB 2006 Study Design: Meta-analysis or Systematic Review Class: M Rating: Positive quality	Risk/Benefit analysis including pooled and meta-analysis.	Relationship between intake of fish and RR of CHD death in pooled analysis of prospective cohort RCTs evaluated non-parametrically using restricted cubic splines and adjusted for each within-study relationship.	RCTs: Two servings per week oily fish or fish oil from one to 3g per day. Prospective cohorts: One to two oily fish servings per week or ~250-500mg EPA+DHA.	Modest consumption of fish ↓ RR of CHD death and SCD by ≥25%. Higher intakes do not substantially further ↓ CHD mortality. This threshold effect explains findings among Japanese populations among whom additional n-3 PUFA intake results in little further ↓ in CHD death, as most of the population is above the threshold for maximum mortality benefits. At typical dietary intakes, anti-arrhythmic effects predominate, reducing risk of SCD and CHD death within weeks.	No detail provided on study populations in pooled analysis.

Panagiotakos et al 2007 Study Design: Prospective Study Class: B Rating: Positive quality		N=542 (men 234; women 308). 79% participation rate. Age: 76+7 years (range 65-100 years). Location: Cyprus.	Fish intake and lipid profile, BP and blood glucose. Fish consumption was assessed by FFQs. Zero: None or very rarely (<four units per month). One: Rare (<four units or 150g per week) Two: Moderate (Four to 12 units or 150 to 300g per week) Three: Frequent (>12 units or >300g per week) Duration (in years) of eating fish. Mediterranean diet score. Physical activity measured.	90% reported consuming fish at least once per week, had the same fish habits for the past 30 years and types consumed mainly included small, lean fishes such as sardine, tope, anchovy, etc. After adjusting for confounders, fish intake inversely associated with SBP (P=0.026), fasting glucose (P<0.001), TC (P=0.012) and TG levels (P=0.024). Multinomial logistic regression revealed a ↓ of 100g per week in fish intake associated with a 19% (95% CI: one to 41) ↑ likelihood of having one additional cardiovascular risk factor (i.e., HTN, hypercholesterolemia, diabetes, obesity).	None.

Seierstad et al 2005 Study Design: Randomized controlled trial Class: A Rating: Positive quality	6-week feeding period. 4 week run-in period.	58 adults with CHD (50 mails, 8 females). Age: 46-75 years. Attrition: 3.33%. Location: Norway.	*Fish Intake + n-3 FA* Consumed 700g per week of Atlantic salmon fillets for a 6-weeks in the following assigned three groups of n-3 PUFAs: Differently fed Atlantic salmon (700g per week), including: (1) 100% fish oil (2) 50% fish oil/50% rapeseed oil (3) 100% rapeseed oil. Before and after analyses: Serum FA profile; serum lipoproteins; markers of vascular inflammation.	Compared to fish and other n-3 FA: Salmon ↓ SBP, DBP and MAP by 4% (P<0.05) Total n-3 PUFAs and n-3/n-6 FA ratio, markedly ↑ in the 100% FO group (p=0.02) compared to all. Significant ↓ in serum TG and of VCAM-1 and IL-6 in subjects receiving 100% fish oil diet compared (P<0.05). Serum FA profiles of subjects after intervention mirrored those of the corresponding salmon fillets and respective salmon feeds. HDL-C significantly higher (p<0.042) at 6 weeks compared to baseline only in FO group. Serum TC were ↓ in all groups, significantly (P<0.028) only in the FO/RO group.	Anthropometric: Groups 1 and 3 differed in BMI (P=0.014).

| Streppel et al 2008

Study Design: Longitudinal Cohort Study

Class: B

Rating:

Positive quality | Zutphen Study, cohort of men born between 1900 and 1920.

Examined repeatedly between 1960 and 2000.

Follow-up: 40 years. | N=1,373 men, born between 1900 and 1920; 348 men diet of CHD (66 died of SCD=19%).

Mean survival age: 77 years.

Location: The Netherlands. | Long-term EPA+DHA intake from fish and SCD.

Men examined repeatedly between 1960 and 2000.

Habitual food consumption collected by a Dutch adaptation of the cross-check dietary history method.

Provides usual food intake pattern, six to 12 months preceding the interview.

Interviews conducted by experienced dietitians.

Up to seven repeated measures of fish consumption and EPA+DHA intake from fish collected over 40 years of follow-up.

Total fish intake divided into fatty (salmon, mackerel, herring, eel and sardines) and lean (codfish, plaice and pollock) fish.

Daily EPA+DHA intake calculated using Dutch food composition tables. | 1,373 men participating in the Zutphen Study died from CHD (66 SCD=19% of all CHD deaths)
Long-term fish consumer: 27% ↓ CHD death. Recent fish consumption not associated with CHD death.

Inversely associated with CHD risk (P=0.16). The strength of the association ↓ from age 50 (HR=0.32, 95% CI: 0.13-0.80) until age 80 (HR=1.34, 95% CI: 0.58-3.12).

Men with a daily EPA+DHA intake from fish <250mg compared with no intake, CHD death risk was ↓ to the same extent as for men with a daily intake >250mg (P for trend=0.27).

Long-term fatty-fish intake (average 7g per day) ↓ SCD risk by 54%; no associations found with total and lean fish intake.

Long-term fatty-fish intake ↓ the risk of CI: 0.27-0.78). | The number of SCD (66 events) observed in the Zutphen Study may have been too small to detect a dose-response relation for EPA+DHA intake.

Could not account for Δ in product composition, due to lack of time-specific food composition tables needed to calculate nutrient intake over a longer period of time.

Not possible to consider different methods of fish preparation like frying fat, which can affect a fish meal's FA composition and TFA which may ↑ cardiovascular risk.

Information on fish consumption was missing for men newly included in the study in 1985 in the period 1960-1970 and had to be estimated. |
|---|---|---|---|---|---|

Turunen et al 2008 Study Design: Cohort Study Class: B Rating: Neutral quality	Follow-up: 1980-2005.	N=4,487 fishermen and their wives. Location: Finland.	Fish intake and CVD mortality Fish consumption measured using self-administered semi-quantitative FFQ. Mortality rates recorded.	Fish consumption, serum long chain n-3 FA and environmental contaminants ↑ in the fishermen and wives than the general population. Fishermen and wives had ↓ mortality for all causes [standard mortality ratio (SMR)=0.78, 95% CI: 0.73-0.82 for fishermen, SMR=0.84, 95% CI: 0.76-0.93 for wives]. Fishermen and wives had ↓ mortality for IHD (SMR=0.73, 95% CI: 0.65-0.81 for fishermen, SMR=0.65, 95% CI=0.50-0.83 for wives). Mortality from cerebrovascular diseases and malignant neoplasm was ↓ among fishermen (SMR=0.67, 95% CI: 0.52-0.85, SMR=0.90, 95% CI: 0.80-1.01, respectively, for fishermen only), but not their wives.	None.

Virtanen et al 2008 Study Design: Prospective Cohort Study Class: B Rating: Positive quality	Health Professionals Follow-up Study Follow-up: 18 years.	Health professionals aged 40-75 years. Location: United States.	Fish and n-3 fatty acid intake and total major chronic disease. Multiple validated FFQ over time used to compute cumulative averages of dietary intake. Fish intake based on 131-item food FFQ. Intake and amounts of four different seafood items: Canned tuna fish, dark meat fish (mackerel, salmon, sardines, bluefish and swordfish), other fish (not specified), and shrimp, lobster or scallops as a main dish. Fish intake in categories: five servings per week.	During 18 years of follow-up, 9715 (24.1%) major chronic disease events occurred: 3,639 CVD events 4,690 cancers 1,386 deaths other causes. Baseline, mean (±SD) EPA+DHA intake was 0.3±0.2g per day and fish intake per day was 0.3±0.3g per day. Men with ↓ fish intake more likely to be physically active, have hypercholesterolemia and HTN, use aspirin and MVN supplements, drink more alcohol and smoke. Men with ↑ fish intake consumption: Have ↑ intakes of energy, PRO, EPA+DHA, PUFA, fiber, fruit, and vegetables and ↓ intakes of SFA, MUFA and TFA. Age-adjusted analyses: Fish intake inversely associated with risk of major chronic disease (P for trend=0.02). Multivariable adjustment Neither fish nor dietary n-3 FA intake was significantly associated with risk of total major chronic disease. Compared with fish consumption of Weekly intake of one serving and of two to four servings associated with a ↓ risk of total CVD by ~15%. Fish intake >five servings per week not associated with ↓ risk. ↑ or ↓ n-6 FA intake: NS modification of the results (P for interaction more than 0.10).	Study population consisted of generally healthy men, the results may not be generalizable to women or to other populations. The databases used may not reflect the rapid Δ in the use of different types of vegetable oils in the food supply. Did not evaluate the potential effects of fish or EPA+DHA intake on other specific disease outcomes, such as heart failure, atrial fibrillation, that may be improved by fish intake.

159

Virtanen JK, Mursu J et al, 2009 Study Design: Prospective Cohort Study Class: B Rating: Positive quality	Kuopio Ischemic Heart Disease Risk Factor Study. Average follow-up: 17.7 years.	N=2,682 men, free of AF at baseline (1984-1989). Younger and healthier; ↓ prevalence of CVD, DM, HTN and current smoking and ↑ education and income. Age: 42-60 years. Location: Finland.	Fish, EPA and DHA intake and atrial fibrillation (AF). Dietary intake of foods and nutrients assessed at the time of blood sampling by use of four-day food record. Serum esterified and non-esterified fatty acids were determined by gas chromate-graphy. All AF events that occurred between study entry and December 31, 2007 were included. Data on events obtained by record linkage from the national computerized Hospital registry. Cox proportional hazards regression models were used to estimate Hazard ratios (HRs).	During 17.7 years of follow-up, 240 AF events. After adjustment for age and exam year, men in the highest serum EPA+DPA+DHA quartile had a 35% (95% CI 7% to 54%; P for trend=0.07) reduction in the HR of AF, compared with the lowest quartile (absolute risk in the reference group 13.4%; absolute risk ↓ 4.7%). Individual exam showed only DHA associated with ↓ risk; with a multivariable-adjusted HR of 38% ↓ (95% CI 8% to 58%; P for trend=0.02) in the highest quartile (reference group absolute risk 13.3%; absolute risk ↓ 5.1%). Mean serum ALA concentration=0.74% (SD 0.24%) of all FAs. No evidence that serum ALA was associated with the risk of AF. Multivariable-adjusted HRs (95% CI) in the serum ALA quartiles were one (ref), 1.26 (0.84 to 1.89), 0.74 (0.46 to 1.20), and 1.14 (0.72 to 1.79; P for trend -0.98), respectively. No association found when EPA+DPA+DHA concenration was ↓ (P for interaction=0.10), nor was there any evidence for interaction with EPA, DPA or DHA when evaluated individually (P for interactions=0.10).	Sources of n-3 FA not documented. Participants in the study (KIHDRFS) did not visit study site regularly, thus only AF events documented on discharge records are included and findings of the present study may apply only to hospitalized AF, which may have weakened the assoc. Serum DHA might only be a marker of a likelihood of being hospital-ized for any cause. However, this is not supported by the lack of association between serum DHA and hospitalization for any cause during the follow-up in the post hoc analysis (HR in the highest vs. lowest serum DHA quartile 1.02, 95% CI 0.72 to 1.46, P for trend=0.76). Fish intake may have Δ during the follow-up. Use of a single measurement of serum long-chain n-3 PUFAs at baseline would underestimate its association with risk of AF. Thus the null results with ALA, a large proportion of which is oxidized, such that serum levels would depend more on recent intake. Observed association may be related to other factors associated with high serum long-chain n-3 PUFA concentration, such as in those consuming fish. No follow-up information about obesity, associated with arrhythmias. Several associations were evaluated, it is possible that the significant association found between serum DHA and risk of AF may have been due to type I error.

Wang et al 2006 Study Design: Systematic Review Class: M Rating: Positive quality		N=46 articles identified: 14 RCTs 25 prospective cohort Seven case control. Secondary prevention trials: 11 RCTs: Total subjects: N=19,403 One prospective cohort study: Total N=415. Primary prevention trials: One RCT 25 cohort (N>340,000) Seven case control. Three estimated ALA intake levels. Location: United States, Europe, China, Japan.	Fish, Fish oil and ALA intake and CVD. Comprehensive search 1966 to July 2005. Primary-prevention studies: Most estimated fish or fish-oil intakes.	After controlling for age, randomization to aspirin and β-carotene and coronary risk factors: Dietary fish intake was associated with a ↓ risk of sudden death, with an apparent threshold effect at a consumption level of one fish meal per week (P for trend=0.03).	No meta-analysis was conducted.

| Whelton et al 2004

Study Design: Meta-analysis

Class: M

Rating: Positive quality | Meta-analysis of observational studies to determine if fish consumption is associated with ↓ fatal and total CHD. | Total of 19 observational studies were included: 14 cohorts and five case-controls.

Used Random Effects model. | Comparison between regular fish consumption and little to no fish consumption groups. | Fish consumption vs. little to no fish consumption was associated with an RR of 0.83 (95% CI 0.76 to 0.90; p <0.005) for fatal CHD RR=0.86 (95% CI 0.81 to 0.92; P<0.005) for total CHD. | No detail provided on study populations. |
|---|---|---|---|---|---|

Yamagishi et al 2008 Study Design: Prospective Cohort Study Class: B Rating: Positive quaity	Average follow-up: 12.7 years.	N=57,972 men and women. Age: 40-79 years Location: Japan.	Fish or n-3 intake and risk of mortality from CVD Self administered questionnaires: life-styles and medical histories of previous CVD or cancer. FFQ33 foods, including four fish: Fresh fish, kamaboko (steamed fish paste), dried or salted fish and deep-fried foods or tempura. Five choices for each item: Rarely; one to two days a month; one to two days a week; three to four days a week; and almost every day. Choices converted to scores of 0, 0.05 (1.5 of 30), 0.214 (1.5 of 7), 0.5 (3.5 of 7) and one, respectively. Quintiles of fish intake, media intake (g per day): Men: 20, 33, 45, 62 and 86 Women: 21, 33, 46, 62 and 85.	Number of events during 735,905 person-years of follow up: Documented 7,008 total death: 419 due to IHD (including 329 MI) 107 due to cardiac arrest 307 due to heart failure 972 due to stroke (including 223 intraparenchymal hemorrhages, 153 subarachnoid hemorrhages, and 319 ischemic strokes) 2,045 total cardiovascular deaths. Inverse associations of fish and omega-3 PUFA intakes with risks of mortality from heart failure (multivariable HR for highest vs. lowest quintiles=0.76 [95% CI: 0.53 to 1.09] for fish and 0.58 [95% CI: 0.36 to 0.93] for n-3. Associations with IHD or MI relatively weak after adjustment for potential risk factors FA. Intakes of fish and n-3 PUFA were associated with 18% to 19%↓ risk of mortality from total CVD.	Type of fish consumed not reported. Underestimated number of times fish was eaten for people in the upper quadrants; potential for under reporting (e.g., authors reported fish intake of 49.5g per day, which is lower than the National Nutrition Survey in 1990 (95.3g per day). High number of exclusion (39%) incomplete dietary information; excluded subjects were older and more likely to be men than women compared with included subjects. Healthy lifestyles or socioeconomic status are possible residual confounding by other factors.

Research recommendations

Investigate further the opposing interactions of high EPA and DHA vs. high methyl mercury, especially in dietary patterns in which these consumptions coexist.

Search plan and results

Inclusion Criteria

Subjects/Population

- *Age*: Adults (19 years +)
- *Setting*: Any, except ICU, Burn Unit or Emergency Care, US and International
- *Health Status*:
  - o Healthy
  - o Dyslipidemia, Hyperlipidemia* or Hypercholesterolemia, CHD, CVD

*According to ATP III (2004), hyperlipidemia is defined as a TC greater than 200 and/or LDL-C greater than 130 without CVD; LDL-C greater than 100 with CVD; and LDL-C greater than 70 for patients with a CHD event, stroke, TIA, peripheral vascular disease AND ONE OF THE FOLLOWING:1) acute coronary syndrome, 2) type 2 diabetes mellitus, 3) metabolic syndrome, 4) a SINGLE POORLY CONTROLLED risk factor, 5) 3 risk factors irrespective of how well controlled.

Note: in ATP III, diabetes is regarded as a CHD risk equivalent.

Nutrition Related Problem/Condition:

- Cardiac Events: MI, arythmia, angioplasty, stent, death

Search Criteria

- *Study design preferences*: Meta-analysis and Systematic reviews, RCT or Clinical Controlled Studies, Large nonrandomized observational studies, Prospective Cohort, large case-control studies, Cross Sectional Studies (last resort), Feeding period must be greater than 4 weeks.
- *Size of study groups*: Sample size must equal 10 subjects for each study group. For example, this would include 10 subjects in the intervention group and 10 subjects in the control or comparison group.Study dropout rate: Less than 20%; preference for smaller dropout rates
- *Year Range*: March 2004 –Dec 2007 (covered by ADA) July 2007 to Aug 2009 (covered by USDA)
- *Authorship*: If an author is included on more than one Review Article or primary research article that is similar in content, the most recent review or article will be accepted and earlier versions will be rejected. If an author is included on more than one Review Article or primary research article and the content is different, then both reviews may be accepted.
- *Languages*: Limited to articles in English
- Other: Article must be published in peer-reviewed journal

Exclusion Criteria

Subjects/Population

- *Age*: Infants, Children and adolescents <19 years
- *Setting*: ICU, Burn Unit, Emergency Care
- *Health Status*: Presence of diabetes, TC less than or equal to 200 and/or LDL-C less than or equal to 130. Also, see inclusion criteria
- *Nutrition Related Problem/Condition*: (i.e., eating disorders)
- *Cardiac Events*: stroke, triglyceride, lipids, inflammatory markers
- *Size of study groups*: Sample sizes < 10
- *Study Designs*: Small case studies, Cross sectional Studies
- Feeding periods <4 weeks.
- Experimental fat must be from natural sources
- *Study Dropout rate*: Dropout rate in a study is 20% or greater
- *Year Range*: Prior to July 2007 included in ADA analysis
- *Authorship*: Studies by same author similar in content
- *Languages*: Articles not in English
- *Other*: Animal studies; Abstracts or presentations

Search Terms and Electronic Databases Used:

PubMed

(arrhythmia* OR "Arrhythmias, Cardiac"[Mesh] OR "Arrhythmia, Sinus"[Mesh]) AND ("Fatty Acids, Omega-3"[Mesh] OR "Docosahexaenoic Acids"[mh] OR "alpha-Linolenic Acid"[Mesh] OR "SR 3 linolenic acid "[Substance Name] OR "8, 11, 14-Eicosatrienoic Acid"[Mesh] OR "Fish Oils"[Mesh] OR "Plant Oils")

("Fatty Acids, Omega-3"[Mesh] OR "Fish Oils"[Mesh] OR "alpha-Linolenic Acid"[Mesh] OR "SR 3 linolenic acid "[Substance Name] OR "8, 11, 14-Eicosatrienoic Acid"[Mesh]) AND ("Death, Sudden, Cardiac"[Mesh OR "Biological Markers"[Mesh] OR "Coronary Disease"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Cardiovascular Diseases"[Mesh])

("Fatty Acids, Omega-3"[Mesh] OR "Docosahexaenoic Acids" "alpha-Linolenic Acid"[Mesh] OR "SR 3 linolenic acid "[Substance Name] OR "8, 11, 14-Eicosatrienoic Acid"[Mesh]) AND ("Fish Oils"[Mesh] OR "Plant Oils") AND ("Biological Markers"[Mesh] OR "Coronary Disease"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Cardiovascular Diseases"[Mesh:NoExp] OR "blood pressure"[mh] OR hypertension[mh])

Date Searched: 08/21/2009

Summary of Articles Identified to Review

- Total hits from all electronic database searches: 371
- Total articles identified to review from electronic databases: 60
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 21
- Number of Review Articles Identified: 4
- Total Number of Articles Identified: 22
- Number of Articles Reviewed but Excluded: 32

Included articles (References)

165

What is the relationship between consumption of seafood n-3 fatty acids and risk of cardiovascular disease?

1. 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):2705-11. PubMed PMID: 15184295.

2. 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):335-46.PMID: 16242600

3. Mozaffarian D. Fish and n-3 fatty acids for the prevention of fatal coronary heart disease and sudden cardiac death.Am J Clin Nutr. 2008 Jun;87(6):1991S-6S.PMID: 18541600

4. Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. JAMA. 2006 Oct 18;296(15):1885-99. Review. Erratum in: JAMA. 2007 Feb 14;297(6):590. PMID: 17047219

5. Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B, Jordan HS, Lau J. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. Am J Clin Nutr. 2006 Jul;84(1):5-17. PMID: 16825676.

6. Whelton SP, He J, Whelton PK, Muntner P. Meta-analysis of observational studies on fish intake and coronary heart disease.Am J Cardiol. 2004 May 1;93(9):1119-23.PMID: 15110203

7. Lindqvist HM, Langkilde AM, Undeland I, Sandberg AS. Herring (Clupea harengus) intake influences lipoproteins but not inflammatory and oxidation markers in overweight men. Br J Nutr. 2009 Feb;101(3):383-90. Epub 2008 Jul 18.PMID: 18634706

8. Lankinen M, Schwab U, Erkkilä A, Seppänen-Laakso T, Hannila ML, Mussalo H, Lehto S, Uusitupa M, Gylling H, Oresic M. Fatty fish intake decreases lipids related to inflammation and insulin signaling--a lipidomics approach.PLoS One. 2009;4(4):e5258. Epub 2009 Apr 23.PMID: 19390588

9. Lara JJ, Economou M, Wallace AM, Rumley A, Lowe G, Slater C, Caslake M, Sattar N, Lean ME. Benefits of salmon eating on traditional and novel vascular risk factors in young, non-obese healthy subjects.Atherosclerosis. 2007 Jul;193(1):213-21. Epub 2006 Oct 27.PMID: 17069820

10. 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):52-9.PMID: 15638820

11. Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, Ma J. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. N Engl J Med. 2002; 346 (15): 1,113-1,118.

12. Brouwer IA, Heeringa J, Geleijnse JM, Zock PL, Witteman JC. Intake of very long-chain n-3 fatty acids from fish and incidence of atrial fibrillation. The Rotterdam Study.Am Heart J. 2006 Apr;151(4):857-62.PMID: 16569549 (ADA)

166

13. Folsom AR, Demissie Z. <u>Fish intake, marine omega-3 fatty acids, and mortality in a cohort of postmenopausal women.</u> Am J Epidemiol. 2004 Nov 15;160(10):1005-10. PMID: 15522857 (ADA)

14. Frost L, Vestergaard P. <u>n-3 Fatty acids consumed from fish and risk of atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study.</u> Am J Clin Nutr. 2005 Jan;81(1):50-4.PMID: 15640459 (ADA)

15. Iso H, Kobayashi M, Ishihara J, Sasaki S, Okada K, Kita Y, Kokubo Y, Tsugane S; JPHC Study Group. <u>Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based (JPHC) Study Cohort I.</u> Circulation. 2006 Jan 17;113(2):195-202. Epub 2006 Jan 9.PMID: 16401768 (ADA)

16. Järvinen R, Knekt P, Rissanen H, Reunanen A. <u>Intake of fish and long-chain n-3 fatty acids and the risk of coronary heart mortality in men and women.</u> Br J Nutr. 2006 Apr;95(4):824-9.PMID: 16571163 (ADA).

17. Mozaffarian D, Ascherio A, Hu FB, Stampfer MJ, Willett WC, Siscovick DS, Rimm EB. <u>Interplay between</u> different polyunsaturated fatty acids and risk of <u>coronary heart disease in men.</u> Circulation. 2005 Jan 18;111(2):157-64. Epub 2005 Jan 3. PMID: 15630029 (ADA).

18. Mozaffarian D, Psaty BM, Rimm EB, Lemaitre RN, Burke GL, Lyles MF, Lefkowitz D, Siscovick DS. <u>Fish intake and risk of incident atrial fibrillation.</u> Circulation. 2004 Jul 27;110(4):368-73. Epub 2004 Jul 19.PMID: 15262826 (ADA).

19. Panagiotakos DB, Zeimbekis A, Boutziouka V, Economou M, Kourlaba G, Toutouzas P, Polychronopoulos E. <u>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).</u> Med Sci Monit. 2007 Jul;13(7):CR307-12. PubMed PMID: 17599024.

20. Streppel MT, Ocké MC, Boshuizen HC, Kok FJ, Kromhout D. <u>Long-term fish consumption and n-3 fatty acid intake in relation to (sudden) coronary heart disease death: the Zutphen study.</u> Eur Heart J. 2008 Aug;29(16):2024-30. Epub 2008 Jul 18. PMID: 18641046.

21. Turunen AW, Verkasalo PK, Kiviranta H, Pukkala E, Jula A, Männistö S, Räsänen R, Marniemi J, Vartiainen T. <u>Mortality in a cohort with high fish consumption.</u> Int J Epidemiol. 2008 Oct;37(5):1008-17. Epub 2008 Jun 25. PubMed PMID: 18579573.

22. Virtanen JK, Mursu J, Voutilainen S, Tuomainen TP. <u>Serum long-chain n-3 polyunsaturated fatty acids and risk of hospital diagnosis of atrial fibrillation in men.</u> Circulation. 2009 Dec 8;120(23):2315-21. Epub 2009 Nov 23.PMID: 19933935

23. Virtanen JK, Mozaffarian D, Chiuve SE, Rimm EB. <u>Fish consumption and risk of major chronic disease in men.</u> Am J Clin Nutr. 2008 Dec;88(6):1618-25. PubMed PMID: 19064523; PubMed Central PMCID: PMC2613199.

24. Yamagishi K, Iso H, Date C, Fukui M, Wakai K, Kikuchi S, Inaba Y, Tanabe N, Tamakoshi A; Japan Collaborative Cohort Study for Evaluation of Cancer Risk Study Group. <u>Fish, omega-3 polyunsaturated fatty acids, and mortality from cardiovascular diseases in a nationwide community-based cohort of Japanese men and women the JACC (Japan Collaborative Cohort Study for Evaluation of</u>

167

Cancer Risk) Study. J Am Coll Cardiol. 2008 Sep 16;52(12):988-96. PMID: 18786479.

25. Bucher HC, Hengstler P, Schindler C, Meier G. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. Am J Med. 2002 Mar;112(4):298-304. PMID: 11893369 (ADA).

26. Erkkila AT, Lehto S, Pyorala K, and Uusitupa MIJ. n-3 Fatty acids and 5-y risks of death and cardiovascular disease events in patients with coronary artery disease. Am J Clin Nutr 2003 July; 78(1):65-71. PMID: 12816772 (ADA).

27. 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):626-32.PMID: 15321802 (ADA).

28. Erkkilä AT, Matthan NR, Herrington DM, Lichtenstein AH.Higher plasma docosahexaenoic acid is associated with reduced progression of coronary atherosclerosis in women with CAD.J Lipid Res. 2006 Dec;47(12):2814-9. Epub 2006 Sep 18. PMID: 16983146 (ADA).

Excluded Articles

Articles	Reasons for Exclusion
Aarsetoey H, Pönitz V, Grundt H, Staines H, Harris WS, Nilsen DW.(n-3) Fatty acid content of red blood cells does not predict risk of future cardiovascular events following an acute coronary syndrome.J Nutr. 2009 Mar;139(3):507-13. Epub 2009 Jan 21. PMID: 19158216.	Measures omega-3 index of admitted ACS patients No intervention. Cross sectional Study.
Astorg P, Bertrais S, Laporte F, Arnault N, Estaquio C, Galan P, Favier A, Hercberg S.Plasma n-6 and n-3 polyunsaturated fatty acids as biomarkers of their dietary intakes: a cross-sectional study within a cohort of middle-aged French men and women.Eur J Clin Nutr. 2008 Oct;62(10):1155-61. Epub 2007 Jul 11. PMID: 17622261.	Cross Sectional Study. Uses plasma fatty acid concentrations as marker to dietary n-3 fatty acids determined by FFQ.
Barceló-Coblijn G, Murphy EJ, Othman R, Moghadasian MH, Kashour T, Friel JK.Flaxseed oil and fish-oil capsule consumption alters human red blood cell n-3 fatty acid composition: a multiple-dosing trial comparing 2 sources of n-3 fatty acid.Am J Clin Nutr. 2008 Sep;88 (3):801-9. PMID: 18779299.	Intervention provided as capsules
Baylin A, Kabagambe EK, Ascherio A, Spiegelman D, Campos H.Adipose tissue alpha-linolenic acid and nonfatal acute myocardial infarction in Costa Rica.Circulation. 2003 Apr; 107(12): 1,586-1,591.	No dietary intervention.

168

Beydoun MA, Kaufman JS, Sloane PD, Heiss G, Ibrahim J.<u>n-3 Fatty acids, hypertension and risk of cognitive decline among older adults in the Atherosclerosis Risk in Communities (ARIC) study.</u> Public Health Nutr. 2008 Jan;11(1):17-29. Epub 2007 Jul 12. PMID: 17625029.	Outcomes measured involved inhibition of cognitive decline in hypertension
Bloedon LT, Balikai S, Chittams J, Cunnane SC, Berlin JA, Rader DJ, Szapary PO.<u>Flaxseed and cardiovascular risk factors: results from a double blind, randomized, controlled clinical trial.</u>J Am Coll Nutr. 2008 Feb;27(1):65-74. PMID: 18460483.	Intervention provided as capsules
Cazzola R, Russo-Volpe S, Miles EA, Rees D, Banerjee T, Roynette CE, Wells SJ, Goua M, Wahle KW, Calder PC, Cestaro B.<u>Age- and dose-dependent effects of an eicosapentaenoic acid-rich oil on cardiovascular risk factors in healthy male subjects.</u>Atherosclerosis. 2007 Jul;193(1):159-67. Epub 2006 Aug 1. PMID: 16879829	Intervention provided as capsules
Chilton FH, Rudel LL, Parks JS, Arm JP, Seeds MC.<u>Mechanisms by which botanical lipids affect inflammatory disorders.</u>Am J Clin Nutr. 2008 Feb;87(2):498S-503S. Review. PMID: 18258646.	Narrative review
Chung H, Nettleton JA, Lemaitre RN, Barr RG, Tsai MY, Tracy RP, Siscovick DS.<u>Frequency and type of seafood consumed influence plasma (n-3) fatty acid concentrations.</u>J Nutr. 2008 Dec;138(12):2422-7. PMID: 19022967.	Studies frequency, processing and type of fish consumption on plasma fatty acids.
Chrysohoou C, Panagiotakos DB, Pitsavos C, Skoumas J, Krinos X, Chloptsios Y, Nikolaou V, Stefanadis C.<u>Long-term fish consumption is associated with protection against arrhythmia in healthy persons in a Mediterranean region--the ATTICA study.</u>Am J Clin Nutr. 2007 May;85(5):1385-91.PMID: 17490977.	Intermediate outcome, not CVD event s
Damsgaard CT, Frøkiaer H, Andersen AD, Lauritzen L.<u>Fish oil in combination with high or low intakes of linoleic acid lowers plasma triacylglycerols but does not affect other cardiovascular risk markers in healthy men.</u>J Nutr. 2008 Jun;138(6):1061	Intermediate outcomes, not CVD event
Damsgaard CT, Frøkiaer H, Lauritzen L.<u>The effects of fish oil and high or low linoleic acid intake on fatty acid composition of human peripheral blood mononuclear cells.</u>Br J Nutr. 2008 Jan;99(1):147-54. Epub 2007 Jul 30. PMID: 17663804.	Reported outcomes limited to FA composition of mononuclear cells

169

DeGiorgio CM, Miller P, Meymandi S, Gornbein JA.n-3 fatty acids (fish oil) for epilepsy, cardiac risk factors, and risk of SUDEP: clues from a pilot, double-blind, exploratory study.Epilepsy Behav. 2008 Nov;13(4):681-4. Epub 2008 Sep 7. PMID: 18721899.	Intervention provided as capsules
Delgado-Lista J, Lopez-Miranda J, Cortés B, Perez-Martinez P, Lozano A, Gomez-Luna R, Gomez P, Gomez MJ, Criado J, Fuentes F, Perez-Jimenez F.Chronic dietary fat intake modifies the postprandial response of hemostatic markers to a single fatty test meal. Am J Clin Nutr. 2008 Feb;87(2):317-22. PMID: 18258620	Intervention does not meet criteria. Single test meal.
De Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean Diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction, final report of the Lyon Diet Heart Study. Circulation. 1999; 99: 779-785. PubMed ID**:**9989963.	Intervention provided as dietary advice
Din JN, Harding SA, Valerio CJ, Sarma J, Lyall K, Riemersma RA, Newby DE, Flapan AD.Dietary intervention with oil rich fish reduces platelet-monocyte aggregation in man.Atherosclerosis. 2008 Mar;197(1):290-6. Epub 2007 Jun 18. PMID: 17575985.	Intermediate outcome not CVD event s
Djoussé L, Rautaharju PM, Hopkins PN, Whitsel EA, Arnett DK, Eckfeldt JH, Province MA, Ellison RC; Investigators of the NHLBI Family Heart Study.Dietary linolenic acid and adjusted QT and JT intervals in the National Heart, Lung, and Blood Institute Family Heart study. J Am Coll Cardiol. 2005 May 17;45(10):1716-22. PMID: 15893192.	Intermediate outcome Qtrr measurments, not CVD events
Dodin S, Cunnane SC, Mâsse B, Lemay A, Jacques H, Asselin G, Tremblay-Mercier J, Marc I, Lamarche B, Légaré F, Forest JC.Flaxseed on cardiovascular disease markers in healthy menopausal women: a randomized, double-blind, placebo-controlled trial. Nutrition. 2008 Jan;24(1):23-30. Epub 2007 Nov 5. PMID: 17981439.	Intermediate outcomes, not CVD event

170

Ebbesson SO, Roman MJ, Devereux RB, Kaufman D, Fabsitz RR, Maccluer JW, Dyke B, Laston S, Wenger CR, Comuzzie AG, Romenesko T, Ebbesson LO, Nobmann ED, Howard BV.Consumption of omega-3 fatty acids is not associated with a reduction in carotid atherosclerosis: the Genetics of Coronary Artery Disease in Alaska Natives study.Atherosclerosis. 2008 Aug;199(2):346-53. Epub 2007 Dec 4. PMID: 18054937.	Intermediate outcome not CVD event s
Egert S, Kannenberg F, Somoza V, Erbersdobler HF, Wahrburg U. Dietary alpha-linolenic acid, EPA, and DHA have differential effects on LDL fatty acid composition but similar effects on serum lipid profiles in normolipidemic humans.J Nutr. 2009 May;139(5):861-8. Epub 2009 Mar 4. PMID: 19261730	Intermediate outcome Qtrr measurments, not CVD events
Fekete K, Marosvölgyi T, Jakobik V, Decsi T.Methods of assessment of n-3 long-chain polyunsaturated fatty acid status in humans: a systematic review.Am J Clin Nutr. 2009 Jun;89(6):2070S-2084S. Epub 2009 May 6.PMID: 19420097.	Study involves Markers ofn–3 LCPUFA. Does not address question
Freund-Levi Y, Hjorth E, Lindberg C, Cederholm T, Faxen-Irving G, Vedin I, Palmblad J, Wahlund LO, Schultzberg M, Basun H, Eriksdotter Jönhagen M.Effects of omega-3 fatty acids on inflammatory markers in cerebrospinal fluid and plasma in Alzheimer's disease: the OmegAD study.Dement Geriatr Cogn Disord. 2009;27(5):481-90. Epub 2009 May 12. PMID: 19439966..	Intervention provided as capsules
Fuentes F, López-Miranda J, Pérez-Martínez P, Jiménez Y, Marín C, Gómez P, Fernández JM, Caballero J, Delgado-Lista J, Pérez-Jiménez F.Chronic effects of a high-fat diet enriched with virgin olive oil and a low-fat diet enriched with alpha-linolenic acid on postprandial endothelial function in healthy men.Br J Nutr. 2008 Jul;100(1):159-65. Epub 2008 Feb 14. PMID: 18275619.	Intermediate outcomes, not CVD event
Galli C, Risé P.Fish consumption, omega 3 fatty acids and cardiovascular disease. The science and the clinical trials.Nutr Health. 2009;20(1):11-20. PMID: 19326716.	Narrative Review

Gissi-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G.Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial.Lancet. 2008 Oct 4;372(9645):1223-30. Epub 2008 Aug 29. PMID: 18757090..	Subjects had chronic heart failure.
Goyens PL, Mensink RP. Effects of alpha-linolenic acid versus those of EPA/DHA on cardiovascular risk markers in healthy elderly subjects. Eur J Clin Nutr. 2006 Aug;60(8):978-84. Epub 2006 Feb 15. PMID: 16482073	Intermediate outcome Qtrr measurments, not CVD events
Guebre-Egziabher F, Rabasa-Lhoret R, Bonnet F, Bastard JP, Desage M, Skilton MR, Vidal H, Laville M.Nutritional intervention to reduce the n-6/n-3 fatty acid ratio increases adiponectin concentration and fatty acid oxidation in healthy subjects.Eur J Clin Nutr. 2008 Nov;62(11):1287-93. Epub 2007 Aug 15. PMID: 17700650.	Study involves n-3/n-6 ratio. Not variables that address the question.
Harris WS.The omega-3 index as a risk factor for coronary heart disease.Am J Clin Nutr. 2008 Jun;87(6):1997S-2002S. PMID: 18541601.	Narrative review
Hartweg J, Perera R, Montori V, Dinneen S, Neil HA, Farmer A.Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus.Cochrane Database Syst Rev. 2008 Jan 23;(1):CD003205. Review. PMID: 18254017	Reviewed outcomes did not distinguish supplements from dietary
He K, Liu K, Daviglus ML, Jenny NS, Mayer-Davis E, Jiang R, Steffen L, Siscovick D, Tsai M, Herrington D.Associations of dietary long-chain n-3 polyunsaturated fatty acids and fish with biomarkers of inflammation and endothelial activation (from the Multi-Ethnic Study of Atherosclerosis [MESA]).Am J Cardiol. 2009 May 1;103(9):1238-43. Epub 2009 Mar 4. PMID: 19406265.	Intermediate outcome not CVD events
He K, Liu K, Daviglus ML, Mayer-Davis E, Jenny NS, Jiang R, Ouyang P, Steffen LM, Siscovick D, Wu C, Barr RG, Tsai M, Burke GL.Intakes of long-chain n-3 polyunsaturated fatty acids and fish in relation to measurements of subclinical atherosclerosis.Am J Clin Nutr. 2008 Oct;88(4):1111-8. PMID: 18842801.	Intermediate outcome not CVD events

172

Hoyos C, Almqvist C, Garden F, Xuan W, Oddy WH, Marks GB, Webb KL.Effect of omega 3 and omega 6 fatty acid intakes from diet and supplements on plasma fatty acid levels in the first 3 years of life.Asia Pac J Clin Nutr. 2008;17(4):552-7. PMID: 19114389.	Reported outcomes limited to FA composition of plasma based on diet

CHAPTER 8. SPECIFIC FATS, FATTY ACIDS, AND CHOLESTEROL – POLYUNSATURATED FATTY ACIDS AND HEALTH OUTCOMES

WHAT IS THE EFFECT OF DIETARY PUFA INTAKE ON HEALTH AND INTERMEDIATE HEALTH OUTCOMES?

Conclusion statement

Strong and consistent evidence indicates that dietary n-6 polyunsaturated fatty acids (PUFA) are associated with improved blood lipids related to cardiovascular disease (CVD), in particular when PUFA is a replacement for dietary saturated fatty acids (SFA) or trans fatty acids. Evidence shows that energy replacement of SFA with PUFA decreases total cholesterol, LDL cholesterol and triglycerides, as well as numerous markers of inflammation. Polunsaturated fatty acid intake significantly decreases risk of CVD and has also been shown to decrease the risk of type 2 diabetes.

Grade

Strong

Evidence summary overview

Ten studies published since 2004 were reviewed to determine the effect of polyunsaturated fatty acids (PUFA) on health outcomes. These studies were conducted in the US, Canada, Europe and Australia. These included one methodologically strong pooled analysis of 11 prospective cohort studies (Jakobsen, 2009); five randomized controlled trials (RCTs), including two methodologically strong studies (Thijssen and Mensink, 2005; Thijssen, 2005) and three methodologically neutral studies (Liou, 2007; St-Onge, 2007; Zhao, 2004) ranging in size from 23 to 45 subjects; and four prospective cohort studies ranging in size from 1,551 to 78,778 subjects. Of these cohort studies, three were methodologically strong (Laaksonen, 2005; Mozaffarian, 2005; Oh, 2005) and one was methodologically neutral (Hodge, 2007). Randomized controlled trials that investigated the effects on serum lipid and lipoprotein levels of replacing saturated fat (SFA) with PUFA showed that PUFA improved serum lipid profiles (St. Onge, 2007; Zhao, 2004). Zhao et al (2004) found that high linoleic acid (LA) or high alpha-linolenic acid (ALA) diets, compared to the average American diet (AAD), decreased serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) similarly. St-Onge et al (2007) reported that replacing snacks high in SFA or trans fats (TFA) with snacks high in PUFA, reduced LDL-C concentrations, TC and TG. However, varying LA, with SFA held constant, showed that high or low LA did not influence TC, LDL-C or high-density lipoprotein cholesterol (HDL-C) levels (Liou, 2007). Comparing individual fatty acids, diets providing 7% of energy from LA, stearic acid or oleic acid showed no significant (NS) differences in serum LDL-C or HDL-C (Thijssen and Mensink, 2005).

Randomized controlled trials that investigated the effects on serum lipid and lipoprotein levels of replacing SFA with PUFA showed that PUFA improved serum lipid profiles (St. Onge, 2007; Zhao, 2004). Zhao et al (2004) found that high LA or high ALA diets compared to the AAD decreased serum TC, LDL-C and TG similarly. St-Onge et al

174

(2007) reported that replacing snacks high in SFA or TFA with snacks high in PUFA reduced LDL-C concentrations, TC and TG. However, varying LA, with SFA held constant, showed that high or low LA did not influence TC, LDL-C or HDL-C levels (Liou, 2007). Comparing individual fatty acids, diets providing 7% of energy from linoleic acid, stearic acid or oleic acid showed no significant (NS) differences in serum LDL-C or HDL-C (Thijssen and Mensink, 2005).

Studies that examined markers of inflammation or measures of oxidative stress showed PUFA improved inflammatory marker levels. Zhao et al (2004) reported that while both high ALA and LA diets decreased C-reactive protein (CRP), the finding was significant only for ALA. Additionally, while both high-PUFA diets similarly decreased intercellular cell adhesion molecule-1 (ICAM-1) vs. the AAD, the ALA diet decreased vascular cell adhesion molecule-1 (VCAM-1) and E-selectin more than the LA diet. The comparison of high vs. low LA, with SFA constant, showed no difference in CRP, interleukin-6 or platelet aggregation (Liou, 2007). Comparison of LA, stearic acid or oleic acid showed that, in men, platelet aggregation time was favorably prolonged with consumption of LA vs. stearic acid, but was not different compared to oleic acid (Thijssen, 2005).

Four prospective cohort studies showed that higher PUFA intake was associated with lower risk of coronary heart disease (CHD) and total mortality (Hodge, 2007; Laaksonen, 2005; Mozaffarian, 2005; Oh, 2005). A pooled analysis of 11 prospective cohort studies showed that risk of coronary events and coronary death was lowest with 5% energy substitution of SFA with PUFA>MUFA>carbohydrate (CHO) (Jakobsen, 2009).

The Nutrition Evidence Library (NEL) review for this question included a prospective study with nested case-cohort analyses on the effects of a dietary PUFA on type 2 diabetes (T2D) risk. The authors reported an inverse association between dietary LA and T2D, compared to a positive association for stearic acid and total SFA (Hodge, 2007). In addition, the review for this question is supplemented by evidence from question one on SFA and T2D risk that reviewed the literature from 2000. This, and the fact that blood lipids are intermediate markers of risk for both CVD and T2D, further supports the association between PUFA intake and decreased T2D risk.

Evidence summary paragraphs

Hodge et al, 2007 (neutral quality) This was a prospective study with nested case-cohort analyses conducted in Australia. The study investigated the associations of fatty acids in plasma and diet with diabetes incidence in the "Melbourne Collaborative Cohort" study of 3,737 adults aged 36 to 72 years old. Fatty acid intake and percent plasma phospholipid fatty acids (PL-FA) were measured at baseline, and diabetes incidence was assessed by self-report four years later. Logistic regression excluding (model 1) and including (model 2) body mass index (BMI) and waist-hip ratio (WHR) was used to calculate odds ratios (ORs) for plasma PL and dietary fatty acids. A positive association was seen for plasma phospholipid and diabetes for stearic acid [OR model 1, highest vs. lowest quintile: 4.14 (95% CI: 2.65, 6.49), P<0.0001] and total SFA [OR model 1: 3.76 (2.43, 5.81), P<0.0001], whereas an inverse association was seen for LA [OR model 1: 0.22 (0.14, 0.36), P<0.0001].

175

Dietary LA [OR model 1: 1.77 (1.19, 2.64), P=0.002], palmitic [OR model 1: 1.65 (1.12, 2.43), P=0.012], and stearic [OR model 1: 1.46 (1.00, 2.14), P=0.030] acids were positively associated with diabetes incidence before adjustment for body size. Within each quintile of LA intake, cases had lower baseline plasma phospholipid LA proportions than did controls. Authors concluded that dietary SFA intake is inversely associated with diabetes risk.

Jakobsen et al, 2009 (positive quality) This pooled analysis evaluated the associations between energy intake from MUFA, PUFA and CHO replacing energy from SFA to prevent CHD. Data from 11 American and European cohort studies involving 344,696 persons were pooled and analyzed for incident of CHD as outcome measures. During four- to 10-year follow-ups, there were 5,249 coronary events and 2,155 coronary deaths. The analysis found that for every 5% lower energy intake from SFAs and a concomitant higher energy intake from PUFAs or CHO, there was a significant inverse association between these energy sources and risk of coronary events, with hazard ratios (HR) as follows for PUFAs: HR, 0.87 (95% CI: 0.77, 0.97); HR for coronary deaths = +0.74 (95% CI: 0.61, 0.89), and for CHO: HR, 1.07 (95% CI: 1.01, 1.14); HR for coronary deaths = 0.96 (95% CI: 0.82, 1.13). Monounsaturated fat intake was not associated with CHD, nor was there modification by sex or age. The authors conclude that replacing SFAs with PUFAs rather than MUFAs or CHO prevents CHD over a wide range of intakes. The country and demographics of subjects not described.

Laaksonen et al, 2005 (positive quality) This was a prospective cohort study conducted in Finland. The study assessed the association of dietary LA and total PUFA intake with CVD and overall mortality in the Kuopio Ischemic Heart Disease Risk Factor (KIHD) Study, a random age-stratified sample (42, 48, 54 or 60 years old at baseline) of 2,682 men living in eastern Finland baseline between 1984 and 1989. One thousand five hundred fifty one middle-aged men participated in this study. Dietary fat composition was estimated with a four-day food record and serum fatty acid composition. During the 15-year follow-up, 78 men died of CVD and 225 of any cause. Total fat intake was not related to CVD or overall mortality. Men with an energy-adjusted dietary intake of LA [relative risk (RR) 0.39; 95% confidence interval (CI), 0.21 to 0.71] and PUFA (RR, 0.38; 95% CI: 0.20 to 0.70) in the upper third were less likely to die of CVD than men with intake in the lower third after adjustment for age. Multivariate adjustment weakened the association somewhat. Mortality from CVD was also lower for men with proportions of serum esterified LA (RR, 0.42; 95% CI: 0.21 to 0.80) and PUFA (RR, 0.25; 95% CI: 0.12 to 0.50) in the upper vs. lower third, with some attenuation in multivariate analyses. Serum and to a lesser extent dietary LA and PUFA were also inversely associated with overall mortality. Authors concluded that dietary fat quality may be more important than fat quantity in the reduction of cardiovascular mortality in men, dietary PUFA and more specifically LA intake may have a substantial cardio-protective benefit that is also reflected in overall mortality.

Liou et al, 2007 (neutral quality) The study was a randomized crossover feeding trial conducted in Canada. During the intervention, energy intake of ALA was a constant 1% of total energy, while LA intake was modified with low or high LA vegetable oils and fats to achieve an LA:ALA ratio of 4:1 or 10:1. 24 healthy subjects enrolled, mean age

176

27.9±1.1 years and 22 completed the study. Subjects consumed either a high-LA diet (10.5±0.53% of energy as LA, 1.1±0.06% as ALA) or low-LA diet (3.8 ± 0.12% of energy as LA, 1.0±0.05% as ALA) for four weeks each, without a washout period between diets. Prepared foods were provided to subjects. Dietary intakes were estimated using three 24-hour food records, kept at least four days apart, during the two four-week study periods. During the high-LA intake period, plasma phospholipids-LA levels were higher and eicosapentaenoic acid (EPA) levels were lower than during the low-LA intake period (P<0.001). Docosapentaenoic acid (DPA) levels declined over the eight-week period (P<0.001). Linoleic acid was inversely associated with EPA (R=-0.729, P<0.001), but positively associated with ALA:EPA ratio (R=0.432, P<0.001). Linoleic acid intake did not have any influence on ALA, arachidonic acid, DPA, docosahexaenoic acid (DHA) or TC, LDL-Cor HDL-C, CRP or interleukin-6 or platelet aggregation.

Mozaffarian et al, 2005 (positive quality) This was a prospective cohort study conducted in the US. The researchers investigated the association between intermediate and long-chain n-3 PUFA and n-6 PUFA intake on the incidence of CHDin participants of the Health Professionals Follow-up Study. Dietary intake was assessed through FFQ administered at baseline and every four years, over 14 years of follow-up. 45,722 male health professionals (aged 40 to 75 years), free of known CVD at baseline, were included in the analysis. Over 14 years of follow-up, 218 sudden deaths, 1,521 non-fatal myocardial infarctions (MIs) and 2,306 total CHD events (combined sudden death, other CHD death and non-fatal MI) were identified. In multivariate-adjusted analyses, both long-chain and intermediate-chain n-3 PUFA intakes were associated with lower CHD risk, without modification by n-6 PUFA intake; intermediate-chain n-3 PUFAs were associated with CHD risk when n-3 PUFA intake was very low. In men with n-3 PUFA intake less than 100mg per day, each 1gper day of intermediate-chain n-3 PUFA intake was associated with an approximately 50% lower risk of nonfatal MI (HR=0.42, 95% CI: 0.23 to 0.75) and total CHD (HR=0.53, 95% CI: 0.34 to 0.83). Omega-6 PUFA intake was 7.6, 11.2 and 15.9g per day. Each 5g per day n-6 PUFA intake was NS associated with the risk of sudden death (HR=0.82; 95% CI: 0.63 to 1.06), non-fatal MI (HR=1.00; 95% CI: 0.91 to 1.11), or total CHD (HR: -0.96; 95% CI: 0.89 to 1.04).

Oh et al, 2005 (positive quality) This was a prospective cohort study (part of the Nurses' Health Study) conducted in the US. In this study the associations between dietary fat and specific types of fat with risk of CHD was examined among 78,778 US women (aged 30 to 55 years) initially free of CVD and diabetes in 1980. One thousand seven hundred sixty six incident CHD cases (including 1,241 non-fatal MI and 525 CHD deaths) were documented during 20 years of follow-up. From 1980 to 1998, the average intake of total fat decreased from 39.0% to 29.0%, SFA intake decreased from 15.65% to 9.4%, MUFA intake decreased from 16.0% to 11.5% and TFA intake decreased from 2.2% to 1.6%. Polyunsaturated fatty acid intake increased from 5.3% to 5.6%. Polyunsaturated fat intake was inversely associated with CHD risk (multivariate RR for the highest vs. the lowest quintile = 0.75, 95% CI: 0.60, 0.92; P=0.004). Trans-fat intake was associated with an elevated risk of CHD (RR = 1.33, 95% CI: 1.07, 1.66; P=0.01). A similar inverse association was observed between LA intake and risk of CHD; the relative risks for LA were one (referent), 1.02,

177

0.91, 0.87 and 0.77 (95% CI: 0.62, 0.95); P=0.01. The associations between intakes of PUFA and TFA with CHD risk were most evident among women younger than age 65 years (for PUFA, RR=0.66, 95% CI: 0.50, 0.85; P=0.002; for TFA, RR=1.50, 95% CI: 1.13, 2.00; P=0.01). The inverse association between PUFA intake and CHD risk was strongest among women whose BMI was 25kg/m^2 or more. (Note: This study was included in the meta-analysis by Jakobsen et al, 2009).

St. Onge et al 2007 (neutral quality) This was a randomized crossover trial conducted in the US to determine whether replacing low-fat and high-fat or high-SFA and high-TFA fat snack foods with snacks foods high in PUFA and low in SFA and TFA improves CVD risk factors. The trial consisted of three 25-day controlled feeding periods with snacks, separated by a four- or eight-week washout period, over a period of seven months. Forty-five subjects were enrolled and 33 (seven male, 26 female, mean age 41.8±1.9 years) subjects completed all three phases. Subjects followed the same base diet except for the types of snacks included, either low-fat (30.8% of energy from fat, 5.2% of energy from PUFAs), high-PUFA (36.3% of energy from fat, 9.7% of energy from PUFAs), or high-fat (37.9% of energy from fat, 5.8% of energy from PUFAs). All food was provided to the subjects. All three diets reduced LDL-C and TC concentrations. LDL cholesteroldecreased by 11.8% on low-fat, 12.5% on high-PUFA, compared with 8.8% on high-fat (P=0.03 and P=0.01, respectively), and TC decreased by 10.5% on low-fat, 10.7% on high-PUFA, compared with 7.9% on high fat (P=0.03 and P=0.02, respectively). There were NS effects of the diets on WC, percentage body fat or BP.

Thijssen et al, 2005; Thijssen and Mensink, 2005 (positive quality) This was a randomized multiple crossover study conducted in the Netherlands. The study compared the effects of stearic, oleic and LA on platelet aggregation, coagulation, fibrinolysis and hematological variables in 45 healthy subjects (18 men and 27 women, mean age 51 years, range 28 to 66 years). Subjects consumed three test diets in random order over three five-week periods, and after each intervention period, there was a washout period of at least one week when participants consumed their habitual diets. The test diets contained approximately 35% of energy from fat, and each diet contained 7% of energy as LA, stearic acid or oleic acid. Subjects visited a dietitian at least once every week to receive a new supply of products and to be weighed. Individual allowances were adjusted when subjects' weight differed by 1.5kg from the initial weight during week one or 2kg during the following weeks. The authors found that in men, ex vivo platelet aggregation time as measured by filtragometry (P=0.036 for diet effects) was favorably prolonged during consumption of the PUFA diet compared with the stearic acid diet (P=0.040). No effect was found in women after the high LA diet. The number of erythrocytes was lower and the mean platelet volume of the subjects decreased during consumption of the stearic acid diet by 0.32fL compared with the oleic acid diet (P<0.001) and by 0.35fL compared with the linoleic acid diet (P<0.001). The effects on coagulation and fibrinolytic variables did not differ among the other two fatty acids. Thijssen and Mensink, 2005, found no significant differences in serum LDL-C (P=0.137 for diet effects) or HDL-C (P=0.866). Very-low-density lipoprotein (VLDL) particle sizes and lipoprotein subclass distributions also did not differ significantly between the three diets.

Zhao et al, 2004 (neutral quality) This was a randomized controlled, three-diet, three-period, crossover study conducted in the US. The study evaluated the effects of ALA diet, LA diet compared to the AAD on multiple cardiovascular disease risk factors. Twenty-three hypercholesterolemic subjects (20 males, three females, mean age 49±1.6 years) enrolled and completed the trial. Subjects consumed three diets for six weeks each, separated by a washout period of less than three weeks. The ALA Diet provided 17% energy from PUFA (10.5% LA; 6.5% ALA); the LA Diet provided 16.4% energy from PUFA (12.6% LA; 3.6% ALA); and the AAD provided 8.7% energy from PUFA (7.7% LA; 0.8% ALA). Each diet period was six week with a three-week or less break between diet periods to improve diet compliance. Both high-PUFA diets, including the LA diet, decreased serum TC, LDL-C and TG similarly ($P<0.05$). The ALA Diet decreased CRP (CRP, $P=0.01$), whereas the LA Diet tended to decrease CRP ($P=0.08$). Both high-PUFA diets similarly decreased intercellular cell adhesion molecule-1 vs. AAD (-19.1% by the ALA Diet, $P<0.01$; -11.0% by the LA Diet, $P<0.01$), the ALA Diet decreased vascular cell adhesion molecule-1 (VCAM-1, -15.6% vs. -3.1%, $P<0.01$) and E-selectin (-14.6% vs. -8.1%, $P<0.01$) more than the LA Diet.

179

Overview table

Author, Year, Study Design, Class, Rating	Study Description, Duration	Study Population, Demographics	Intervention	Significant Outcomes	Limitations
Hodge AM, English DR et al, 2007 Study Design: Prospective Cohort Study Class: B Rating: Neutral quality		N=3,737 adults. Age: 36 to 72 years. Location: Australia.	Assessed FA intake and Plasma PL-FA and diabetes. Diabetes incidence assessed by self report four years later. Conducted logistic regression: Excluding (model 1) Including (model 2). BMI and WHR used to calculate OR for plasma PL and dietary FA.	Positive association between plasma PL and diabetes for: Stearic acid [OR model 1 highest vs. lowest quintile: 4.14 (95% CI: 2.65, 6.49), P≤0.0001]. Total SFA [OR model 1: 0.22 (0.14, 0.36), P≤0.0001] An inverse association for: LA [OR model 1: 3.76 (2.43, 5.81) P≤0.0001]. Dietary LA [OR model 1: 1.77 (1.19, 2.64), P≤0.002].	None.

Jakobsen MU, O'Reilly EJ et al, 2009 Study Design: Meta-analysis or Systematic Review Class: M Rating: Positive quality	Review of pooled analysis: Proporttional Hazards Model.	Pooled data from 11 American and European cohort studies published between 1966 and 1993. Four- to 10-year follow-up. Location: International.	Replacement of SFA intake with MUFA, PUFA and CHO. 5,249 coronary events and 2,155 coronary deaths occurred among 344,696 persons (71% women).	Significant inverse association between substitution of SFA with PUFAs and risk of: Coronary events (HR: 0.87, 95% CI: 0.77, 0.97) Coronary deaths (HR: 0.74, 95% CI: 0.61, 0.89). Association between substitution of MUFAs and risk of coronary events (HR: 1.19; 95% CI: 1.00, 1.42), but not risks of coronary deaths. Significant association between substitution of CHO and risk of coronary events (HR: 1.07; 95% CI: 1.01, 1.14) but not risks of coronary deaths. No effect modification by sex or age.	Demo-graphics of US or European populations not described. Type of CHO in the diet not taken into account (i.e., extent of processing, fiber content or glycemic index).

Laaksonen DE, Nyyssonen K et al, 2005 Study Design: Prospective Cohort Study Class: B Rating: Positive quality	15-year follow-up.	Initial N=2,682 men who were 42, 48, 54 or 60 years of age at baseline. Final N=1,551. Mean age = 52 years. Mean BMI = $26.5\pm3.4kg/m^2$. Location: Finland.	Assess the association of dietary fat quantity and quality (LA and ALA) with CVD and overall mortality.	Median follow-up: 14.6 years. 78 men died of CVD; 225 died of any cause. Men with lower dietary intake of LA and ALA had a higher CVD and overall mortality after adjustment for age and year of examination (P<0.01 to P<0.05). Intake of total fat, SFA, MUFA and cholesterol was not associated with CVD. Men with dietary LA acid intake in the upper third were up to 61% less likely to die of CVD than their counterparts whose intake was in the lower third (RR, 0.39; 95% CI: 0.19 to 0.1, P<0.01). ALA acid was NS associated with CVD mortality. Dietary PUFA intake in the upper third associated with up to 62% ↓ risk of CVD mortality (RR, 0.38; 95% CI: 0.20 to 0.70, P<0.001).	None.

182

Liou et al 2007 Study Design: Randomized Crossover Trial Class: A Rating: Neutral quality	Two diets Four-week period. No washout period.	24 healthy men. Age: 27.9±1.1 years. Attrition: 8%. Location: Canada.	Replaced high LA oils with low in LA oils on plasma n-3 FA, while maintaining constant ALA. 10-week study design: Two-week pre-study phase to avoid fish and seafood. Followed by four weeks of: ALA at a constant 1% of energy, with LA:ALA ratio of ~4:1 or 10:1 High LA (10.5±0.53% of energy as LA, 1.1±0.06% as ALA) Low LA (3.8±0.12% of energy as LA, 1.0±0.05% as ALA). Measured plasma lipids and inflammatory biomarkers.	Plasma phospholipid-LA higher and EPA lower with intake of high LA than low LA (P<0.001). DHA ↓ over the eight-week period (P<0.001). LA was inversely associated with EPA (R=-0.729, P<0.001), but positively associated with ALA:EPA (R=0.432, P<0.001). LA intake did not influence ALA, arachidonic acid, DPA, DHA, TC, LDL-C; HDL-C. LA intake did not affect CRP, interleukin-6 or platelet aggregation.	Relatively small sample size; only men studied. No washout period.

183

Mozaffarian D, Ascherio A et al, 2005 Study Design: Prospective 14-year follow-up study of dietary n-3 and n-6 intake assessed by administration of a self-administered validated FFQ at multiple time points and development of CHD assessed by biennial health history questionnaire. Class: B Rating: Positive quality	Health Professionals Follow-up Study. 14-year follow-up.	N=45,722 male health professionals. Age: 40 to 75 years. Free of known CVD at baseline. Location: United States.	Investigated the association between intermediate and long-chain n-3 and n-6 PUFA intake on the incidence of CHD. Self-administered FFQ at baseline and every four years to assess dietary intake. Development of CHD assessed by biennial health history questionnaire.	Both long-chain and intermediate-chain n-3 PUFA intakes were associated with ↓ CHD risk, without modification by n-6 PUFA intake. Intermediate-chain n-3 PUFAs were associated with CHD risk, when n-3 PUFA intake was very ↓. In men with n-3 PUFA intake <100mg per day, each 1g per day of intermediate-chain n-3 PUFA intake associated with an ~50% lower risk of non-fatal MI (HR=0.42, 95% CI: 0.23 to 0.75) and total CHD (HR=0.53, 95% CI: 0.34 to 0.83).	None.

Oh K, Hu FB et al, 2005 Study Design: Prospective Cohort Study Class: B Rating: Positive quality	Nurses' Health Study.	N=78,778 (females, registered nurses). Age: 30 to 55 years in 1976. Average BMI: 24 kg/m^2. Location: United States.	61-item FFQ expanded to 116-items for use in 1984 to 1998. Collected data on dietary intake during the previous year (1980). Follow-up to assess CHD incidence was conducted through June 1, 2000. Endpoint: Non-fatal MI or fatal CHD that occurred after 1980.	1,766 incident CHD cases documented during follow-up (1,241 nonfatal MI; 525 CHD deaths). PUFA intake inversely associated with CHD risk (multivariate RR for the highest vs. lowest quintiles = 0.75, 95% CI: 0.60 to 0.92, P<0.004). TFA intake associated with ↑ risk of CHD (RR=1.33, 95% CI: 1.07 to 1.66, P<0.01). SFA and MUFA not predictors of CHD. Associations of PUFA and TFA were most evident among women <65 years (PUFA: RR=0.66, 95% CI: 0.50 to 0.85, P<0.002; TFA: RR=1.50, 95% CI: 1.13 to 2.00, P<0.01). PUFA intake and CHD risk was strongest among women with a ≥BMI of 25kg/m^2(RR=0.63, 95% CI: 0.47 to 0.84, P<0.002).	None.

St-Onge et al 2007 Study Design: Randomized Crossover Trial Class: A Rating: Neutral quality	Three 25-day feeding periods. Separated by four- or eight-week washout over seven months.	33 subjects (seven male, 26 female). Age: 41.8±1.9 years. Attrition rate: 26%. Location: United States.	Replaced low-fat, high-fat or high-SFA and high-TFA snack foods with high PUFA and low in SFA and TFA snacks. Same base diet except for the types of snacks followed. Low fat: 30.8% of energy from fat, 5.2% of energy from PUFAs. High-PUFA: 36.3% of energy from fat, 9.7% of energy from PUFAs. High-fat: 37.9% of energy from fat, 5.8% of energy from PUFAs. All foods were provided.	All three diets reduced LDL-C and TC concentrations. LDL-C ↓ by 11.8% on low-fat, 12.5% on high-PUFA. Compared with 8.8% on high fat (P=0.03 and P=0.01, respectively). TC ↓ by 0.5% on low-fat,10.7% on high-PUFA. Compared with:7.9% on high fat (P=0.03 and P=0.02, respectively).	High attrition rate. Limited power and ability to generalize results. Compliance not clear. Sponsored by Frito Lay.
Thijssen et al 2005 Study Design: Randomized Crossover Trial Class: A Rating: Positive quality	Three test diets for five weeks. Washout period of at least a week between diets.	N=45 (18 men, 27 women) healthy subjects. BMI: 24.9±2.7kg/m^2. Mean age: 51±10 years (range, 28 to 66 years). Location: Netherlands.	Stearic vs. oleic vs. linoleic acids. Platelet aggregation, coagulation, fibrinolysis and hematological variables. Three test diets consumed in random order over three five-week periods. Test diets: ~35% energy from test fats.	High LA diet: Number of erythrocytes ↓; platelet aggregation favorably prolonged compared to stearic. Stearic acid: ↓ platelet volume compared to LA and OA (P<0.001); no FA effects on coagulation and fibrinolytic variables.	Sponsored by the Dutch Dairy Association.

Thijssen MA and Mensink RP, 2005 Study Design: Randomized Controlled Trial Class: A Rating: Positive quality	Three test diets consumed over three five-week periods. Washout period of at least a week between diets.	N=45 (18 men, 27 females) healthy subjects. BMI: $24.9\pm2.7kg/m^2$. Mean age: 51 ± 10 years. Age range: 28 to 66 years. Location: Netherlands.	Compared effects of stearic acid, oleic acid and linoleic acid on serum lipids and lipoproteins. Three test diets consumed in random order over three five-week periods. Test diets: ~35% energy from test fats.	NS diet-induced Δ in serum lipids and lipoproteins were found. Mean serum LDL (mmol per L): Stearic acid: 3.79+0.9. Oleic acid: 3.71+0.79. LA: 3.65+0.91. (P=0.137). Mean serum HDL (mmol per L): Stearic acid: 1.45+0.43. Oleic acid: 1.46+0.45. LA: 1.46+0.44. (P=0.866). LDL, HDL and VLDL particle sizes and lipoprotein subclass distributions did not differ significantly.	Recruitment methods were not described. Sponsored by the Dutch Dairy Association.

Zhao et al 2004 Study Design: Randomized Crossover Trial Class: A Rating: Neutral quality	Three diets. Six weeks each. Washout period less than three weeks.	N=23 (20 men, three women). Mean age: 49.8±1.6 years. Moderate hypercholesterolemia: Serum TC=5.17 to 6.21mmol per L; LDL-C = 40th to 90th percentile. Body weight (kg) (mean±SEM): All, 86.7+2.8; males, 88.5+2.8; females, 74.9+8.3. BMI (kg/m^2) (mean+SEM): All, 28.1+0.7; men, 28.0+0.7; women: 28.5+2.4. Location: United States	ALA vs. LA vs. Average American Diet (AAD). Two test diets: 35% of energy as fat, 50% as CHO, 15% as PRO and 300mg per day of cholesterol. ALA diet: 17% of energy from PUFA (10.5% LA, 6.5% ALA). LA diet:16.4% of energy from PUFA (12.6% LA, 3.6% ALA). AAD: 8.7% of energy from PUFA (7.7% LA, 0.8% ALA).	Both high-PUFA diets ↓ serum TC, LDL-C and TG similarly (P<0.05). ALA diet significantly ↓ CRP (P<0.01) with greater reduction in intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin.	Small sample size; mostly of men. AAD not well defined. Sponsor: California Walnut Com-mission.

Research recommendations

Determine the benefits and risks of MUFA vs. PUFA as an isocaloric substitute for SFA. Determine the mechanism by which dietary PUFA improve serum lipids, glucose metabolism, insulin levels, HOMA scores, inflammatory markers and blood pressure in both healthy persons and in persons with T2D.

Search plan and results

Inclusion Criteria

Health Outcomes

- Lipid and lipoprotein levels (LDL-C, HDL-C, non-HDL-C)
- Markers of inflammation
- Glucose tolerance, HbA1c values, insulin resistance.

Subjects/Population

- Age: Two years to adult
- Setting: US and international
- Health status: Healthy population and those with elevated chronic risk (CHD or CVD, type 2 diabetes, metabolic syndrome and obesity).

188

Search Criteria

- Study design preferences: RCT or clinical controlled studies, large non-randomized observational studies, meta-analysis and systematic reviews. Feeding period must be greater than four weeks
- Size of study groups: Sample size more than 10 subjects for each study group
- Study dropout rate: Less than 20%; preference for smaller dropout rates
- Year range: 2004 to October 2009
- Languages: Limited to articles in English
- Other: Article must be published in peer-reviewed journal.

Exclusion Criteria

Subjects/Population

- Age: Infants less than two years
- Setting: Inpatients
- Health status: None.

Search Criteria

- Size of study groups: Sample sizes less than 10
- Study designs: Cross-sectional; feeding periods less than four weeks; experimental fat must be from natural source
- Study dropout rate: If the dropout rate in a study is 20% or greater, the study will be rejected
- Year range: Prior to December 2003
- Other: Animal studies, abstracts or presentations.

Search Terms and Electronic Databases Used

PubMed

"Fatty Acids, Omega-6"[Majr:NoExp] AND (triglycerides[majr] OR cholesterol[majr] OR "Diabetes Mellitus, Type 2"[mh] OR Myocardial infarction[majr] OR "Coronary Disease"[majr] "Heart Diseases"[majr] OR "Cardiovascular Diseases"[majr:NoExp]) lim eng/humans

oleic acid[mh] AND (glucose[majr] OR metabolic syndrome* OR insulin sensitivit* OR "Diabetes Mellitus, Type 2"[Mesh] OR hyperglycemia OR lipidemia OR "Body weight"[majr])

((n-6 AND (polyunsaturated OR PUFA*)) OR "Linolenic Acids"[Mesh] OR "Linoleic Acid"[Mesh] OR "Arachidonic Acid"[Mesh]) AND "Diabetes Mellitus, Type 2"[Mesh]

(n-6 AND (polyunsaturated OR PUFA*)) AND (Myocardial infarction[majr] OR "Coronary Disease"[majr] "Heart Diseases"[majr] OR "Cardiovascular Diseases"[majr:NoExp])

((n-6 AND (polyunsaturated OR PUFA*)) OR "Linolenic Acids"[Mesh] OR "Linoleic Acid"[Mesh] OR "Arachidonic Acid"[Mesh]) AND (triglycerides[majr] OR cholesterol[majr])

("Linolenic Acids"[Mesh] OR "Linoleic Acid"[Mesh] OR "Arachidonic Acid"[Mesh] OR

189

oleic acid[mh]) AND (Myocardial infarction[mh] OR "Coronary Disease"[mh] OR "Cerebrovascular Disorders"[mh:NoExp] OR "Stroke"[mh:NoExp] OR "Heart Diseases"[mh] OR "Cardiovascular Diseases"[mh:NoExp]) 68 + 25 = 93 hits (limit to clinical trials, prospective studies, systematic reviews/meta)

oleic acid[mh] AND (Myocardial infarction[mh] OR "Coronary Disease"[majr] OR "Cerebrovascular Disorders"[majr:NoExp] OR "Stroke"[Majr:NoExp] OR "Heart Diseases"[majr] OR "Cardiovascular Diseases"[Majr:NoExp] OR "Triglycerides"[Mesh] OR "Arrhythmias, Cardiac"[Mesh] OR clotting OR Inflammation[mh] OR "Blood Pressure"[mh])

("Linolenic Acids"[Mesh] OR "Linoleic Acid"[Mesh] OR "Arachidonic Acid"[Mesh]) AND (Myocardial infarction[mh] OR "Coronary Disease"[majr] OR "Cerebrovascular Disorders"[majr:NoExp] OR "Stroke"[Majr:NoExp] OR "Heart Diseases"[majr] OR "Cardiovascular Diseases"[Majr:NoExp] OR "Triglycerides"[Mesh] OR "Arrhythmias, Cardiac"[Mesh] OR clotting OR Inflammation[mh] OR "Blood Pressure"[mh])

("Coronary Disease"[Mesh] OR "Cerebrovascular Disorders"[Mesh:NoExp] OR "Stroke"[Mesh:NoExp] OR "Heart Diseases"[Mesh] OR "Cardiovascular Diseases"[Mesh:NoExp] OR "Diabetes Mellitus, Type 2"[Mesh]) AND "Dietary Fats, Unsaturated"[Mesh] AND (Polyunsaturated OR PUFA* OR Monounsaturated OR MUFA*)

"Diabetes Mellitus, Type 2"[Mesh] AND (Polyunsaturated OR PUFA* OR Monounsaturated OR MUFA*)

Date Searched: 06/21/2009 to 08/11/2009, 10/26/2009

Summary of Articles Identified to Review

- Total hits from all electronic database searches: 871
- Total articles identified to review from electronic databases: 65
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 23
- Number of Review Articles Identified: 1
- Total Number of Articles Identified: 24
- Number of Articles Reviewed but Excluded: 41

Included Articles

MUFA and Health Outcomes

What is the effect of dietary intake of MUFA when substituted for SFA on increased risk of CVD and type 2 diabetes (T2D), including intermediate markers such as lipid and lipoprotein levels and inflammation?

Systematic Reviews/Meta-analysis

1. Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, Bälter K, Fraser GE, Goldbourt U, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Ascherio A. Major types of dietary fat and risk of coronary heart disease: A pooled analysis of 11 cohort studies. Am J Clin Nutr. 2009 May; 89(5): 1, 425-1, 432. Epub 2009 Feb 11. PMID: 19211817.

Primary Articles

1. Allman-Farinelli MA, Gomes K, Favaloro EJ, Petocz P. A diet rich in high-oleic-acid sunflower oil favorably alters low-density lipoprotein cholesterol, triglycerides, and factor VII coagulant activity. J Am Diet Assoc. 2005 Jul; 105(7): 1, 071-1, 079. PMID: 15983523.

2. Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER 3rd, Conlin PR, Erlinger TP, Rosner BA, Laranjo NM, Charleston J, McCarron P, Bishop LM; OmniHeart Collaborative Research Group. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: Results of the OmniHeart randomized trial. JAMA. 2005 Nov 16; 294(19): 2, 455-2, 464. PMID: 16287956.

3. Berglund L, Lefevre M, Ginsberg HN, Kris-Etherton PM, Elmer PJ, Stewart PW, Ershow A, Pearson TA, Dennis BH, Roheim PS, Ramakrishnan R, Reed R, Stewart K, Phillips KM; DELTA Investigators. Comparison of monounsaturated fat with carbohydrates as a replacement for saturated fat in subjects with a high metabolic risk profile: Studies in the fasting and postprandial states. Am J Clin Nutr. 2007 Dec; 86(6): 1, 611-1, 620. PMID: 18065577.

4. Binkoski AE, Kris-Etherton PM, Wilson TA, Mountain ML, Nicolosi RJ. Balance of unsaturated fatty acids is important to a cholesterol-lowering diet: Comparison of mid-oleic sunflower oil and olive oil on cardiovascular disease risk factors. J Am Diet Assoc. 2005 Jul; 105(7): 1, 080-1, 086. PMID: 15983524.

5. Clifton PM, Noakes M, Keogh JB. Very low-fat (12%) and high monounsaturated fat (35%) diets do not differentially affect abdominal fat loss in overweight, nondiabetic women. J Nutr. 2004 Jul; 134(7): 1, 741-1, 745. PMID: 15226463.

6. Due A, Larsen TM, Mu H, Hermansen K, Stender S, Astrup A. Comparison of 3 ad libitum diets for weight-loss maintenance, risk of cardiovascular disease, and diabetes: A six-month randomized, controlled trial. Am J Clin Nutr. 2008 Nov; 88(5): 1, 232-1, 241. PMID: 18996857.

7. Haban P, Klvanova J, Zidekova E, Nagyova A. Dietary supplementation with olive oil leads to improved lipoprotein spectrum and lower n-6 PUFAs in elderly subjects. Med Sci Monit. 2004 Apr; 10(4): PI49-PI54. PMID: 15039655.

8. Paniagua JA, de la Sacristana AG, Sánchez E, Romero I, Vidal-Puig A, Berral FJ, Escribano A, Moyano MJ, Peréz-Martinez P, López-Miranda J, Pérez-Jiménez F. A MUFA-rich diet improves posprandial glucose, lipid and GLP-1 responses in insulin-resistant subjects. J Am Coll Nutr. 2007 Oct; 26(5): 434-444. PMID: 17914131.

9. Rasmussen BM, Vessby B, Uusitupa M, Berglund L, Pedersen E, Riccardi G, Rivellese AA, Tapsell L, Hermansen K; KANWU Study Group. Effects of dietary saturated, monounsaturated, and n-3 fatty acids on blood pressure in healthy subjects. Am J Clin Nutr. 2006 Feb; 83(2): 221-226. PMID: 16469978.

10. Thijssen MA, Hornstra G, Mensink RP. Stearic, oleic, and linoleic acids have comparable effects on markers of thrombotic tendency in healthy human subjects. J Nutr. 2005 Dec; 135(12): 2, 805-2, 811. PMID: 163171242.

11. Thijssen MA, Mensink RP. Small differences in the effects of stearic acid, oleic acid, and linoleic acid on the serum lipoprotein profile of humans. Am J Clin Nutr. 2005 Sep; 82(3): 510-516. PMID: 16155261.

Archived from www.NEL.gov on March 21, 2017

What is the effect of replacing a high carbohydrate diet with a high MUFA diet in persons with T2D?

Primary Articles

1. Brehm BJ, Lattin BL, Summer SS, Boback JA, Gilchrist GM, Handacek RJ, D'Alessio DA. One-year comparison of a high-monounsaturated fat diet with a high-carbohydrate diet in type 2 diabetes. Diabetes Care. 2009; 32: 215-220. PMID: 18957534.
2. Brunerova L, Smejkalova V. Potockova J, Andel M. A comparison of the influence of a high-fat diet enriched in monounsaturated fatty acids and conventional diet on weight loss and metabolic parameters in obese non-diabetic and Type 2 diabetic patients. Diabet Med. 2007 May; 24(5): 533-540. Epub 2007 Mar 22. PMID: 17381504.
3. Gerhard GT, Ahmann A, Meeuws K, McMurry MP, Duell PB, Connor WE. Effects of a low-fat diet compared with those of a high-monounsaturated fat diet on body weight, plasma lipids and lipoproteins, and glycemic control in type 2 diabetes. Am J Clin Nutr. 2004 Sep; 80(3): 668-673. PMID: 15321807.
4. Rodriguez-Villar C, Pérez-Heras A, Mercadé I, Casals E, Ros E. Comparison of a high-carbohydrate and a high-monounsaturated fat, olive oil-rich diet on the susceptibility of LDL to oxidative modification in subjects with Type 2 diabetes mellitus. Diabet Med. 2004 Feb; 21(2): 142-149. PMID: 14984449.
5. Shah M, Adams-Huet B, Bantle JP, Henry RR, Griver KA, Raatz SK, Brinkley LJ, Reaven GM, Garg A. Effect of a high-carbohydrate versus a high--cis-monounsaturated fat diet on blood pressure in patients with type 2 diabetes. Diabetes Care. 2005 Nov; 28(11): 2, 607-2, 612. PMID: 16249527.

N-6 PUFA and Health Outcomes

Systematic Reviews/Meta-analysis

1. Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, Bälter K, Fraser GE, Goldbourt U, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Ascherio A. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. Am J Clin Nutr. 2009 May; 89(5): 1, 425-1, 432. Epub 2009 Feb 11. PMID: 19211817.

Primary Articles

1. Hodge AM, English DR, O'Dea K, Sinclair AJ, Makrides M, Gibson RA, Giles GG. Plasma phospholipid and dietary fatty acids as predictors of type 2 diabetes: Interpreting the role of linoleic acid. Am J Clin Nutr. 2007 Jul; 86(1): 189-197. PMID: 17616780.
2. Laaksonen DE, Nyyssönen K, Niskanen L, Rissanen TH, Salonen JT. Prediction of cardiovascular mortality in middle-aged men by dietary and serum linoleic and polyunsaturated fatty acids. Arch Intern Med. 2005 Jan 24; 165(2): 193-199. PMID: 15668366.
3. Liou YA, King DJ, Zibrik D, Innis SM. Decreasing linoleic acid with constant alpha-linolenic acid in dietary fats increases (n-3) eicosapentaenoic acid in plasma phospholipids in healthy men. J Nutr. 2007 Apr; 137(4): 945-952. PMID: 17374659.

4. Mozaffarian D, Ascherio A, Hu FB, Stampfer MJ, Willett WC, Siscovick DS, Rimm EB. Interplay between different polyunsaturated fatty acids and risk of coronary heart disease in men. Circulation. 2005 Jan 18; 111(2): 157-164. Epub 2005 Jan 3. PMID: 15630029.

5. Oh K, Hu FB, Manson JE, Stampfer MJ, Willett WC. Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the nurses' health study. Am J Epidemiol. 2005 Apr 1; 161(7): 672-679. PMID: 15781956.

6. St-Onge MP, Aban I, Bosarge A, Gower B, Hecker KD, Allison DB. Snack chips fried in corn oil alleviate cardiovascular disease risk factors when substituted for low-fat or high-fat snacks. Am J Clin Nutr. 2007 Jun; 85(6): 1, 503-1, 510. PMID: 17556685.

7. Thijssen MA, Hornstra G, Mensink RP. Stearic, oleic, and linoleic acids have comparable effects on markers of thrombotic tendency in healthy human subjects. J Nutr. 2005 Dec; 135(12): 2, 805-2, 811. PMID: 16317124.

8. Thijssen MA, Mensink RP. Small differences in the effects of stearic acid, oleic acid, and linoleic acid on the serum lipoprotein profile of humans. Am J Clin Nutr. 2005 Sep; 82(3): 510-516. PMID: 16155261.

9. Zhao G, Etherton TD, Martin KR, West SG, Gillies PJ, Kris-Etherton PM. Dietary alpha-linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women. J Nutr. 2004 Nov; 134(11): 2, 991-2, 887. PMID: 15514264.

Excluded Articles

Article	Reason for Exclusion
Berry SE, Miller GJ, Sanders TA. <u>The solid fat content of stearic acid-rich fats determines their postprandial effects.</u> *Am J Clin Nutr.* 2007 Jun; 85(6): 1, 486-1, 494. PMID: 17556683.	Both study arms involve high fat. Outcomes are related to commercial randomization of oils.
Bondia-Pons I, Schröder H, Covas MI, Castellote AI, Kaikkonen J, Poulsen HE, Gaddi AV, Machowetz A, Kiesewetter H, López-Sabater MC. <u>Moderate consumption of olive oil by healthy European men reduces systolic blood pressure in non-Mediterranean participants.</u> *J Nutr.* 2007 Jan; 137(1): 84-87. PMID: 17182805.	Treatment period too short (three weeks).

Carrero JJ, Baró L, Fonollá J, González-Santiago M, Martínez-Férez A, Castillo R, Jiménez J, Boza JJ, López-Huertas E. <u>Cardiovascular effects of milk enriched with omega-3 polyunsaturated fatty acids, oleic acid, folic acid, and vitamins E and B$_6$ in volunteers with mild hyperlipidemia.</u> *Nutrition.* 2004 June; 20(6): 521-527. PMID 15165614.	Does not address questions. Study involves effect of milk enrichment and does not look at the relationship of variables in question.
Carrero JJ, Fonollá J, Marti JL, Jiménez J, Boza JJ, López-Huertas E. <u>Intake of fish oil, oleic acid, folic acid, and vitamins B$_6$ and E for 1 year decreases plasma C-reactive protein and reduces coronary heart disease risk factors in male patients in a cardiac rehabilitation program.</u> *J Nutr.* 2007 Feb; 137(2): 384-390. PMID: 17237316.	Multiple variables supplimented at same time.
Cicero AF, Nascetti S, López-Sabater MC, Elosua R, Salonen JT, Nyyssönen K, Poulsen HE, Zunft HJ, Kiesewetter H, de la Torre K, Covas MI, Kaikkonen J, Mursu J, Koenbick C, Bäumler H, Gaddi AV; EUROLIVE Study Group. <u>Changes in LDL fatty acid composition as a response to olive oil treatment are inversely related to lipid oxidative damage: The EUROLIVE study.</u> *J Am Coll Nutr.* 2008 Apr; 27(2): 314-320. PMID: 18689564.	Intervention provided as capsule.
Covas MI, Nyyssönen K, Poulsen HE, Kaikkonen J, Zunft HJ, Kiesewetter H, Gaddi A, de la Torre R, Mursu J, Bäumler H, Nascetti S, Salonen JT, Fitó M, Virtanen J, Marrugat J, EUROLIVE Study Group. <u>The effect of polyphenols in olive oil on heart disease risk factors: a randomized trial.</u> *Ann Intern Med.* 2006 Sep 5; 145(5): 333-341. PMID: 16954359.	Does not address question. Studies effect of polyphenols in olive oil on heart disease risk factors.

194

Damsgaard CT, Frøkiaer H, Andersen AD, Lauritzen L. <u>Fish oil in combination with high or low intakes of linoleic acid lowers plasma triacylglycerols but does not affect other cardiovascular risk markers in healthy men.</u> *J Nutr.* 2008 Jun; 138(6): 1, 061-1, 066. PMID: 18492834.	Intervention provided as capsule. Other nutrients unaccounted for.
Djoussé L, Hunt SC, Arnett DK, Province MA, Eckfeldt JH, Ellison RC. <u>Dietary linolenic acid is inversely associated with plasma triacylglycerol: the National Heart, Lung, and Blood Institute Family Heart Study.</u> *Am J Clin Nutr.* 2003 Dec; 78(6): 1, 098-1, 1102. PMID: 14668270.	Does not meet inclusion criteria. Cross-sectional study.
Engler MM, Engler MB. <u>Omega-3 fatty acids: role in cardiovascular health and disease.</u> *J Cardiovasc Nurs.* 2006 Jan-Feb; 21(1): 17-24, quiz 25-26. Review. PMID: 16407732.	Does not address questions. Descriptive. Metabolic effects of n-3.
Erkkilä AT, Matthan NR, Herrington DM, Lichtenstein AH. <u>Higher plasma docosahexaenoic acid is associated with reduced progression of coronary atherosclerosis in women with CAD.</u> *J Lipid Res.* 2006 Dec; 47(12): 2, 814-2, 819. Epub 2006 Sep 18. PMID: 16983146.	Moved to n-3 marine and plant questions.
Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Ruiz-Gutiérrez V, Covas MI, Fiol M, Gómez-Gracia E, López-Sabater MC, Vinyoles E, Arós F, Conde M, Lahoz C, Lapetra J, Sáez G, Ros E; PREDIMED Study Investigators. <u>Effects of a Mediterranean-style diet on cardiovascular risk factors: A randomized trial.</u> *Ann Intern Med.* 2006 Jul 4; 145(1): 1-11. PMID: 16818923.	Does not look at relationships between variables. Examines Mediterranean Pattern, not specifically MUFA or PUFA.

195

Fitó M, Cladellas M, de la Torre R, Martí J, Alcántara M, Pujadas-Bastardes M, Marrugat J, Bruguera J, López-Sabater MC, Vila J, Covas MI; The members of the SOLOS Investigators. <u>Antioxidant effect of virgin olive oil in patients with stable coronary heart disease: A randomized, crossover, controlled, clinical trial.</u> Ath*erosclerosis.* 2005 Jul; 181(1): 149-158. Epub 2005 Feb 12. PMID:15939067.	Does not look at relationships between variables. Compares antioxidant effect of two olive oils, one with higher phenolic content.
Fitó M, Cladellas M, de la Torre R, Martí J, Muñoz D, Schröder H, Alcántara M, Pujadas-Bastardes M, Marrugat J, López-Sabater MC, Bruguera J, Covas MI; SOLOS Investigators. <u>Anti-inflammatory effect of virgin olive oil in stable coronary disease patients: A randomized, crossover, controlled trial.</u> *Eur J Clin Nutr.* 2008 Apr; 62(4): 570-574. Epub 2007 Mar 21. PMID: 17375118.	Does not look at relationships between variables. Compares antioxidant effect of two olive oils, one with higher phenolic content.
Freese R, Vaarala O, Turpeinen AM, Mutanen M. <u>No difference in platelet activation or inflammation markers after diets rich or poor in vegetables, berries and apples in healthy subjects.</u> *Eur J Nutr.* 2004 Jun; 43(3): 175-182. Epub 2004 Jan 6. PMID: 15168040.	Does not address question. Variables studied are vegetables, berries and apples.
Garg A. <u>High-monounsaturated-fat diets for patients with diabetes mellitus: A meta-analysis.</u> *Am J Clin Nutr.* 1998 Mar; 67(3 Suppl): 577S-582S. PMID: 9497173.	Does not meet inclusion criteria. Study conducted 1998.
Gaullier JM, Halse J, Høye K, Kristiansen K, Fagertun H, Vik H, Gudmundsen O. <u>Conjugated linoleic acid supplementation for one year reduces body fat mass in healthy overweight humans.</u> *Am J Clin Nutr.* 2004 Jun; 79(6): 1, 118-1, 125. PMID: 15159244.	Intervention provided as capsule.

196

Gradek WQ, Harris MT, Yahia N, Davis WW, Le NA, Brown WV. <u>Polyunsaturated fatty acids acutely suppress antibodies to malondialdehyde-modified lipoproteins in patients with vascular disease.</u> *Am J Cardiol.* 2004 Apr 1; 93(7): 881-885. PMID: 15050493.	Does not meet inclusion criteria for feeding period. Short-term,postprandial metabolic study.
Harper CR, Jacobson TA. <u>Usefulness of omega-3 fatty acids and the prevention of coronary heart disease.</u> *Am J Cardiol.* 2005 Dec 1; 96(11): 1, 521-1, 529. Epub 2005 Oct 21. PMID: 16310434.	Non-systematic negative review.
Harris WS. <u>Linoleic acid and coronary heart disease.</u> Prostaglandins Leukot Essent Fatty Acids. 2008 Sep-Nov;79(3-5):169-71. Epub 2008 Oct 31. PMID: 18951772	Narrative review
Hartweg J, Farmer AJ, Holman RR, Neil A.<u>Potential impact of omega-3 treatment on cardiovascular disease in type 2 diabetes.</u> *Curr Opin Lipidol.* 2009 Feb; 20(1): 30-38. PMID: 19133409.	Treatment uses of omega-3 fatty acids.
Hilpert KF, West SG, Kris-Etherton PM, Hecker KD, Simpson NM, Alaupovic P. <u>Postprandial effect of n-3 polyunsaturated fatty acids on apolipoprotein B-containing lipoproteins and vascular reactivity in type 2 diabetes.</u> *Am J Clin Nutr.* 2007 Feb; 85(2): 369-376. PMID: 17284731.	Does not meet feeding criteria. Feeding period less than four weeks.
Kabagambe EK, Baylin A, Ascherio A, Campos H. <u>The type of oil used for cooking is associated with the risk of nonfatal acute myocardial infarction in Costa Rica.</u> *J Nutr.* 2005 Nov; 135(11): 2, 674-2, 679. PMID: 16251629.	Does not meet inclusion criteria. Case control study.

Kontogianni MD, Panagiotakos DB, Chrysohoou C, Pitsavos C, Zampelas A, Stefanadis C. The impact of olive oil consumption pattern on the risk of acute coronary syndromes: The CARDIO2000 case-control study. *Clin Cardiol.* 2007 Mar; 30(3): 125-129. PMID: 17385704.	Does not meet inclusion criteria. Case control study.
Kris-Etherton PM, Hecker KD, Binkoski AE. Polyunsaturated fatty acids and cardiovascular health. *Nutr Rev.* 2004 Nov; 62(11): 414-426. Review. PMID: 15622714.	Non-systematic narrative review.
Kris-Etherton PM, Pearson TA, Wan Y, Hargrove RL, Moriarty K, Fishell V, Etherton TD. High-monounsaturated fatty acid diets lower both plasma cholesterol and triacylglycerol concentrations. *Am J Clin Nutr.* 1999 Dec; 70(6): 1, 009-1, 015. PMID: 10584045.	Addresses the question. Published prior to inclusion dates.
Levick SP, Loch DC, Taylor SM, Janicki JS. Arachidonic acid metabolism as a potential mediator of cardiac fibrosis associated with inflammation. *J Immunol.* 2007 Jan 15; 178(2): 641-646. PMID: 17202322.	Does not address questions. Narrative review.
López S, Bermúdez B, Pacheco YM, López-Lluch G, Moreda W, Villar J, Abia R, Muriana FJ. Dietary oleic and palmitic acids modulate the ratio of triacylglycerols to cholesterol in postprandial triacylglycerol-rich lipoproteins in men and cell viability and cycling in human monocytes. *J Nutr.* 2007 Sep; 137(9): 1, 999-2, 005. PMID: 17709433.	Postprandial study lasting three and five hours does not meeting intake criteria. Studies fatty acid ratios.
Lovegrove JA. CVD risk in South Asians: The importance of defining adiposity and influence of dietary polyunsaturated fat. *Proc Nutr Soc.* 2007 May; 66(2): 286-298. Review. PMID: 17466109.	Negative review. Not systematic. Restricted to a defined foreign population

Madigan C, Ryan M, Owens D, Collins P, Tomkin GH. <u>Comparison of diets high in monounsaturated versus polyunsaturated fatty acid on postprandial lipoproteins in diabetes.</u> *J Med Sci.* 2005 Jan-Mar; 174(1): 8-20. PMID: 15868884.	Does not meet inclusion criteria. Short-term, postprandial study.
Malpuech-Brugère C, Verboeket-van de Venne WP, Mensink RP, Arnal MA, Morio B, Brandolini M, Saebo A, Lassel TS, Chardigny JM, Sébédio JL, Beaufrère B. <u>Effects of two conjugated linoleic acid isomers on body fat mass in overweight humans.</u> *Obes Res.* 2004 Apr; 12(4): 591-598. PMID: 15090626.	Does not meet inclusion criteria. Study investigates isomers of CLA.
Manning PJ, Sutherland WH, McGrath MM, de Jong SA, Walker RJ, Williams MJ. <u>Postprandial cytokine concentrations and meal composition in obese and lean women.</u> *Obesity (Silver Spring).* 2008 Sep; 16(9): 2, 046-2, 052. PMID: 19186329.	Does not meet inclusion criteria for feeding period. Short-term feeding followed by postprandial tests.
Montoya MT, Porres A, Serrano S, Fruchart JC, Mata P, Gerique JA, Castro GR. <u>Fatty acid saturation of the diet and plasma lipid concentrations, lipoprotein particle concentrations, and cholesterol efflux capacity.</u> *Am J Clin Nutr.* 2002 Mar; 75(3): 484-491. PMID: 11864853.	Note: Key evidence addressing the question presents data first published in 1996. New data is limited to lipoprotein particle distribution.
Moore CS, Bryant SP, Mishra GD, Krebs JD, Browning LM, Miller GJ, Jebb SA. <u>Oily fish reduces plasma triacylglycerols: A primary prevention study in overweight men and women.</u> *Nutrition.* 2006 Oct; 22(10): 1, 012-1, 024. PMID: 17027436.	Does not meet inclusion criteria. Covers omega-3 fatty acids.
Mozaffarian D. <u>Does alpha-linolenic acid intake reduce the risk of coronary heart disease? A review of the evidence.</u> *Altern Ther Health Med.* 2005 May-Jun; 11(3): 24-30; quiz 31, 79. PMID: 15945135.	Narrative review.

Mullen A, Moloney F, Nugent AP, Doyle L, Cashman KD, Roche HM. <u>Conjugated linoleic acid supplementation reduces peripheral blood mononuclear cell interleukin-2 production in healthy middle-aged males.</u> *J Nutr Biochem.* 2007 Oct; 18(10): 658-666. Epub 2007 Mar 21. PMID: 17368881.	Intervention provided as capsules.
Njelekela M, Ikeda K, Mtabaji J, Yamori Y.<u>Dietary habits, plasma polyunsaturated fatty acids and selected coronary disease risk factors in Tanzania.</u> *East Afr Med J.* 2005 Nov; 82(11): 572-578. PMID: 16463751.	Cross-sectional population study.
Nugent AP, Roche HM, Noone EJ, Long A, Kelleher DK, Gibney MJ. <u>The effects of conjugated linoleic acid supplementation on immune function in healthy volunteers.</u> *Eur J Clin Nutr.* 2005 Jun; 59(6): 742-750. PMID: 15827560.	Intervention provided as capsules
Oda E, Hatada K, Katoh K, Kodama M, Nakamura Y, Aizawa Y. <u>A case-control pilot study on n-3 polyunsaturated fatty acid as a negative risk factor for myocardial infarction.</u> *Int Heart J.* 2005 Jul; 46(4): 583-591. PMID: 16157949.	Pilot study, small number of participants.
Oda E, Hatada K, Kimura J, Aizawa Y, Thanikachalam PV, Watanabe K. <u>Relationships between serum unsaturated fatty acids and coronary risk factors: Negative relations between nervonic acid and obesity-related risk factors.</u> *Int Heart J.* 2005 Nov; 46(6): 975-985. PMID: 16394593.	Does not address question. Correlates blood lipids with weight and height of control participants in a previous case study.

Pacheco YM, Bermúdez B, López S, Abia R, Villar J, Muriana FJ. <u>Ratio of oleic to palmitic acid is a dietary determinant of thrombogenic and fibrinolytic factors during the postprandial state in men.</u> *Am J Clin Nutr.* 2006 Aug; 84(2): 342-349. PMID: 16895881.	Does not look at relationships between variables asked in question. Studies effect of ratios of MUFA:PUFA.

CHAPTER 9. SPECIFIC FATS, FATTY ACIDS, AND CHOLESTEROL – SATURATED FAT INTAKE ON INCREASED RISK OF CARDIOVASCULAR DISEASE OR TYPE 2 DIABETES

WHAT IS THE EFFECT OF SATURATED FAT INTAKE ON INCREASED RISK OF CARDIOVASCULAR DISEASE OR TYPE 2 DIABETES?

Conclusion statement

Strong evidence indicates that dietary saturated fatty acids (SFA) are positively associated with intermediate markers and end-point health outcomes for two distinct metabolic pathways: 1) increased serum total cholesterol (TC) and LDL cholesterol (LDL-C) and increased risk of cardiovascular disease (CVD) and 2) increased markers of insulin resistance and increased risk of type 2 diabetes (T2D). Conversely, decreased SFA intake improves measures of both CVD and T2D risk. The evidence shows that a five percent energy decrease in SFA, replaced by monounsaturated fatty acids (MUFA) or polyunsaturated fatty acids (PUFA), decreases risk of CVD and T2D in healthy adults and improves insulin responsiveness in insulin resistant and T2D subjects.

Grade

Strong

Evidence summary overview

The Nutrition Evidence Library (NEL) review of the literature published since 2004 on the association of dietary saturated fat (SFA) and cardiovascular disease (CVD) identified 12 studies in healthy adults or those at elevated chronic disease risk. Studies were conducted in the US, Europe and South America, and overall, 10 randomized controlled trials (RCTs), one non-randomized trial and an analysis of 11 pooled cohorts with meta-analysis were identified. The intervention studies ranged in sample size from 14 to 191 subjects and the pooled analysis included 344,696 subjects. Of the 12 studies, eight were methodologically strong (Azadbakht, 2007; Berglund, 2007; Chen, 2009; Furtado, 2008; Jakobsen, 2009; Kralova, 2008; Lefevre, 2005; Lichtenstein, 2005) and four were methodologically neutral (Buenacorso, 2007; Bourque, 2007; Chung, 2004; Dabadie, 2005).

Most methodologically strong studies were feeding trials with an "average American" diet at baseline, which involved a reduction in SFA through replacement with monounsaturated fat (MUFA), polyunsaturated fat (PUFA) or, to a lesser extent, carbohydrates (CHO). Dietary SFA replacement (5% to 7% of energy) with either MUFA (Berglund, 2007; Lichtenstein, 2005) or PUFA (Chung, 2004; Kralova, 2008; Lichtenstein, 2005) significantly decreased total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C). Replacement of SFA with CHO decreased plasma total and LDL-C. However, compared to MUFA or PUFA, CHO decreased high-density lipoprotein (HDL-C) and increased serum triglycerides (TG) (Berglund, 2007). A study by Lefevre et al (2005) included two levels of total fat (30% and 25%) and SFA (9%

202

and 6%) in the Step I and Step II diets, respectively, and demonstrated a dose-response effect in lowering LDL-C. However, compared to the average American diet, the Step I and Step II diets also decreased HDL-C and raised TG levels in the blood. Furthermore, these authors showed that subjects who were insulin resistant responded less favorably to the Step II diet than did those with normal insulin sensitivity. A study by Kralova et al (2008) examined changes in cholesterol efflux to determine whether reduced HDL-C, on a high PUFA/low SFA diet, had a negative effect on reverse cholesterol transport. The study showed no change in cholesterol efflux.

One meta-analysis examined effects of SFA reduction on incident coronary heart disease (CHD) outcomes by estimating the anticipated effects from statistical models where SFA is exchanged for equal energy from MUFA, PUFA or CHO (Jakobsen, 2009). These authors examined 11 American and European cohort studies and found a significant inverse association for PUFA (with 5% substitution for SFA) and coronary events (hazard ratio (HR) = 0.87, 95% CI: 0.77 to 0.97, and coronary death HR = 0.74, 95% CI: 0.61 to 0.89). They also found a positive association between substitution of MUFA or CHO for SFA and risk of coronary events, but not risk of coronary deaths.

The NEL systematic review of the literature published since 2000 on the association of dietary SFA and type 2 diabetes (T2D) identified 12 studies conducted in the US, Europe, Canada and China that examined the effect of dietary SFA on altered glucose metabolism, markers of insulin resistance and T2D risk. Two were methodologically strong review articles, including one that evaluated 15 trials, nine trials in 358 non-diabetic subjects and six trials in 93 subjects with T2D (Galgani, 2008) and one reviewing 14 prospective cohort and five cross-sectional studies (Hu, 2001). Nine were RCTs ranging in size from 11 to 522 subjects, including six methodologically strong studies (Han, 2001; Lindstrom, 2006a; Lindstrom, 2006b; Lopez, 2008; Perez-Jimenez, 2001; Vesby, 2001) and three methodologically neutral studies (Paniagua, 2007; Shah, 2007; St-Onge, 2003). The one prospective cohort study with 84,204 subjects from the Nurses' Health Study was methodologically strong (Salmeron, 2001).

Evidence summary paragraphs

Cardiovascular Disease (CVD)

Azadbakht et al, 2007 (positive) This was an RCT conducted in Tehran, Iran to determine the effects of the National Cholesterol Education Program (NCEP) Step II diet on LDL-C and HDL-C particle size in dyslipidemic adolescents. 46 subjects (23 female, 23 male, mean age 14.5 years, range 10 to 18 years) with hypercholesterolemia (TC more than 170mg per dL; LDL-C higher than 110mg per dL) were recruited from among the participants in the Tehran Lipid and Glucose Study and randomized to either the control group (instructed to "eat as usual") or the Step II diet intervention group. Subjects in the Step II group were given individualized diets based on energy needs that were 30% total fat, less than 7% SFA, less than 200mg cholesterol, less than 15% of energy as MUFA and less than 10% of energy as PUFA. Subjects were visited every two weeks (three-day diet record) and were in daily contact with a nutritionist. Forty-four subjects completed the trial, and there were no significant (NS) changes in body weight or physical activity in the two groups.

Lipoprotein particle size was the major outcome variable, measured at three months. Comparisons were made by repeated measurement analysis of variance (ANOVA). The Step II diet resulted in a greater reduction in TC (-13±4 vs. -2±3mg per dL, P<0.001) and LDL-C (-9±2 vs. 3±0.6mg per dL, P<0.01) and a higher increase in the size of the LDL particle (1.7±0.4 vs. 0.1±0.4nm, P<0.001). High-density lipoprotein cholesterol particle size did not change significantly.

Berglund et al, 2007 (positive quality) This was a randomized crossover trial conducted in the US that compared MUFA with CHO as a replacement for SFA in subjects with a high metabolic risk profile. Fifty-two men and 33 women, selected to have any combination of HDL-C 30th percentile, triacylglycerol (TG) 70th percentile or insulin 70th percentile, were enrolled. Four research centers each enrolled participants between ages 21 and 65 years. The subjects consumed an average American diet (AAD; 36% of energy from fat) and two additional diets in which 7% of energy from SFA was replaced with either CHO (CHO diet) or MUFA (MUFA diet). (It should be noted that the CHO diet also contained more fiber than the AAD).The three diets were fed in a double-blind, three-way crossover with each diet lasting seven weeks with a washout period of four to six weeks. All food was provided (following NCEP Step I guidelines). Blood samples were drawn at weeks five, six and seven of each of the three diets. Initially, 110 subjects were enrolled in the study, but only 85 completed all three diets (33 females, 52 males, mean age 35.5±9.2 years, range 21 to 61 years). Relative to the AAD, LDL-C was lower with both the CHO-replacement diet (-7.0%) and MUFA-replacement diet (-6.3%) with NS difference between the latter two diets, whereas the difference in HDL-C was significantly smaller (P<0.01) during the MUFA-replacement diet (-4.3%) than during the CHO-replacement diet (-7.2%). In addition, whereas plasma TG concentrations tended to be lower with the MUFA diet than with the AAD (-4.9%; P<0.03), TG concentrations were significantly higher with the CHO diet than with either the AAD (6.5%) or the MUFA (11.4%) diet (P<0.01 for each comparison). Lipoprotein (a) concentrations increased with both the CHO-replacement diet (20%) and MUFA-replacement diet (11%) relative to the AAD, although the difference between MUFA and CHO was not statistically significant. The authors conclude that in the study population who were at increased risk of CHD, MUFA replacement of SFA provided a greater protective effect than CHO replacement of SFA in the diet.

Buonacorso et al, 2007 (neutral quality) This was an RCT conducted in Brazil that examined the effects on HDL2 and HDL3 composition and rates of cell cholesterol efflux (CE) from macrophages induced by whole plasma and HDL-C subfractions. The RCT compared trans fatty acids (TFA), SFA and PUFA-enriched diets in healthy subjects under fasting and post-prandial conditions. After a two-week run-in period where subjects consumed diets that met the NCEP-ATPIII recommendations (30% energy from fat, less than 10% energy SFA, less than 300mg cholesterol per day), 30 healthy subjects (nine male, 21 female, matched for age, sex and body mass index (BMI) were assigned to a four-week experimental diet period composed of fat-free ad lib breakfast plus prepared frozen lunches and dinners. All experimental diets had 30% of energy as fat, and the composition of the custom-made fat was two thirds of total fat intake. The oil composition was calculated to provide minimal variation in MUFA and maximal differences in the proportions of TFA, PUFA, and SFA in the

experimental diets [8.3% TFA (N=10), 14.6% PUFA (N=10) or 13.2% SFA (N=10)]. Plasma TC and triacylglycerol levels were NS changed by the diets, by time (basal vs. final test), or period (fasting vs. post-prandial) according to repeated-measures analysis. However, there were modest, but significant, differences in the chemical composition of HDL subfractions, primarily in HDL2 (the largest, least-dense HDL). Trans fatty acids increased HDL2-C, apoAI and AII, and decreased the ratio of lipids:apoA, whereas SFA decreased HDL2-C and apoAI and AII; PUFA decreased only lipids:apoA over time. Total HDL-C changes were similar to those for HDL2. However, despite the modifications in HDL2 and total HDL with diets, the percentage of radioactive cholesterol efflux from macrophages did not change, possibly due to the modest difference in the composition of the HDL fraction under conditions of maintaining 30% energy as fat.

Bourque et al, 2007 (neutral quality) This was a randomized, single-blind, crossover study to examine whether consumption of medium-chain triglycerides (MCT) with phytosterols and n-3 PUFA improves serum lipid profiles. The study evaluated the effect of a functional oil (FctO) with MCT as 50% of fat, phytosterols (22mg per kg body weight) and n-3 FA as 5% of fat, compared with beef tallow-based diet (BT) as control (treatment fat completely beef tallow), on circulating lipids and aminothiol concentrations. In this partially in-patient trial, 17 overweight women (mean age 44±4 years, BMI=32kg/m2) consumed each oil as part of an energy controlled diet [three isocaloric meals a day [45% CHO; 15% protein (PRO); 40% FAT] with 75% fat as treatment fat)] for 27 days, with a four-week washout between phases. Meals were consumed at the Clinical Nutrition Research Unit (CNRU) at McGill University. Fasting blood samples were taken at days one, 26 and 28. Mean plasma TC was 9.1% lower on FctO (4.37±0.20mmol per L) vs. BT (4.80±0.20mmol per L) (P<0.0001). Mean plasma LDL-C was also lower following FctO (2.39±0.15mmol per L) vs. BT (2.86±0.16mmol per L) (P<0.0001), representing a 16% difference between diets. High-density lipoprotein cholesterol and circulating TG remained unaffected by treatment. Ratios of HDL:LDL and HDL:TC were higher by 22% and 11% (P<0.01), respectively, on FctO vs. BT. The authors conclude that consumption of a functional oil composed of MCT, phytosterols and n-3 fatty acids for 27 days improved the cardiovascular risk profile of overweight women.

Chen et al, 2009 (positive quality) This was a randomized, double-blind cross-over study to determine the effect of three daily servings of plant sterol (PS), in the context of two background diets on serum lipids, lipoproteins, retinol, tocopherols and carotenoids. Overall, there were four diets as follows: 1) Typcial American Diet (TAD) with and without 3.8g per day PS, and 2) the Step I diet with and without 3.8g per day PS. This was a cross-over design with 23 days per diet period and no washout between diets. All foods were provided by the Beltsville Human Nutrition Research Center at US Department of Agriculture (USDA). Measurements were taken at baseline and day 22 and 24. Significant differences were measured in plasma TC, HDL-C, LDL-C, Apo A1 and Apo B; these were 4.3%, 5.3%, 4.5%, 2.8% and 2.5% lower, respectively, with the Step I diet vs. TAD. Diet had no effect on the TC/HDL-C ratio. Plant sterol intake significantly lowered TC, LDL-C and Apo B by 9.0%, 12.4% and 6.1% and the TC/HDL-C ratio by 9.6%, respectively. However, HDL-C and Apo A1 were not affected by PS. The authors concluded that the PS effect in lowering plasma

205

TC and LDL-C was independent of, and additive to, the effect of dietary fat reduction with the Step 1 diet. Plasma levels of the retinoids, carotenoids and tocopherols measured were significantly decreased with PS intake, except for retinol and d-tocopherol. This was the first study to compare the influence of diets vs. PS intake on blood lipoprotein concentrations. The findings confirm that LDL-C-reducing effects resulting from PS intake and from the Step I diet are independent of each other and that the PS effect is quantitatively greater.

Chung et al, 2004 (neutral quality) This was a randomized crossover trial conducted in the US that examined the acute and chronic effects of consuming a PUFA- or SFA-rich diet on lipoprotein cholesterol levels and the impact of post-prandial TG-rich lipoproteins (TRLs) in determining lipoprotein cholesterol levels. The effects of PUFA-rich [ratio of PUFAs to SFAs (P:S) = 2.0] and SFA-rich (P:S=0.25) diets on fasting and post-prandial plasma lipid and lipoprotein-cholesterol concentrations was conducted with 16 normolipidemic subjects. Eight men (seven white and one black) aged 33 to 49 years (35.3±4.5 years) and eight post-menopausal women (five white and three black) aged 45 to 62 years (51.9±6.6 years) were recruited from the General Clinical Research Center (GCRC) of the University of Alabama at Birmingham Medical Center. The mean BMI (kg/m2) of men and women were 25.3±4.1 and 29.6±4.5, respectively. The subjects adopted each diet for a 20-day period, with three- to four-week washout. Meals were prepared by the GCRC and contained 15% energy as PRO, 50% energy as CHO, 35% energy as fat and 175mg cholesterol per 1,000kcal. The SFA-rich diet provided 18.8% SFA, 11.5% MUFA and 4.7% PUFA, while the PUFA-rich diet provided 7.5% SFA, 12% MUFA and 15.5% PUFA. Fasting TC decreased significantly (-8%, P<0.05) after the PUFA-rich diet due to a decrease in LDL-C (-12.3%, P<0.05) and HDL-C (-3.8%, NS) but did not change after a SFA-rich diet. The appearance of post-prandial TRLs in plasma at four hours was linked to a significant lowering of both LDL-C (-7.4%) and HDL-C (-4.8%) after a PUFA-rich diet, but not after the SFA-rich diet. At seven hours, LDL-C and HDL-C returned to near fasting concentrations without post-prandial TRL accumulation after a PUFA-rich diet but with significant post-prandial TRL accumulation after an SFA-rich diet. Thus, in vivo post-prandial clearance of cholesterol in LDL+HDL was greater after a PUFA-rich diet than after an SFA-rich diet.The appearance of post-prandial TRLs in plasma increased the cholesteryl ester transfer protein (CETP)-mediated transfer of cholesteryl ester from LDL+HDL to TRLs in vitro. The authors conclude that dietary fat-mediated alterations in the rate of hepatic removal of post-prandial TRLs, which carry cholesterol accepted from LDL+HDL via CETP in vivo, may contribute to the dietary fat-mediated change in lipoprotein cholesterol.

Dabadie et al, 2005 (neutral quality) This was a non-randomized clinical trial, comparing the effects of two moderate intakes of myristic acid on plasma lipids in 25 male members of a Benedictine monastery in the Southwest of France (mean age 61 years, range 35 to 88 years). Two different test diets were given for five weeks, separated by a four-week washout with subjects' usual diet. Both intervention diets provided approximately 2,200kcal and 15% energy as PRO, 12% from oleic acid, 6% from linoleic acid (LA), 1% from alpha-linolenic acid (ALA) and 200mg cholesterol per day. In diet one, 30% of the calories came from fat (8% SFA, 0.6% myristic acid) (PUFA:SFA =1), while in diet two, 34% of the calories came from fat (11% SFA, 1.2%

206

myristic acid) (PUFA:SFA=0.75). In comparison with baseline (fat and SFA intakes of 34.5% and 13%, respectively), both diets decreased TC, LDL-C and TG (P<0.001); HDL-C was not modified and the apo A-I/apo B ratio was increased (P<0.001). Plasma TG were lower after diet two than after diet one, whereas, HDL-C was higher (P<0.05). This was unexpected as diet one closely resembles the Step II diet, whereas diet two more closely resembles the Step 1 diet, except for the differences in myristic acid. Both diets were associated with an increase in ALA in cholesteryl esters (P<0.05), but only diet two was associated with an increase in docosahexaenoic acid (DHA) in cholesteryl esters (P<0.05). The authors conclude that moderate intake of myristic acid (1.2% of total calories) has beneficial effects on serum lipids and increases DHA content of cholesterol esters, due to increased elongation and desaturation of ALA.

Furtado et al, 2008 (positive quality) This was a randomized crossover trial that examined the differences in apo B-containing lipoproteins with and without apo C-III after three healthy diets based on the Dietary Approaches to Stop Hypertension (DASH) trial diet. Apo B–containing lipoproteins with apo C-III have slower clearance from plasma and the concentration of apo C-III in very-low density lipoprotein (VLDL) cholesterol and LDL-C is a newly emerged, predictive indicator of CHD. Study diets were modeled on the DASH diet and emphasized CHO, unsaturated fatty acids or protein. Subjects were participants in the Omni-Heart trial and each participant was randomly assigned each of three diets for six weeks, with a two-week washout in between. The three diets differed as follows: 1) Carb diet [58% of energy from CHO, 27% fat (6% SFA, 13% MUFA, 8% PUFA) and 15% PRO (5.5% meat, 9.5% plant and dairy)]; 2) Unsat diet [48% of energy from CHO, 37% fat (6% SFA, 21% MUFA, 10% PUFA) and 15% PRO (5.5% meat, 9.5% plant and dairy)] and 3) Prot diet [48% of energy from CHO, 27% fat (6% SFA, 13% MUFA, 8% PUFA) and 25% protein (9% meat, 15% plant and dairy)]. One hundred ninety-one adult men and women from Boston, MA and Baltimore, MD (44% women, mean age 53±10 years) were enrolled, 162 completed the trial. Compared with the Carb diet, the Prot diet reduced plasma apo B and triglycerides in VLDL with apo C-III (16%, P=0.07; 11%, P=0.05, respectively), and apo B in LDL with apo C-III (16%, P=0.04). Compared with the Unsat diet, the Prot diet reduced TG in VLDL with apo C-III (16%, P=0.02), and compared with baseline (subjects' usual diet was higher in SFA), the Prot diet reduced apo B in LDL with apo C-III (11%, P=0.05). Compared with baseline, all three diets reduced plasma total apo B (6% to 10%, P<0.05), apo B in the major type of LDL [LDL without apo C-III (8% to 10%, P < 0.01)], and reduced the ratio of apo C-III to apo E in VLDL. The major conclusion of the authors was that substituting PRO for CHO, in the context of a healthy diet like DASH, reduced atherogenic apo CIII-containing LDL and its precursor, apoCIII-containing VLDL, resulting in the most favorable profile of apo B lipoproteins.

Jakobsen et al, 2009 (positive quality) This was a follow-up study in which data from 11 American and European cohort studies were pooled and analyzed using the Proportional Hazards Model. The outcome measure was incident CHD. Within each study, hazard ratios (HR) with 95% CI for the incidence of CHD and mortality from CHD were calculated using the Cox proportional hazards regression with time in study (y) as the time metric. The purpose of this pooled analysis was to investigate the associations between replacing SFA intake with MUFA, PUFA or CHO and risk of

207

CHD, while assessing the potential effect-modifying role of sex and age. The inclusion criteria for what is entitled the "Pooling Project of Cohort Studies on Diet and Coronary Disease" were the following: 1) Published follow-up studies with more than 150 incident coronary events; 2) availability of usual dietary intake; and 3) validation or repeatability study of the diet-assessment method. Exclusion criteria were based on subjects and included: 1) Age less than 35 years, 2) history of CVD, T2D or cancer, and 3) high energy intake. During four- to 10-year follow-up, 5,249 coronary events and 2,155 coronary deaths occurred among 344,696 persons. Overall, Jakobsen found a significant inverse association between 5% substitution of PUFAs for SFAs and risk of coronary events (HR: 0.87; 95% CI: 0.77, 0.97) and risks of coronary deaths (HR: 0.74; 95% CI: 0.61, 0.89). There was indication of a positive association between substitution of MUFAs and risk of coronary events (HR: 1.19; 95% CI: 1.00, 1.42), but not risks of coronary deaths. There was also a modest, but significant, association between substitution of CHO and risk of coronary events (HR: 1.07; 95% CI: 1.01,1.14) but not risk of coronary deaths. There was no effect modification by gender or age. The authors concluded that the associations found suggest that replacing SFA intake with PUFA intake, rather than MUFA or CHO intake, prevent CVD over a wide range of intakes among all middle-aged and older men and women. Limitations of this report were that the authors did not describe the demographics of any of the American or European subject populations and the methods of handling withdrawals was not described. It is also important to note that the type of CHO in the diet was not taken into account in this analysis (i.e., extent of processing, fiber content or glycemic index).

Kralova et al, 2008 (positive quality) This was a randomized cross-over study to determine if a decrease in HDL-C in a diet enriched with PUFA is detrimental to reverse cholesterol transport (RTC) by measuring changes in cholesterol efflux (CHE). The dietary intervention consisted of two isocaloric diets that were 40% energy from fat, one high in SFA (52% of fat; SFA diet) and one high in PUFA (41% of fat; PUFA diet). Blood samples were taken at baseline and at the end of each four-week period. Serum lipids were measured by standard methods and weight and waist circumference (WC) at baseline and at the end of each four-week period. Cholesterol eflux was measured using cells in culture in medium containing labeled cholesterol. Overall, the authors found that the PUFA diet resulted in significantly lower concentrations of TC, LDL-C and HDL-C, compared to the SFA diet. Similarly, apoB and apoA1 concentrations were lower, although not significantly so. CHE was not different on either diet and was comparable to baseline. No correlation was found between CHE and lipids and lipoprotein concentrations on either diet. In conclusion, the decrease in HDL-C resulting from replacement of SFA by PUFA in the diet does not affect the rate of CHE and does not have a detrimental effect. According to the authors, this is the first study to show that replacement of SFA by PUFA in humans does not influence CHE from macrophages to the blood.

Lefevre et al, 2005 (positive quality) This was a randomized, double-blind, three-period crossover study to examine the relationship between indices of adiposity and insulin resistance and the magnitude of lipid response in healthy men, comparing diets that were reduced in TC and SFA. This study examined the effects of three diets that differed in total fat on serum lipids: The Average American Diet (AAD), the Step I diet

208

and the Step II diet. Free-living participants were provided prepared meals throughout the study from the Pennington Biomedical Research Center (each day, one complete meal underwent chemical analysis in Pennington's food analysis laboratory). The diet periods were six weeks and fed to healthy men aged 22 to 64 years at levels to maintain body weight. Blood samples were taken at baseline and at weeks four, five and six. Step I and II diets lowered LDL-C by 6.8% and 11.7%, HDL-C by 7.5% and 11.2%, and raised TG by 14.3% and 16.2%, respectively, compared to the AAD. There was a significant positive correlation between the Step II diet and changes in LDL-C, ratio of TC to HDL-C and baseline percentage body fat, BMI and insulin. Subdivision of the subjects based on fasting insulin levels showed that people in the upper one-half of fasting insulin concentrations averaged only 57% of the reduction in LDL-C of subjects in the lower half, with the Step II diet. The authors conclude that people who are insulin resistant respond less favorably to the Step II diet than do those with normal insulin sensitivity.

Lichtenstein et al, 2006 (positive quality) This was an RCT to assess the efficacy of soybean oils (SO) with modified fatty acid profiles, compared to soybean and partially hydrogenated SO, on CVD risk in middle-aged and older moderately hyper-cholesterolemic and postmenopausal women and men. Subjects were randomly assigned to five experimental diets for a 35-day period. Subjects ate one meal per day on site and the remaining meals were provided in containers. Diets were designed to provide 30% energy from fat and two-thirds of fat was provided by experimental oils. Experimental oils were provided by Solea Co (St Louis, MO) as follows: 1) SO, 2) low SFA SO, 3) high oleic acid SO, 4) low ALA SO, and 5) commercially available partially hydrogenated SO. Analysis of variance with main effect of diet and subject as repeated measure was carried out for each outcome. This was followed by Tukey's significant difference type of adjustment for the pairwise comparison among each of the five treatment protocols. Both plasma fatty acid (FA) profiles and lipids and lipoproteins were assessed by standard methods. Fasting (12 hours) blood samples were taken three times after day 28 of the diet feeding period. The authors found that the phospholipids fraction of plasma reflected the predominate fat in the diet at the end of each study and was evidence of dietary compliance. Low-density lipoprotein cholesterol concentrations were highest in subjects who consumed the Hydrog-SO enriched diets. The effects of modified SOs were modest. Relative to the SO diet, the percentage of difference in LDL-C concentrations were: -3.2% for LoSFA-SO diet; 1.4% for HiOleic-SO diet; 0.8% for LoALA-SO diet; and 5.6% for the Hydrog-SO diet. This pattern of difference was reflected in the Apo B concentrations. High-density lipoprotein cholesterol concentrations were not different across modified SO diets, although for men, HDL-C concentrations on the HiOleic-SO diet were significantly greater than with the SO diet. Apo A1 concentrations were consistent with the HDL-C levels. The TC/HDL-C ratio was highest for the Hydrog-SO diet. No significant effect was observed on VLDL, triacylglycerol, Lp[a] or C-reactive protein (CRP) in the different SO-enriched diets. Overall, all of the unhydrogenated SOs resulted in a more favorable lipoprotein profile than Hydrog-SO.

Type 2 Diabetes

Galgani et al, 2008 (positive quality) This was a systematic review to analyze the

209

effect of specific dietary fatty acids on insulin sensitivity and modification of T2D incidence in humans. The authors conducted a literature search in PubMed for randomized clinical trials on human subjects published up to August 2007. As background, descriptive epidemiological studies reported that dietary SFA is directly, and unsaturated fat is inversely, associated with incidence of T2D or impaired insulin sensitivity. This review focused on controlled intervention studies. Forty-one studies were identified in the search, but only 15 trials met the authors' quality criteria that included well-powered studies, evidence of dietary compliance, body weight stability and glucose disposal rate corrected for hepatic glucose production. According to these criteria, the authors included nine trials in non-diabetic subjects (N=358) and six trials in subjects with T2D (N=93). Three studies reported a differential effect on insulin sensitivity, showing decreased insulin sensitivity after SFA diets vs. MUFA or PUFA diets, yet increased insulin resistance was observed after fish oil supplementation in T2D individuals. Of these three studies, the best rated study was by Vesby et al (2001) who reported a significant decrease in insulin sensitivity of 10% after consuming a SFA diet for 12 weeks; whereas, there was no decrease in insulin sensitivity observed with MUFA diet. Twelve of fifteen studies found no effect relating to fat acid type on insulin sensitivity; however, these studies had multiple methodological and design flaws. In contrast, the high-quality Vesby et al study found that SFA diet decreased insulin sensitivity in comparison to a high MUFA diet. Overall, the authors conclude that the role of dietary fatty acids on insulin sensitivity in human subjects should be further studied.

Han et al, 2007 (positive quality) This was an RCT conducted in a group of 40 free-living subjects in an urban area of China. The trial tested if MCT intake has beneficial effects on body weight, insulin sensitivity and serum lipid profiles when administered at moderate dose to overweight T2D subjects. Subjects were randomized to consume 18g per day of either MCT oil or long chain TG (LCT)-rich corn oil administered as part of daily food intake for a 90-day test period. No additional dietary restrictions were recommended. Forty subjects completed the trial (eight males and 32 females, aged 45 to 65 years). The MCT group demonstrated an across-time reduction in body weight and WC, an increase in serum C-peptide concentration, a reduction in homeostasis model assessment of insulin resistance (HOMA-IR) and a decrease in serum cholesterol concentration (P<0.05, repeated measures) and between groups, while there were no differences in these parameters in the LCT group. These changes in the MCT group were also associated with an involuntary reduction in energy intake in the MCT group (P<0.05, repeated measures). The results suggest a link between moderate consumption of MCT and improved risk factors in moderately overweight T2D subjects.

Lindstrom, Ilanne-Parikka et al, 2006 (positive quality) The Finnish Diabetes Prevention Study (DPS) RCT assessed long-term results of the lifestyle intervention originally aimed at reducing risk for developing T2D in high-risk individuals. Overweight (mean BMI=31.1) middle-aged men (N=172) and women (N=350) with impaired glucose tolerance (IGT) were randomly assigned to a lifestyle intervention or control group. After a median of four years of active intervention, participants who were still free of diabetes were followed up for a median of three years, with median total follow-up of seven years. Diabetes incidence, body weight, physical activity and dietary

intakes of fat, SFA and fiber were measured. Subjects in the intervention group were provided with intensive diet-exercise counseling with goals of: Weight reduction more than 5%, less than 30% energy from fat, less than 10% energy from SFA, fiber intake more than 15g per 1,000kcal and 30-minute moderate activity per day. The duration of the intervention ranged from less than one year to six years, with a median length of four years. There were 190 subjects in the intervention group and 165 subjects in the control group at the first post-intervention follow-up visit. During the seven-year follow-up, 75 subjects in the intervention group and 110 in the control group were diagnosed with T2D; the incidence of T2D was 4.3 per 100 person-years in the intervention group and 7.4 per 100 person-years in the control group (P=0.0001), indicating a 43% reduction in relative risk (RR). Beneficial lifestyle changes were maintained after the discontinuation of the intervention, and the corresponding incidence rates during the post-intervention follow-up were 4.6 per 100 person-years in the intervention group and 7.2 per 100 person-years in the control group (P=0.0401), indicating 36% reduction in RR.

Lindstrom, Peltonen et al, 2006 (positive quality) This was an RCT to examine the association of macronutrient composition and energy density on body weight, WC and T2D incidence in the Finnish Diabetes Prevention Study (DPS). Overweight (mean BMI=31.1kg/m2), middle-aged men (N=172) and women (N=350) with IGT were randomized to receive either 'standard care' (control) or intensive dietary and exercise counseling. Baseline and annual examinations included assessment of dietary intake with three-day food records and diabetes status by repeated 75g OGTTs. For these analyses, the treatment groups were combined and only subjects with follow-up data (N=500) were included. Originally, 522 men and women (mean age 55 years) were randomized to either the intervention (N=265, 66% women) or the control group (N=257, 69% women); after exclusion for missing dietary data or lack of follow-up, 500 subjects remained. Subjects in the control group were given general verbal and written health behavior information at baseline without specific individualized advice. Subjects in the intervention group were provided with intensive diet-exercise counseling with goals of: Weight reduction more than 5%, less than 30% energy from fat, less than 10% energy from SFA, fiber intake more than 15g per 1,000kcal, and 30-minute moderate activity per day. The duration of the intervention ranged from less than one year to six years, with a median length of four years. After a mean follow-up of 4.1 years, 114 out of 500 of the participants had been diagnosed with T2D. Comparing the highest to the lowest quartile, hazard ratios (HR) for T2D incidence were 0.38 (95% CI: 0.19 to 0.77) for fiber intake, 2.14 (95% CI: 1.16 to 3.92) for fat intake and 1.73 (95% CI: 0.89 to 3.38) for SFA intake, after adjustment for confounding variables. The authors conclude that dietary fat and fiber intake are significant predictors of sustained weight reduction and progression to T2D in high-risk subjects, even after adjustment for other risk factors.

Lopez et al, 2008 (positive quality) This was a randomized, single-blinded, within-subject crossover controlled trial of 14 healthy men in Spain to determine the degree to which unsaturation of dietary fatty acids influences the postprandial control of insulin secretion and insulin sensitivity. The post-prandial response to high-fat meals enriched in SFAs or MUFAs was assessed using mixed meals with common foods. The isocaloric diet interventions included 9% more fat, replacing carbohydrate in the control

211

NCEP diet, and were as follows: 1) NCEP Step I, 2) high butter (MUFA:SFA, 0.48:1.0), 3) refined olive oil (ROO) (MUFA:SFA, 5.43:1.0), 4) high palmitic sunflower oil (HPSO) (MUFA:SFA, 2.42:1.0), and 5) mixture of vegetable and fish oils (VEFO) (MUFA:SFA, 7.08:1.0). Subjects were normo-triglyceridemic and had normal fasting blood glucose and glucose tolerance. Results showed that high-fat meals increased the post-prandial concentrations of insulin, TG and FFAs, and they increased post-prandial b-cell activity as assessed by the insulinogenic index (IGI), a surrogate measure of first-phase insulin secretion; IGI/HOMA-IR ratio; AUC insulin/glucose ratio; and HOMA of b-cell function (HOMA-B). High-fat meals also decreased post-prandial insulin sensitivity assessed by a glucose and TG tolerance test meal (GTTTM)-determined insulin sensitivity test and the post-prandial Belfiore indices for glycemia and blood FFAs. These effects were significantly improved, in a linear relationship, when MUFAs were substituted for SFAs; subjects became less insulin resistant post-prandially as the proportion of MUFAs, compared with SFAs, in dietary fats increased (VEFO>ROO>HPSO>butter). When the early post-prandial insulin response was used as a measure of b-cell activity, it decreased as the ratio of MUFA/SFA increased. Overall, the findings suggest that b-cell function and insulin sensitivity progressively improve in the post-prandial state as the proportion of MUFAs, relative to SFAs, increases in the diet, suggesting that MUFAs moderate the post-prandial hyperactivity of the pancreatic b-cell. The underlying mechanism likely involves different insulinotropic potentials of individual FFA (e.g., oleic acid has been reported to elicit half the insulin secretion from b-cells as palmitic or stearic acids).

Paniagua et al, 2007 (neutral quality) This was a randomized crossover study on offspring of obese, T2D patients recruited from diabetic patients' records at primary care centers in Cordoba Spain. 59 potential subjects were recruited, but 27 subjects either did not meet the inclusion criteria or refused to participate. Qualifying subjects underwent an OGTT, after which 11 insulin resistant (IR) subjects (four men, seven women) remained in the study. Subjects had a BMI=25kg/m2. Subjects were randomly assigned to three groups and underwent three diet periods of 28 days in a crossover design: 1) Diet high in SFA (SAT) increased 15% energy as SFA, 2) diet high in MUFA (MUFA) increased 15% energy as MUFA, and 3) diet high in CHO increased 18% energy as carbohydrate. Body weight and resting energy expenditure (REE) were not changed over any of the diet interventions. Fasting serum glucose decreased during the MUFA and CHO diet periods compared with SAT diet (5.02±0.1, 5.03±0.1, 5.50±0.2mmol per L, respectively. ANOVA was less than 0.05). The MUFA diet improved insulin sensitivity indicated by lower HOMA-IR, compared to CHO and SAT diets (2.32±0.3, 2.52±0.4, 2.72±0.4, respectively, ANOVA was less than 0.01). Compared to a CHO breakfast, the AUC of post-prandial glucose and insulin were lower with MUFA or SAT breakfasts (11.9±2.7, 7.8±1.3, 5.84±1.2mmol x 180 minutes per L, ANOVA less than 0.05; and 2,667±329, 1,004±147, 1,253±140, pmol x 180 minutes per L, ANOVA was less than 0.01, respectively). Integrated glucagon-like peptide-1 increased with MUFA and SAT breakfasts compared with isocaloric CHO breakfast. Fasting and post-prandial HDL-C increased with MUFA diet and the AUC of TG decreased with CHO diet. Fasting pro-insulin decreased, while stimulated ratio PI/I was not changed by MUFA diet. Overall, weight maintenance with a MUFA-rich diet improves HOMA-IR and fasting proinsulin levels in IR subjects.

212

Pérez-Jiménez et al 2001 (positive quality) This was a randomized crossover study to investigate the effect of substitution of SFA in the diet with MUFA (Mediterranean diet) or a high-CHO diet for 28 days each. Fifty-nine normolipidemic subjects (30 men, 29 women; mean age=23.1) were recruited and completed the trial. Dietary information was collected over seven consecutive days. The initial run-in period included all subjects on a SFA-enriched diet with 38% fat (20% SFA). All participants were randomized in a crossover design with two dietary periods: High MUFA and high CHO. In comparison to the SFA diet, the CHO and MUFA diets decreased LDL-C and HDL-C. Steady state plasma glucose decreased and basal and insulin-stimulated 2-deoxy-glucose uptake increased in both diets, indicating improved insulin sensitivity. Fasting free fatty acids levels were correlated positively with plasma glucose levels.

Salmeron et al, 2001 (positive quality) This was a prospective cohort analysis of subjects from the Nurses' Health Study. Information from 98,462 respondents (women aged 34 to 59 years) whose dietary intake was assessed in 1980 was used; dietary information was assessed from a validated, semi-quantitative food-frequency questionnaire (FFQ) and updated in 1984, 1986 and 1990. After exclusion, 84,204 respondents were followed for T2D incidence from 1980 to 1994. During 14 years of follow-up, 2,507 incident cases of T2D were diagnosed. Both SFA and MUFA intakes were associated with increased RR of T2D in age and BMI adjusted analyses. This effect was greatly attenuated for SFA with multivariate analysis, including all major types of fatty acids and there was NS positive association between MUFA intake and risk of T2D after multivariate analysis. Polyunsaturated fatty acid intake, on the other hand, was inversely associated with T2D risk in all analyses. Trans fatty acid and dietary cholesterol were positively associated with risk of T2D. Using isocaloric energy substitutions, the substitution of 5% of energy from SFA with PUFA resulted in a 35% lower risk of T2D; whereas replacement of 5% SFA with CHO resulted in no change in T2D risk. Replacement of 2% energy from TFA with PUFA was associated with a 40% decreased risk of T2D.

Shah et al, 2007 (neutral quality) This was a randomized crossover trial, conducted at the General Clinical Research Center of the University of Texas Southwestern Medical Center at Dallas, which examined the effects of specific fatty acids on post-prandial TG, glucose and insulin concentrations in 11 men with T2D (mean age 54.6±12.2 years). All subjects received an isocaloric background diet containing 15% energy as PRO, 35% as fat and 50% as CHO throughout the study period. At intervals of three to four days, after an overnight fast, each subject consumed a mixed test meal for post-prandial assessment on four occasions. Each test meal provided 1,000kcal with 15% energy as PRO, 35% as CHO and 50% as fat. The type of fat in the test meal varied on each occasion, and was rich in palmitic acid, oleic acid, LA or eicosapentaenoic acid (EPA) and DHA (made using palm oil, olive oil, safflower oil and salmon oil, respectively). According to repeated measures ANOVA, the insulin response (P=0.0002), but not the glucose response, was significantly different between meals; the insulin response was lower in meals rich in oleic acid or EPA and DHA than in meals rich in palmitic acid or LA (P<0.01). The TG response did not reach statistical significance (P=0.06), but tended to be lower with EPA and DHA than with the other fatty acids. Overall, compared to palmitic or linoleic acids, oleic acid or EPA and DHA may modestly lower the insulin response in T2D patients, without

213

deteriorating the glucose response.

St. Onge et al, 2003 (neutral quality) This was a randomized crossover trial conducted in Canada to determine whether MCT or long chain triglyceride (LCT) consumption influences energy expenditure (EE) and substrate oxidation in overweight women. Twenty-two women (mean age 44.3±3.8 years) became inpatients at the Mary Emily Clinical Nutrition Research Unit (CNRU) of McGill University and were enrolled in two dietary phases lasting 27 days each, separated by a four- or eight-week washout period of habitual diet. All meals were provided and diets contained 40% energy as fat, 15% energy as PRO and 45% energy as CHO. During the LCT phase, 75% of fat was derived from beef tallow or a blend of SFA and unsaturated vegetable oils, while during the MCT phase, 50% of fat was provided by MCT oil, 10% by olive oil, and 5% by butter, coconut oil and flaxseed oil each. Seventeen subjects completed the trial. There were NS differences between diet phases in total and subcutaneous adipose tissue volume; however, average EE and fat oxidation were greater (P<0.05) during MCT than LCT consumption (0.95±0.019 vs. 0.90±0.024kcal per minute, respectively, for EE and 0.080±0.0026 vs. 0.075±0.0022g per minute, respectively, for fat oxidation, respectively, both P<0.05). These results show that long-term consumption of MCT enhances EE and fat oxidation in obese women compared to LCT consumption, and MCT may, therefore, decrease weight gain due to increased EE.

Vessby et al, 2001 (positive quality) This was an RCT, conducted in five centers (Sweden, Italy, Finland, Denmark and Australia) as part of the KANWU study, that examined whether a change of dietary fat quality affects insulin sensitivity in humans. The KANWU study included 162 healthy subjects (86 males, 76 females, aged 30 to 65 years) chosen at random to receive a controlled, isocaloroic diet for three months containing either a high concentration of SFA or MUFA (within the context of 37% energy as fat). Additionally, within groups, there was a second random assignment of subjects to supplements with fish oil (3.6g n-3 fatty acids per day) or olive oil placebo as capsules. The study duration was 90 days, preceded by a two-week stabilization period. Insulin sensitivity was significantly impaired in subjects on the SFA diet (-10%, P=0.03) but did not change on the MUFA diet (+2%, NS); the difference between diets was statistically significant (P=0.05). Insulin sensitivity was 12.5% lower on the SFA diet and 8.8% higher on the MUFA diet (P=0.03), but these beneficial effects were only seen at a total fat intake below median (37% of energy). Insulin secretion, however, was not affected. The addition of n-3 fatty acids did not influence insulin sensitivity or secretion. The beneficial effects of substituting a MUFA for a SFA diet on insulin sensitivity were only seen when total fat intake was below 37% of energy. Under these conditions, insulin sensitivity was 12.5% lower and 8.8% higher on the SFA diet and MUFA diets, respectively (P=0.03). Low-density lipoprotein cholesterol increased on the SFA diet (+4.1%, P<0.01), but decreased on the MUFA diet (-5.2%, P<0.001), while lipoprotein (a) [Lp(a)] increased by 12% on the MUFA diet (P<0.001). Overall, a change in the proportion of dietary fat, replacing SFA with MUFA, improves insulin sensitivity, but has no effect on pancreatic insulin secretion. However, the beneficial effect of MUFA on insulin sensitivity is lost in individuals with high fat intake.

Overview table

214

Author, Year, Study Design, Class, Rating	Study Description, Duration	Study Population, Demographics	Intervention	Significant Outcomes	Limitations
Azadbakht L, Mirmiran P et al, 2007 Study Design: Randomized controlled trial Class: A Rating: Positive quality	Three months.	46 dyslipidemic adolescents. 23 female, 23 male. Mean age: 14.5 years (range 10 to 18 years). 44 subjects completed study.	Determined effects of the NCEP Step II diet on LDL and HDL size. Subjects randomized to control group (instructed to "eat as usual") or the Step II diet. Intervention group received diets that were 30% total fat, <7% SFA, <200mg cholesterol, <15% MUFA and <10% PUFA. Subjects visited every two weeks and contacted by a nutritionist daily. Subjects completed three-day diet records every two weeks.	NS Δ in body weight or physical activity in either group. Step II diet resulted in greater ↓ in TC (-13±4 vs. -2±3mg per dL, $P<0.001$) and LDL-C (-9±2 vs. 3±0.6mg per dL, $P<0.01$) and higher ↑ in LDL particle size (1.7±0.4 vs. 0.1±0.4nm, $P<0.001$). NS Δ in HDL particle size.	Small sample size covering broad age range. Results not reported by gender.

215

Berglund L, Lefevre M et al, 2007 Study Design: Randomized Crossover Trial Class: A Rating: Positive quality	Three diets were fed in double-blind, three-way crossover. Seven-week diet period with four- to six-week washout.	110 subjects with high metabolic risk profile enrolled; 85 completed all three diets. 52 men, 33 women. Mean age: 35.5±9.2 years (range 21 to 61 years). Location: United States.	Compared MUFA with CHO as a replacement for SFA. The three diets were average American diet (AAD), carb-replacement diet (CHO) and MUFA-replacement diet (MUFA). 7% energy from SFA replaced with either CHO (primarily complex) or MUFA. All food was provided (following NCEP step I). Blood samples drawn at five, six and seven weeks of each diet.	LDL-C was lower with CHO (-7.0%) and MUFA (-6.3%) diets, compared to AAD. HDL-C) differences were less for MUFA (-4.3%) than CHO diet (-7.2%). Lipoprotein (a) [Lp(a)]concentration ↑ with both CHO (20%) and MUFA (11%) diets, relative to AAD.	Subjects body weights maintained, so dietary effects on lipid levels under "free-living" conditions were not determined.

216

Bourque C, St-Onge MP et al, 2003 Study Design: Randomized Crossover Trial Class: A Rating: Positive quality	27-day diet phases with eight-week washout. Partially inpatient trial.	22 overweight women enrolled; 17 completed trial. Mean age: 44±4 years. BMI: 32kg/m^2.	Compared Functional oil (FctO) with MCT as 50% of fat, phytosterols (22mg per kg BW) and n-3 FA as 5% of fat with beef tallow-based diet (BT) as control (treatment fat completely beef tallow). 17 overweight women consumed each oil as part of an energy controlled diet [three isocaloric meals per day (45% CHO; 15% PRO; 40% FAT with 75% fat as treatment fat)] for 27 days, with four-week washout. Meals were consumed at the Clinical Nutrition Research Unit (CNRU) at McGill University. Fasting blood samples taken at days one, 26 and 28 of each diet phase.	TC was 9.1% ↓ on FctO (4.37±0.20mmol per L) vs. BT (4.80±0.20mmol per L) ($P<0.0001$). Mean plasma LDL-C ↓ with FctO (2.39±0.15mmol per L) vs. BT (2.86±0.16mmol per L) ($P<0.0001$), a 16% difference between diets. No Δ in HDL-C and TG during both dietary phases. Ratios of HDL:LDL and HDL:TC ↑ by 22% and 11% ($P<0.01$), respectively, on FctO vs. BT. No Δ in plasma total homocysteine with FctO, but ↓ ($P<0.05$) with control, ↑ total homocysteine end points with FctO (6.95±0.33mmol per L) vs. BT (6.27±0.28mmol per L) ($P<0.05$). Plasma glutathione ↑ by 0.41mmol per L with FctO. Consumption of a functional oil composed of MCT, phytosterols and n-3 FAs for 27 days improved the lipid profile of overweight women.	22 subjects enrolled, but only 17 completed trial; eight were postmeno-pausal and four were smokers.

217

Buonacorso V, Nakandakare ER et al, 2007 Study Design: Randomized controlled trial. Class: A Rating: Positive quality	Two-week run-in followed by four-week diet.	30 health subjects (nine male, 21 female, matched for age, sex and BMI). Location: Brazil.	Examined effects of TFA, SFA and PUFA enriched diets on HDL2 and HDL3 composition under fasting and postprandial conditions. Also examined rates of cholesterol efflux from macrophages induced by whole plasma and HDL-C subfractions. After a two-week run-in (30% energy=fat, less than 10%=SFA, less than 300mg cholesterol per day), subjects were assigned to a four-week experimental diet period. Three diets had similar [MUFA], but had either 8.3% TFA (N=10), 14.6% PUFA (N=10) or 13.2% SFA (N=10).	NS differences over time in plasma TC and TG concentration (repeated measures analysis). Modest, but significant differences in composition of HDL2, HDL3 and HDL2+HDL3. For HDL2: TFA diet ↑ concentrations of HDL2 TC, phospho-lipids, apoAI and apoAII; ↓ ratio of lipids:apoA over time. SFA diet ↓ TC, and apoAI and apoAII and ↑ lipids:apoA over time; the PUFA diet ↓ only lipids:apoA over time. HDL2 TG did not differ with diet (three-way factor interaction analysis), but ↓ over time (final P=0.041). Total HDL: TFA diet ↑ TC, phsopholipids, apoAII and ↓ lipids:apoA; SFA diet ↓ TC, phospholipids, apoAI and apoAII. HDL3: When time and period were considered together, compared with SFA diet, phospholipids, apoAI and apoAII were higher and lipids:apoA was ↓ with TFA diet; apoAI and apoAII were ↑ and lipids:apoA was ↓ with PUFA diet. No Δ in cholesterol efflux (CHE) (% radioactive cholesterol removal) with diets.	Subject number small. Although there were significant differences in lipid and apoA composition of HDL subfractions with diet, differences were modest and may not be biologically important. Potential bias as recruited subjects were medical school employees.

218

Chen SC, Judd JT et al, 2009 Study Design: Randomized Crossover Trial Class: A Rating: Positive quality	Randomized cross-over design: 23 days per diet (no wash out). Mixed effects model for analysis of data for repeated measurements. T-test to compare mean baseline values of men and women.	N=23 (14 men, nine women). Mildly hyper-cholesterolemic. Attrition: One. Mean age: 51.7±2.4 years. BMI: 28.0±0.6kg/m^2. No information on ethnicity or demographics. Location: United States.	Typical American Diet (TAD) designed to provide 34% energy from fat with ratio of SFA:MUFA:PUFA of 1:1:0.5. TAD was tested ±PS at 3.3g per day (1.8g per serving of PS as ester from vegetable oil). Step I diet designed to provide <30% energy from fat and <7% energy from SFA with ratio of SFA:MUFA:PUFA of 1:1.5:1. Step I was tested ±PS at 3.3g per day (1.8g per serving of PS as ester from vegetable oil).	TC, HDL-C, LDL-C, ApoA1 and ApoB were 4.3%, 5.3%, 4.5%, 2.8% and 2.5% lower, respectively, with Step I diet vs. TAD. Diet had no effect on the TC:HDL-C ratio. PS significantly ↓ TC, LDL-C, and ApoB by 9.0%, 12.4% and 6.1% and TC/HDL-C ratio by 9.6%, respectively. HDL-C and ApoA1 were not affected by PS. PS effect in lowering plasma TC and LDL-C was independent of, and additive to, the effect of Step 1 diet. Plasma levels of retinoids, carotenoids and tocopherols were significantly ↓ with PS intake, except for retinol and alpha tocopherol.	Subject population was restricted to mildly hyper-cholesterol-emic adults, in particular, middle-aged men and non-HRT postmenopausal women. No washout between diet phases.

Chung BH, Cho BH et al, 2004 Study Design: Randomized crossover trial. Class: A Rating: Positive quality	Subjects on two diets for 20 days, with three- to four-week washout.	16 healthy normo-lipidemic men and postmenopausal women. Eight men (seven white, one black), mean age: 35.3±4.5 years (range 33 to 49 years). Eight women (five white, three black), mean age: 51.9±6.6 years (range 45 to 62 years). All enrolled and completed both diet phases. Location: United States.	Subjects adopted each of two diets for 20-day period, with three- to four-week washout. Meals prepared by the research center with (%energy) 15% PRO, 50% CHO, 35% fat and 175mg cholesterol per 1,000kcal. SFA-rich diet: 18.8% SFA, 11.5% MUFA and 4.7% PUFA; PUFA:SFA=0.25. PUFA-rich diet: 7.5% SFA, 12% MUFA and 15.5% PUFA; PUFA:SFA=2.0.	TC ↓ significantly with PUFA diet due to ↓ LDL-C (-12.3%, P<0.05) and HDL-C (-3.8%, NS); no Δ after a SFA diet. Appearance of postprandial TRLs in plasma at four hours was linked to significant ↓ in LDL-C (-7.4%) and HDL-C (-4.8%) after PUFA diet; not observed after SFA diet. At seven hours, LDL-C and HDL-C returned to fasting concentrations without postprandial TRL accumulation after PUFA diet, but with significant postprandial TRL accumulation after SFA diet. The in vivo postprandial clearance of LDL-C and HDL-C was ↑ after PUFA- than SFA-rich diet. Appearance of postprandial TRLs in plasma ↑ the CETP-mediated transfer of cholesteryl esters from LDL and HDL to TRLs in vitro. Interpretation is that there is ↑ in rate of hepatic removal of post-prandial TRLs, which carry cholesterol accepted from LDL and HDL, after PUFA vs. SFA diet.	Small sample size and recruitment methods not described.

Dabadie H et al 2005 Study Design: Randomized Crossover Trial Class: A Rating: Positive quality	Two test diets for five weeks separated by four-week washout.	25 monks at Benedictine monastery. Mean age: 61 years (range 35 to 88 years). Location: France.	Compared effects of two moderate intakes of myristic acid on plasma lipids. Both intervention diets provided 2,200kcaland 15% energy from PRO, 12% from oleic acid, 6% from LA, 1% from ALA and 200mg cholesterol per day. In diet one, 30% calories were from fat (8% SFA, 0.6% myristic acid); in diet two, 34% calories were from fat (11% SFA, 1.2% myristic acid).	Compared to baseline, both diets ↓ TC, LDL-C and TG (P<0.001). Plasma TG were ↓ after diet two than after diet one, whereas HDL-C was ↑ (P<0.05). Both diets increased alpha-linolenate of cholesteryl esters (CE) (P< 0.05). Only diet two ↑ DHA of CE (P<0.05). Overall, moderate intake of myristic acid (1.2% total kcal) has beneficial effect and ↑ DHA of CE.	Small sample size of a relatively homogenous group of men.

221

| Furtado et al 2008

Study Design: Randomized Crossover Trial

Class: A

Rating:

Positive quality | Subjects on each of three diets for six weeks, two-week washout. | N=191 adult men and women (44% women, mean age 53±10 years) enrolled; N=162 completed the trial.

Location: United States. | Examined difference in apoB lipoproteins with and without apoC-III after three healthy diets based on DASH diet.

Subjects were randomly assigned each of three diets for six weeks.

The three diets differed by emphasis on either CHO (Carb) [58% energy CHO, 27% fat (6% SFA, 13% MUFA, 8% PUFA) and 15% Prot (5.5% meat, 9.5% plant/dairy)].

Unsaturated fat (Unsat) [48% of energy from CHO, 37% fat (6% SFA, 21% MUFA, 10% PUFA) and 15% Prot (5.5% meat, 9.5% plant/dairy)].

Protein (Prot) [48% of energy from CHO, 27% fat (6% SFA, 13% MUFA, 8% PUFA) and 25% PRO (9% meat, 15% plant/dairy)]. | Compared to Carb diet, Prot diet ↓ plasma apoB and TG in VLDL with apoC-III (16%, P=0.07; 11%, P=0.05, respectively) and apoB in LDL with apoC-III (16%, P=0.04).

Compared with the Unsat diet, Prot diet ↓ TG in VLDL with apoC-III (16%, P=0.02) and compared with baseline, Prot diet ↓ apoB in LDL with apoC-III (11%, P=0.05).

All three diets reduced plasma total apoB (6% to 10%, P<0.05), apoB in the major type of LDL, LDL without apoC-III (8% to 10%, P <0.01), and ↓ the ratio of apoC-III to apo E in VLDL. | Four-week results were similar to the six-week results, suggesting a plateau in diet effect. |

Galgani JE et al. 2008 Study Design: Systematic Review Class: M Rating: Positive quality	Literature search in PubMed for RCTs published up to Aug 2007.	41 studies were identified; only 15 trials met the authors' quality criteria that included well-powered studies, evidence of dietary compliance, BW stability and glucose disposal rate corrected for hepatic glucose production. According to these criteria, the authors included nine trials in non-diabetic subjects (N=358) and six trials in subjects with T2D (N=93). Location: International studies.	Systematic review to analyze effect of specific dietary FAs on insulin sensitivity and modification of T2D incidence.	Three studies reported a differential effect of FA intake on insulin sensitivity, showing ↓ insulin sensitivity after SFA diets vs. MUFA or PUFA diets. ↑ insulin resistance was observed after fish oil supplementation in T2D subjects. Best rated study was by Vesby et al (2001) who reported a significant 10% ↓ in insulin sensitivity after consuming a SFA diet for 12 weeks; there was no ↓ in insulin sensitivity after the MUFA diet. 12 of 15 studies found no effect of FA type on insulin sensitivity. Role of dietary FAs on insulin sensitivity in human subjects should be further studied.	Studies that did not report an association had multiple methodological and design flaws.

223

Han JR et al 2007 Study Design: Randomized Controlled Trial Class: A Rating: Positive quality	90 days.	40 subjects enrolled and completed the trial (Eight males; 32 females). Age: 45 to 65 years. Free-living, moderately overweight T2D urban residents. Location: China.	Trial tested if MCT intake has beneficial effects on body weight, insulin sensitivity and serum lipid profile when administered at a moderate dosage to overweight T2D subjects. Subjects were randomized to consume 18g per day of either MCT oil or LCT-rich corn oil for 90-day period. No additional dietary restrictions were recommended.	MCT group demonstrated a ↓ in body weight and WC, an ↑ in serum C-peptide, a ↓ in HOMA-IR and ↓ in TC over time (all P<0.05) and between groups. No differences in these parameters in LCT group. Results suggest a link between moderate consumption of MCT and improved risk factors in overweight T2D subjects.	Homo-geneous study sample.
Hu FB, Van Dam RM et al, 2001 Study Design: Meta-analysis or Systematic Review Class: M Rating: Positive quality	Medline database search from 1966 - 2000. Included cited references when relevant.	International Men and women in subpopulations in US, Europe, and Israel. Age range 25 - 89 years N = 20-4,903 subjects	14 epidemiologic studies and 5 cross-sectional studies of dietary fat and carbohydrate and association with developing hyperglycemia or type 2 diabetes	Higher intakes of polyunsaturated fatty acids (PUFA improved glucose metabolism and insulin resistance Long chain PUFA also improved glucose metabolism and insulin resistance Higher intakes of saturated fatty acids (SFA) adversely affected glucose metabolism and insulin resistance High intakes of vegetable fat and PUFA were associated with a decreased risk of type 2 diabetes	

Jakobsen MU, O'Reilly EJ et al, 2009 Study Design: Meta-analysis or Systematic Review Class: M Rating: Positive quality	Review of pooled analysis: Proportional Hazards Model.	Specific for each study.	Replacement of SFA intake with MUFA, PUFA and CHO. During four- to 10-year follow-up, 5,249 coronary events and 2,155 coronary deaths occurred among 344,696 persons (71% women).	Significant inverse association between substitution of SFA with PUFAs and risk of coronary events (HR: 0.87, 95% CI: 0.77, 0.97) and risks of coronary deaths (HR: 0.74, 95% CI: 0.61, 0.89). Association between substitution of MUFAs and risk of coronary events (HR: 1.19; 95% CI: 1.00, 1.42), but not risks of coronary deaths. Significant association between substitution of CHO and risk of coronary events (HR: 1.07; 95% CI: 1.01, 1.14), but not risks of coronary deaths. No effect modification by sex or by age.	Authors did not describe demo-graphics of American or European populations.
Kralova Lesna I, Suchanek P et al, 2008 Study Design: Randomized Crossover Trial Class: A Rating: Positive quality	Four weeks per diet (no wash-out).	14 males; no attrition. Caucasian. Age: 18 to 55 years.	Two isocaloric diets with 40% fat: 1) SFA diet: 52% SFA, 34% MUFA, 14% PUFA 2) PUFA diet: 26%SFA, 33% MUFA, 41% PUFA.	PUFA diet significantly ↓ TC, LDL-C and HDL-C, compared to SFA diet. ApoB and apoA1 concentrations were lower, although not significantly. Cholesterol efflux CHE was not different on either diet and was comparable to baseline. No correlation between CHE and lipids and lipoprotein concentrations on either diet. ↓ in HDL-C resulting from replacement of SFA by PUFA does not affect rate of CHE.	Only generalizable to population of healthy Caucasian men; however, this is a population at risk.

225

Lefevre M, Champagne CM et al, 2005 Study Design: Non-Randomized Crossover Trial Class: C Rating: Positive quality		87 men. Age: 22 to 64 years. 84% white, 11% African American. Location: United States.	Three diets that differed in total fat: The Average American Diet (AAD), the Step I diet and Step II diet.	Step I and II diets ↓ LDL-C by 6.8% and 11.7%, HDL-C by 7.5% and 11.2% and ↑ TG by 14.3% and 16.2%, respectively, compared to AAD. Significant positive correlation between Step II diet and Δ in LDL-C, ratio of TC to HDL-C and baseline percentage body fat, BMI and insulin. Subjects in the upper one-half of fasting insulin concentrations averaged only 57% of the ↓ in LDL-C of subjects in the lower half, with the Step II diet.	None.
Lichtenstein AH, Matthan NR et al, 2006 Study Design: Randomized Controlled Trial Class: A Rating: Positive quality		30 subjects (16 women, 14 men). Mean age: 63 years. Ethnicity was not identified. Mean BMI: $26.2 kg/m^2$. Location: United States.	Subjects randomly assigned to five experimental diets for 35-day period. Diets provided 30% energy from fat; two-thirds of fat provided by experimental oils. Experimental oils: 1) SO, 2) LoSFA-SO, 3) HiOleic-SO, 4) loALA-SO, and 5) Hydrog-SO. Analysis of variance with main effect of diet and subject as repeated measure was carried out for each outcome.	LDL-C levels were highest in subjects on Hydrog-SO or loALA-SO diets. In men, HDL-C was significantly ↑ with HiOleic-SO. Ratios of LDL to apoB and HDL to apoAI were similar at end of diet phases. NS differences in VLDL, TG, Lp[a] or CRP in the different SO-enriched diets.	None.

226

Lindstrom J, Ilanne-Parikka P et al 2006 Study Design: Randomized Controlled Trial Class: A Rating: Positive quality	Finnish Diabetes Prevention Study. Duration of intervention from less than one year to six years; median, four years.	522 men and women. Mean age: 55 years. Randomized to intervention (N=265, 66% women) or control (N=257, 69% women). 190 subjects in intervention group and 165 subjects in the control group at the first post-intervention follow-up visit. Location: Finland.	Intervention group provided with intensive diet-exercise counseling with goals of weight reduction of ≥5%, <30% energy from fat, <10% energy from SFA, 15g per 1,000kcal fiber and 30 minutes of moderate physical activity per day.	During a seven-year follow-up, 75 subjects in intervention group and 110 in control group were diagnosed with T2D. Incidence of T2D was 4.3 of 100 person-years in the intervention group and 7.4 of 100 person-years in the control group (P=0.0001), indicating a 43% ↓ in RR. Lifestyle Δ maintained after intervention stopped; T2D incidence rates for post-intervention follow-up were 4.6 of 100 person-years in the intervention group and 7.2 of 100 person-years in control (P=0.0401), indicating 36% ↓ in RR.	Subjects may be more health conscious than the general population.
Lindstrom J, Peltonen M et al 2006 Study Design: Randomized Controlled Trial Class: A Rating: Positive quality	Finnish Diabetes Prevention Study. Duration of intervention from less than one year to six years; median, four years.	522 men and women. Mean age: 55 years. Overweight (mean BMI: 31.1kg/m^2), middle-aged men (N=172) and women (N=350) with IGT. Randomized to intervention (N=265, 66% women) or control (N=257, 69% women) to receive either standard care or intensive dietary and exercise counseling. Location: Finland.	Baseline and annual examinations included assessment of dietary intake with three-day food records and diabetes status by repeated 75g OGTTs. Intervention counseling with goals of weight reduction >5%, <30% energy from fat, <10% energy from SFA, >15g per 1,000 kcal fiber and 30 minutes of moderate activity per day.	After a mean follow-up of 4.1 years, 114 out of 500 of the participants had been diagnosed with T2D. Comparing highest to lowest quartile, HR for T2D incidence = 0.38 (95% CI: 0.19 to 0.77) for fiber intake, 2.14 (95% CI: 1.16 to 3.92) for fat intake and 1.73 (95% CI: 0.89 to 3.38) for SFA intake, after adjustment for confounding variables.	None.

227

Lopez S, Bermudez B et al, 2008 Study Design: Randomized Crossover Trial Class: A Rating: Positive quality		14 men (healthy, normotriglyceridemic with normal glucose tolerance). Mean age: 27 years. Mean BMI: 23.9kg/m^2. Location: Spain.	Four isocaloric diets with 9% ↑ fat (replacing CHO in Step I diet as control): 1) Control Step I 2) High butter (MUFA:SFA, 0.48:1.0) 3) Refined olive oil (ROO) (MUFA:SFA, 5.43:1.0) 4) High palmitic sunflower oil (HPSO) (MUFA:SFA, 2.42:1.0) 5) Mixture of vegetable and fish oils (VEFO) (MUFA:SFA, 7.08:1.0).	High fat meals: ↑ postprandial insulin, TG and FFAs ↑ pancreatic b-cell activity ↓ insulin sensitivity. Postprandial insulin sensitivity ↑ and as proportion of MUFA vs. SFA ↑. VEFO>ROO>HPSO>Butter. B-cell activity, measured as early postprandial insulin response, ↓ as proportion of MUFAs vs. SFAs ↑.	Relatively ↓ subject number (N=14).

228

Paniagua JA, de la Sacristana AG et al, 2007 Study Design: Prospective Cohort Study Class: B Rating: Positive quality		Crossover design. Offspring of obese, T2D patients. 59 subjects originally recruited. 27 subjects did not meet inclusion criteria. Qualifying subjects underwent OGTT, after which 11 insulin-resistant (IR) subjects (four men, seven women) remained in the study. Subjects had a BMI: 25kg/m^2. Location: Spain.	Three diet periods; 28 days. Crossover design: 1) High SFA: ↑ 15% energy as SFA 2) High MUFA: ↑ 15% energy as MUFA 3) High CHO: ↑ 18% energy as CHO.	No Δ in BW and REE were with any intervention. ↓ fasting serum glucose with MUFA and CHO diet compared with SFA. (5.02±0.1, 5.03±0.1, 5.50±0.2mmol per L, respectively; ANOVA<0.05). MUFA diet. ↓ HOMA-IR, compared to CHO and SFA diets (2.32±0.3, 2.52±0.4, 2.72±0.4, respectively, ANOVA<0.01). Compared to CHO breakfast, ↓ AUC postprandial glucose and insulin with MUFA or SFA breakfasts (11.9±2.7, 7.8±1.3, 5.84±1.2mmol x 180 minutes per L, ANOVA<0.05 and 2,667±329, 1,004±147, 1,253±140, pmol x 180 minutes per L, ANOVA<0.01, respectively). ↑ fasting and postprandial HDL-C with MUFA and ↓ AUC of TG with CHO diet. Fasting proinsulin (PI). No Δ in stimulated PI/I with MUFA. ↑ GLP-1 with MUFA and SFA breakfasts compared with isocaloric CHO breakfast. ↑ fasting and postprandial HDL-C with MUFA and ↓ AUC of TG with CHO diet. ↓ fasting proinsulin (PI). No Δ stimulated PI/I with MUFA.	None.

Perez-Jimenez F, Lopez-Miranda J et al, 2001 Study Design: Randomized Controlled Trial Class: A Rating: Positive quality	28-day run-in and dietary periods.	59 normolipidemic subjects (30 men, 29 women). Mean age: 23.1 years.	Dietary information collected over seven consecutive days. Run-in period: All subjects on SFA diet 38% fat (20% SFA). Randomized to two dietary periods: 1) MUFA: 38% fat (22% MUFA) 2) CHO: 57% CHO, 28% fat (<10% SFA, 12% MUFA).	In comparison to SFA diet, CHO and MUFA diets ↓ mean plasma LDL-C (P<0.001) and HDL-C (P<0.001). Fasting plasma insulin and non-esterified FA (NEFA) were significantly ↑ during SFA diet than CHO or MUFA diets. Steady state plasma glucose ↓ on both CHO and MUFA diets. 2-deoxy glucose uptake ↑ in both CHO (P<0.001) and MUFA (P<0.001) diets. Fasting FFA levels were correlated positively with plasma glucose levels.	None.

Salmeron J, Hu F et al, 2001 Study Design: Prospective Cohort Study Class: B Rating: Positive quality	Nurses' Health Study. 14-year follow-up.	98,462 subjects with FFQ data in 1980. Women aged 34 to 59 years. After exclusion, 84,204 Nurses were followed for T2D incidence from 1980 to 1994. Location: United States.	Dietary assessment with validated, semi-quantitative 61-item FFQ in 1980; FFQ expanded to 116 food items in 1984. FFQ administered in 1980, 1984, 1986 and 1990. Two-year follow-up on diabetes diagnosis (exclusion of T1D and gestational diabetes). Criteria for T2D diagnosis was that of National Diabetes Group and WHO.	2,507 cases of T2D in 14-year follow-up. SFA and MUFA intakes associated with ↑ RR of T2D in age and BMI adjusted analyses. Positive association of SFA with RR for T2D was greatly attenuated with multivariate analysis including all major types of FAs NS positive association of MUFA and RR for T2D after multivariate analysis. PUFA intake was inversely associated with T2D risk in all analyses. TFA and dietary cholesterol were positively associated with risk of T2D. With isocaloric energy substitutions, substitution of 5% energy from SFA with PUFA resulted in a 35% ↓ risk of T2D. Replacement of 5% SFA with CHO resulted in no Δ in T2D risk. Replacement of 2% energy from TFA with PUFA associated with 40% ↓ risk of T2D.	None.

Shah M et al 2007 Study Design: Randomized Crossover Trial Class: A Rating: Positive quality	Three- to four-day intervals (after overnight fast); each subject consumed mixed test meal on four occasions.	11 men with T2D. Mean age: 54.6±12.2 years. Location: United States.	All subjects received an isocaloric diet with 15% energy as PRO, 35% as fat and 50% as CHO. The type of fat in test meal varied on each occasion, and was rich in either: 1) Palmitic acid, 2) oleic acid, 3) LA or 4) EPA and DHA.	The insulin response (P=0.0002), but not glucose response, was significantly different between meals. The insulin response was ↓ in meals rich in oleic acid or EPA and DHA than to meals rich in palmitic acid or linoleic acid (P<0.01). The TG response did not reach statistical significance (P=0.06), but tended to be ↓ with DHA+EPA than in meals rich in the other FAs. Oleic acid or EPA+DHA may modestly ↓ the insulin response in T2D patients, without harming glucose tolerance.	Small sample size.
St-Onge MP et al 2003 Study Design: Randomized Crossover Trial Class: A Rating: Positive quality	Subjects were enrolled in two dietary phases of 27 days each, separated by a four- or eight-week washout of habitual diet.	22 overweight women. Mean age: 44.3±3.8 years. 17 subjects completed trial. Location: Canada.	All meals were provided and diets contained 40% energy as fat, 15% energy as PRO and 45% energy as CHO. During the long chain triglyceride (LCT) phase, 75% of fat was from beef tallow or a blend of SFA and unsaturated vegetable oils. During the MCT phase, 50% of fat was provided by MCT oil, 10% by olive oil and 5% by butter, coconut oil and flaxseed oil.	NS differences between diet phases in total and subcutaneous adipose tissue volumes. Average energy expenditure (EE) and fat oxidation were greater during MCT than LCT consumption. 0.95±0.019 vs. 0.90±0.024kcal per minute for EE P<0.05. 0.080±0.0026 vs. 0.075±0.0022g per minute for fat oxidation, P<0.05. Results show that long-term consumption of MCT enhances EE and fat oxidation in obese women compared to LCT consumption. MCT may ↑ weight loss due to increased EE.	None.

Vessby B et al 2001

Study Design: Randomized Controlled Trial

Class: A

Rating:

Positive quality | Part of the KANWU study.

Three months, proceeded by a two-week stabilization period. | 162 adults (86 males, 76 females)

Age: 30 to 65 years.

Location: Five centers (Sweden, Italy, Finland, Denmark and Australia). | Subjects were randomized to diets comprised of 37% energy (E) from fat as either high SFA or high MUFA.

SFA %E 17%±8%.

Within groups, there was a second assignment to fish oil (3.6g n-3 FA per day) capsules or olive oil-placebo capsules. | Insulin sensitivity was significantly impaired on SFA diet (-10%, P=0.03), but did not Δ on MUFA diet (+2%, NS). Difference between diets was statistically significant (P=0.05).

Insulin sensitivity was 12.5% ↓ on the SFA diet and 8.8% ↑ on the MUFA diet (P=0.03).

Beneficial effects only seen at a total fat intake <37% of energy.

Insulin secretion was not affected.

The addition of n-3 fatty acids did not influence insulin sensitivity or secretion.

LDL-C ↑ on the SFA diet (+4.1%, P <0.01), but ↓ on the MUFA diet (-5.2%, P <0.001).

Lipoprotein (a) ↑ by 12% on the MUFA diet (P <0.001). | None. |

Research recommendations

Determine the benefits and risks of MUFA vs. PUFA as an isocaloric substitute for SFA. Confirm the metabolic pathways through which dietary SFA affect serum lipids, especially as some SFA (e.g., stearic acid) do not appear to affect blood lipid levels.

Search plan and results

Inclusion Criteria

Subjects/Population

- *Age*: Two years through adult
- *Setting*: US and International
- *Health status*: Healthy and those with elevated chronic disease risk (CHD/CVD, type 2 diabetes, metabolic syndrome and obesity).

Nutrition Related Problem/Condition

Search criteria:

- *Study design preferences*: RCT or clinical controlled studies, large non-

233

randomized observational studies, meta-analysis and systematic reviews. Feeding period must be greater than four weeks

- *Size of study groups*: The sample size must be more than 10 subjects for each study group (for e.g., this would include 10 patients in the intervention group and 10 patients in the control or comparison group)
- *Study dropout rate*: Less than 20%; preference for smaller dropout rates
- *Year range*: 2004 to present for cardiovascular disease; 2000 to present for type 2 diabetes
- *Languages*: Limited to articles in English
- *Other*: Article must be published in peer-reviewed journal.

Exclusion Criteria

Subjects/Population

- *Age*: Infants or children less than two years
- *Setting*: Inpatients
- *Health status*: None.

Nutrition Related Problem/Condition

Search criteria:

- *Size of study groups*: Sample sizes less than 10
- *Study designs*: Cross-sectional, Feeding periods less than four weeks, Studies that substituted fatty acids with carbohydrate or protein
- *Study dropout rate*: If the dropout rate in a study is 20% or greater
- *Year range*: Prior to January 2004
- *Authorship*: Studies by same author with similar in content
- *Languages*: Articles not in English
- *Other*: Animal studies; abstracts or presentations.

Search Terms and Electronic Databases Used

PubMed:

Cardiovascular Disease

"Lipoproteins, LDL"[Mesh] AND "dietary fats"[mh] AND saturated AND ("clinical trial"[filter]) AND "English and humans"[Filter]

"Lipoproteins, LDL"[Mesh] AND "dietary fats"[mh] AND saturated AND ("Cohort Studies"[Mesh] OR "clinical trial"[filter]) AND "English and humans"[Filter]

"Cardiovascular Disease"[Mesh] AND "dietary fats"[mh] AND saturated AND ("clinical trial"[filter]) AND "English and humans"[Filter]

"Cardiovascular Disease"[Mesh] AND "dietary fats"[mh] AND saturated AND ("Cohort Studies"[Mesh] OR "clinical trial"[filter]) AND "English and humans"[Filter]

"Inflammation"[Mesh] AND "dietary fats"[mh] AND saturated AND ("clinical trial"[filter]) AND "English and humans"[Filter]

"Inflammation"[Mesh] AND "dietary fats"[mh] AND saturated AND ("Cohort

234

Studies"[Mesh] OR "clinical trial"[filter]) AND "English and humans"[Filter]

 Saturated Fat Dietary LDL (key words)

 Saturated Fat Dietary Cardiovascular Disease (key words)

 Saturated Fat Dietary Inflammation (key words)

 Type 2 Diabetes

"Glucose Metabolism Disorders"[Mesh] AND "dietary fats"[mh] AND saturated AND ("clinical trial"[filter]) AND "English and humans"[Filter]

"Glucose Metabolism Disorders"[Mesh] AND "dietary fats"[mh] AND saturated AND ("Cohort Studies"[Mesh] OR "clinical trial"[filter]) AND "English and humans"[Filter]

"Insulin Resistance"[Mesh] AND "dietary fats"[mh] AND saturated AND ("clinical trial"[filter]) AND "English and humans"[Filter]

"Insulin Resistance"[Mesh] AND "dietary fats"[mh] AND saturated AND ("Cohort Studies"[Mesh] OR "clinical trial"[filter]) AND "English and humans"[Filter]

"Diabetes Mellitus, Type 2"[Mesh] AND "dietary fats"[mh] AND saturated AND ("clinical trial"[filter]) AND "English and humans"[Filter]

"Diabetes Mellitus, Type 2"[Mesh] AND "dietary fats"[mh] AND saturated AND ("Cohort Studies"[Mesh] OR "clinical trial"[filter]) AND "English and humans"[Filter]

Saturated Fat Dietary NIDDM (Key words)

Date Searched: 07/17/2009

Summary of Articles Identified to Review

- Total hits from all electronic database searches: 196
- Total articles identified to review from electronic databases: 132
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 20
- Number of Review Articles Identified: 4
- Total Number of Articles Identified: 24
- Number of Articles Reviewed but Excluded: 108

Included Articles (References)

Related to Cardiovascular Disease

Systematic Review/Meta-analysis:

1. Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, Bälter K, Fraser GE, Goldbourt U, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Ascherio A. Major types of dietary fat and risk of coronary heart disease: A pooled analysis of 11 cohort studies. Am J Clin Nutr. 2009 May; 89(5): 1, 425-1, 432. Epub 2009 Feb 11. PMID: 19211817.

Primary Articles:

1. Azadbakht L, Mirmiran P, Hedayati M, Esmaillzadeh A, Shiva N, Azizi F. Particle size of LDL is affected by the National Cholesterol Education Program (NCEP)

235

step II diet in dyslipidaemic adolescents. Br J Nutr. 2007 Jul; 98(1): 134-139. Epub 2007 Apr 20. PMID: 17445337.

2. Berglund L, Lefevre M, Ginsberg HN, Kris-Etherton PM, Elmer PJ, Stewart PW, Ershow A, Pearson TA, Dennis BH, Roheim PS, Ramakrishnan R, Reed R, Stewart K, Phillips KM; DELTA Investigators. Comparison of monounsaturated fat with carbohydrates as a replacement for saturated fat in subjects with a high metabolic risk profile: Studies in the fasting and postprandial states. Am J Clin Nutr. 2007 Dec; 86(6): 1, 611-1, 620. PMID: 18065577.

3. Buonacorso V, Nakandakare ER, Nunes VS, Passarelli M, Quintão EC, Lottenberg AM. Macrophage cholesterol efflux elicited by human total plasma and by HDL subfractions is not affected by different types of dietary fatty acids. Am J Clin Nutr. 2007 Nov; 86(5): 1, 270-1, 277. PMID: 17991635.

4. Chen SC, Judd JT, Kramer M, Meijer GW, Clevidence BA, Baer DJ. Phytosterol intake and dietary fat reduction are independent and additive in their ability to reduce plasma LDL cholesterol. Lipids. 2009 Mar; 44(3): 273-281. Epub 2009 Jan 15. PMID: 19145455.

5. Chung BH, Cho BH, Liang P, Doran S, Osterlund L, Oster RA, Darnell B, Franklin F. Contribution of postprandial lipemia to the dietary fat-mediated changes in endogenous lipoprotein-cholesterol concentrations in humans. Am J Clin Nutr. 2004 Nov; 80(5): 1, 145-1, 158.PMID: 15531660.

6. Dabadie H, Peuchant E, Bernard M, LeRuyet P, Mendy F. Moderate intake of myristic acid in sn-2 position has beneficial lipidic effects and enhances DHA of cholesteryl esters in an interventional study J Nutr Biochem. 2005 Jun; 16(6): 375-382. PMID: 15936650.

7. Furtado JD, Campos H, Appel LJ, Miller ER, Laranjo N, Carey VJ, Sacks FM. Effect of protein, unsaturated fat, and carbohydrate intakes on plasma apolipoprotein B and VLDL and LDL containing apolipoprotein C-III: Results from the OmniHeart Trial. Am J Clin Nutr. 2008 Jun; 87(6): 1, 623-1, 630. PMID: 18541549.

8. Kalova Lesna I, Suchanek P, Kovar J, Stavek P, Poledne R. Replacement of dietary saturated FAs by PUFAs in diet and reverse cholesterol transport. J Lipid Res. 2008 Nov; 49(11): 2, 414-2, 418. Epub 2008 Jul 9. PMID: 18614815.

9. Lefevre M, Champagne CM, Tulley RT, Rood JC, Most MM. Individual variability in cardiovascular disease risk factor responses to low-fat and low-saturated-fat diets in men: Body mass index, adiposity, and insulin resistance predict changes in LDL cholesterol. Am J Clin Nutr. 2005 Nov; 82(5): 957-963; quiz, 1, 145-1, 146. PMID: 16280425.

10. Lichtenstein AH, Matthan NR, Jalbert SM, Resteghini NA, Schaefer EJ, Ausman LM. Novel soybean oils with different fatty acid profiles alter cardiovascular disease risk factors in moderately hyperlipidemic subjects. Am J Clin Nutr. 2006 Sep; 84(3): 497-504. PMID: 16960162.

Related to Type 2 Diabetes

Reviews:

1. Galgani JE, Uauy RD, Aguirre CA, Díaz EO. Effect of the dietary fat quality on insulin sensitivity. Br J Nutr. 2008 Sep; 100(3): 471-479. Epub 2008 Apr 8.

Review. PMID: 18394213.

2. Hu FB, van Dam RM, Liu S. Diet and risk of Type II diabetes: The role of types of fat and carbohydrate. Diabetologia. 2001 Jul; 44(7): 805-817. Review. PMID: 11508264.

Primary Articles:

1. Bourque C, St-Onge MP, Papamandjaris AA, Cohn JS, Jones PJ. Consumption of an oil composed of medium chain triacyglycerols, phytosterols, and N-3 fatty acids improves cardiovascular risk profile in overweight women. Metabolism. 2003 Jun; 52(6): 771-777. PMID: 12800105.

2. Han JR, Deng B, Sun J, Chen CG, Corkey BE, Kirkland JL, Ma J, Guo W. Effects of dietary medium-chain triglyceride on weight loss and insulin sensitivity in a group of moderately overweight free-living type 2 diabetic Chinese subjects. Metabolism. 2007 Jul; 56(7): 985-991. PMID: 17570262.

3. Lindström J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hemiö K, Hämäläinen H, Härkönen P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Mannelin M, Paturi M, Sundvall J, Valle TT, Uusitupa M, Tuomilehto J; Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet. 2006 Nov 11; 368(9, 548): 1, 673-1, 679. PMID: 17098085.

4. Lindström J, Peltonen M, Eriksson JG, Louheranta A, Fogelholm M, Uusitupa M, Tuomilehto J. High-fibre, low-fat diet predicts long-term weight loss and decreased type 2 diabetes risk: The Finnish Diabetes Prevention Study. Diabetologia. 2006 May; 49(5): 912-920. Epub 2006 Mar 16. PMID: 16541277.

5. López S, Bermúdez B, Pacheco YM, Villar J, Abia R, Muriana FJ. Distinctive postprandial modulation of beta cell function and insulin sensitivity by dietary fats: Monounsaturated compared with saturated fatty acids. Am J Clin Nutr. 2008 Sep; 88(3): 638-644. PMID: 18779278.

6. Paniagua JA, de la Sacristana AG, Sánchez E, Romero I, Vidal-Puig A, Berral FJ, Escribano A, Moyano MJ, Peréz-Martinez P, López-Miranda J, Pérez-Jiménez F. A MUFA-rich diet improves posprandial glucose, lipid and GLP-1 responses in insulin-resistant subjects J Am Coll Nutr. 2007 Oct; 26(5): 434-444. PMID: 17914131.

7. Schwab US, Niskanen LK, Maliranta HM, Savolainen MJ, Kesäniemi YA, Uusitupa MI. Lauric and palmitic acid-enriched diets have minimal impact on serum lipid and lipoprotein concentrations and glucose metabolism in healthy young women. J Nutr. 1995 Mar; 125: 466-473. PMID: 7876922.

8. Shah M, Adams-Huet B, Brinkley L, Grundy SM, Garg A. Lipid, glycemic, and insulin responses to meals rich in saturated, cis-monounsaturated, and polyunsaturated (n-3 and n-6) fatty acids in subjects with type 2 diabetes. Diabetes Care. 2007 Dec; 30(12): 2, 993-2, 998. Epub 2007 Sep 5. PMID: 17804680.

9. St-Onge MP, Bourque C, Jones PJ, Ross R, Parsons WE. Medium- vs. long-chain triglycerides for 27 days increases fat oxidation and energy expenditure without resulting in changes in body composition in overweight women. Int J Obes Relat Metab Disord. 2003 Jan; 27(1): 95-102. PMID: 12532160.

237

10. Vessby B, Unsitupa M, Hermansen K, Riccardi G, Rivellese AA, Tapsell LC, Nälsén C, Berglund L, Louheranta A, Rasmussen BM, Calvert GD, Maffetone A, Pedersen E, Gustafsson IB, Storlien LH; KANWU Study. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU Study. Diabetologia. 2001 Mar; 44(3): 312-319.PMID: 11317662.

Excluded Articles

Article	Reason for Exclusion
Related to Cardiovascular Disease	
Aitken WA, Chisholm AW, Duncan AW, Harper MJ, Humphries SE, Mann JI, Murray Skeaff C, Sutherland WH, Wallace AJ, Williams SM. Variation in the cholesteryl ester transfer protein (CETP) gene does not influence individual plasma cholesterol response to changes in the nature of dietary fat. *Nutr Metab Cardiovasc Dis.* 2006 Jul; 16(5): 353-363. Epub 2005 Oct 19. PMID: 16829344.	Topic is CETP gene polymorphisms. More appropriate for Question 3.1 on genetic polymorphisms.
Ascherio A. Trans fatty acids and blood lipids. *Atheroscler Suppl.* 2006 May; 7(2): 25-27. Epub 2006 May 19. Review. PMID: 16713394.	More appropriate for Question 3.5 on TFAs.
Baer DJ, Judd JT, Clevidence BA, Tracy RP. Dietary fatty acids affect plasma markers of inflammation in healthy men fed controlled diets: A randomized crossover study. *Am J Clin Nutr.* 2004 Jun; 79(6): 969-973. PMID: 15159225.	Better addresses the trans FA and stearic acid questions.
Binkoski AE, Kris-Etherton PM, Wilson TA, Mountain ML, Nicolosi RJ. Balance of unsaturated fatty acids is important to a cholesterol-lowering diet: comparison of mid-oleic sunflower oil and olive oil on cardiovascular disease risk factors. *J Am Diet Assoc.* 2005 Jul; 105(7): 1, 080-1, 086. PMID: 15983524.	Topic is unsaturated FAs, not SFA, and CVD risk.

238

Biong AS, Müller H, Seljeflot I, Veierød MB, Pedersen JI. <u>A comparison of the effects of cheese and butter on serum lipids, haemostatic variables and homocysteine.</u> *Br J Nutr.* 2004 Nov; 92(5): 791-797.PMID: 15533268	Very narrow experimental design; comparison of Jarlsburg cheese vs. butter consumption. Cheese consumption resulted in a better lipid profile than butter consumption.
Bray GA, Most M, Rood J, Redmann S, Smith SR. <u>Hormonal responses to a fast-food meal compared with nutritionally comparable meals of different composition.</u> *Ann Nutr Metab.* 2007;51(2):163-71. Epub 2007 May 29. PMID: 17536194	Comparison of organic beef-containing meal to fast-food beef-containing meal. Fast food meal was higher in SFA and trans FA and resulted in higher LDL-C than the organic beef meal.
Brinkworth GD, Noakes M, Buckley JD, Keogh JB, Clifton PM. <u>Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 months.</u> *Am J Clin Nutr.* 2009 Jul; 90(1): 23-32. Epub 2009 May 13. PMID: 19439458.	Addresses low CHO vs. low fat question.
Brunner EJ, Rees K, Ward K, Burke M, Thorogood M. <u>Dietary advice for reducing cardiovascular risk.</u> *Cochrane Database Syst Rev.* 2007 Oct 17; (4): CD002128. Review. PMID: 17943768.	Behavioral study.
Brunner EJ, Thorogood M, Rees K, Hewitt G. <u>Dietary advice for reducing cardiovascular risk.</u>*Cochrane Database Syst Rev.* 2005 Oct 19;(4): CD002128. Review. Update in: *Cochrane Database Syst Rev.* <u>2007; (4): CD002128</u>. PMID: 16235299.	Behavioral study.
Burke LE, Dunbar-Jacob J, Orchard TJ, Sereika SM. <u>Improving adherence to a cholesterol-lowering diet: A behavioral intervention study.</u> *Patient Educ Couns.* 2005 Apr; 57(1): 134-142. PMID: 15797163	The topic is dietary adherence, not biochemical or health outcomes.

239

Burke LE, Styn MA, Steenkiste AR, Music E, Warziski M, Choo J. <u>A randomized clinical trial testing treatment preference and two dietary options in behavioral weight management: preliminary results of the impact of diet at 6 months--PREFER study.</u> *Obesity (Silver Spring).* 2006 Nov; 14(11): 2, 007-2, 017. PMID: 17135618.	The topic of this report is dietary adherence, not biochemical outcomes.
Chardigny JM, Malpuech-Brugère C, Dionisi F, Bauman DE, German B, Mensink RP, Combe N, Chaumont P, Barbano DM, Enjalbert F, Bezelgues JB, Cristiani I, Moulin J, Boirie Y, Golay PA, Giuffrida F, Sébédio JL, Destaillats F. <u>Rationale and design of the TRANSFACT project phase I: A study to assess the effect of the two different dietary sources of trans fatty acids on cardiovascular risk factors in humans.</u> *Contemp Clin Trials.* 2006 Aug; 27(4): 364-373. PMID: 16632411.	More appropriate for Question 3.5 on trans FAs.
Chen ZY, Jiao R, Ma KY. <u>Cholesterol-lowering nutraceuticals and functional foods.</u> *J Agric Food Chem.* 2008 Oct 8; 56(19): 8, 761-8, 773. Epub 2008 Sep 9. Review. PMID: 18778072.	Does not address the effects of dietary fat, but is focused on nutraceuticals and functional foods.
Chisholm A, Mc Auley K, Mann J, Williams S, Skeaff M. <u>Cholesterol lowering effects of nuts compared with a Canola oil enriched cereal of similar fat composition.</u> *Nutr Metab Cardiovasc Dis.* 2005 Aug; 15(4): 284-292. PMID: 16054553.	Both diets tested were low SFA diets.
Cortés B, Núñez I, Cofán M, Gilabert R, Pérez-Heras A, Casals E, Deulofeu R, Ros E. <u>Acute effects of high-fat meals enriched with walnuts or olive oil on postprandial endothelial function.</u> *J Am Coll Cardiol.* 2006 Oct 17; 48(8): 1, 666-1, 671. PMID: 17045905.	Comparison of two high fat, high SFA, diets with olive oil or walnuts. The walnut-supplemented diet showed improved flow mediated dilation (FMD) of blood vessels, over the olive oil supplemented diet. (Both diets were the same - high - in SFA.)
Craig WJ. <u>Health effects of vegan diets.</u> *Am J Clin Nutr.* 2009 May; 89(5): 1, 627S-1, 633S. Epub 2009 Mar 11. Review. PMID: 19279075.	Descriptive review.

Dale KS, McAuley KA, Taylor RW, Williams SM, Farmer VL, Hansen P, Vorgers SM, Chisholm AW, Mann JI. <u>Determining optimal approaches for weight maintenance: A randomized controlled trial.</u> *CMAJ.* 2009 May 12; 180(10): E39-46. PMID: 19433812.	Compared high-CHO diet to high-MUFA diet with behavioral and advice input.
De Lorgeril M. <u>Essential polyunsaturated fatty acids, inflammation, atherosclerosis and cardiovascular diseases.</u> *Subcell Biochem.* 2007; 42: 283-297. Review. PMID: 17612056.	More appropriate for Question 2.4 on PUFAs.
Dorgan JF, McMahon RP, Friedman LA, Van Horn L, Snetselaar LG, Kwiterovich PO Jr, Lauer RM, Lasser NL, Stevens VJ, Robson A, Cooper SF, Chandler DW, Franklin FA, Barton BA, Patterson BH, Taylor PR, Schatzkin A. <u>Diet and sex hormones in boys: findings from the dietary intervention study in children.</u> *J Clin Endocrinol Metab.* 2006 Oct; 91(10): 3, 992-3, 996. PMID: 16868056	Does not address the question. This study examined low fat intake effects on serum sex hormones in adolescent boys related to onset of puberty.
Fard NM, Mehrabian F, Sarraf-Zadegan N, Sajadi F. <u>Fat-modified diets during pregnancy and lactation and serum lipids after birth.</u> *Indian J Pediatr.* 2004 Aug; 71(8): 683-687. PMID: 15345867.	Pregnancy not in inclusion criteria.
Fassett RG, Ball MJ, Robertson IK, Geraghty DP, Coombes JS. <u>Baseline serum lipids and renal function in chronic kidney disease patients entering the LORD trial.</u> *Int J Clin Pharmacol Ther.* 2006 Nov; 44(11): 580-588. PMID: 17176625.	Chronic kidney disease not in inclusion criteria.
Friedman LA, Snetselaar L, Stumbo P, Van Horn L, Singh B, Barton BA. <u>Influence of intervention on beverage choices: trends in the dietary intervention study in children (DISC).</u> *J Am Diet Assoc.* 2007 Apr; 107(4): 586-594. PMID: 17383264.	Nutrition education/behavioral study.

241

Gardner CD, Coulston A, Chatterjee L, Rigby A, Spiller G, Farquhar JW. <u>The effect of a plant-based diet on plasma lipids in hypercholesterolemic adults: A randomized trial.</u> *Ann Intern Med.* 2005 May 3; 142(9): 725-733. PMID: 15867404.	Authors compared two equally low-fat diets, with and without nutrient-dense plant-based foods.
Garg A, Simha V. <u>Update on dyslipidemia.</u> *Clin Endocrinol Metab.* 2007 May; 92(5): 1, 581-1, 589. Review. PMID: 17483372.	This is an update on the genetic basis for dyslipidemias, more appropriate for Question 3.1 on genetic polymorphisms.
Gigleux I, Jenkins DJ, Kendall CW, Marchie A, Faulkner DA, Wong JM, de Souza R, Emam A, Parker TL, Trautwein EA, Lapsley KG, Connelly PW, Lamarche B. <u>Comparison of a dietary portfolio diet of cholesterol-lowering foods and a statin on LDL particle size phenotype in hypercholesterolaemic participants.</u> *Br J Nutr.* 2007 Dec; 98(6): 1, 229-1, 236. Epub 2007 Jul 30. PMID: 17663803.	Report on the effect of statins and plant sterols on benefits of a low-saturated fat diet on LDL particle size.
Grynberg A. <u>Hypertension prevention: From nutrients to (fortified) foods to dietary patterns. Focus on fatty acids.</u> *J Hum Hypertens.* 2005 Dec; 19 Suppl 3: S25-33. Review. PMID: 16302007.	Reviews both human and animal studies. Hypertension was not included in the initial Question 3.2.
Giugliano D, Ceriello A, Esposito K. <u>The effects of diet on inflammation: Emphasis on the metabolic syndrome.</u> *J Am Coll Cardiol.* 2006 Aug 15; 48(4): 677-685. Epub 2006 Jul 24. Review. PMID: 16904534.	Narrative review.
Hall WL. <u>Dietary saturated and unsaturated fats as determinants of blood pressure and vascular function.</u> *Nutr Res Rev.* 2009 Jun; 22(1): 18-38. Epub 2009 Feb 26. Review. PMID: 19243668.	Narrative review.

Hilpert KF, Kris-Etherton PM, West SG. <u>Lipid response to a low-fat diet with or without soy is modified by C-reactive protein status in moderately hypercholesterolemic adults.</u> *J Nutr.* 2005 May; 135(5): 1, 075-1, 079. PMID: 15867284.	Does not address the question. The authors report that inflammation (elevated CRP) interferes with cholesterol-lowering diet.
Hunter JE. <u>Dietary trans fatty acids: review of recent human studies and food industry responses.</u> *Lipids.* 2006 Nov; 41(11): 967-992. Review.	More appropriate for Question 3.5 on trans FAs.
Iughetti L, Predieri B, Balli F, Calandra S. <u>Rational approach to the treatment for heterozygous familial hypercholesterolemia in childhood and adolescence: a review.</u> *J Endocrinol Invest.* 2007 Sep; 30(8): 700-719. Review. PMID: 17923804.	More appropriate for Question 3.1 on genetic polymorphisms.
Jenkins DJ, Kendall CW, Marchie A, Faulkner DA, Wong JM, de Souza R, Emam A, Parker TL, Vidgen E, Trautwein EA, Lapsley KG, Josse RG, Leiter LA, Singer W, Connelly PW. <u>Direct comparison of a dietary portfolio of cholesterol-lowering foods with a statin in hypercholesterolemic participants.</u> *Am J Clin Nutr.* 2005 Feb; 81(2): 380-387. PMID: 15699225.	The control diet is a low SFA diet and comparisons are made to: 1) + levastatin or 2) + portfolio diet. Levels of SFA are the same in all diets.
Jenkins DJ, Kendall CW, Nguyen TH, Marchie A, Faulkner DA, Ireland C, Josse AR, Vidgen E, Trautwein EA, Lapsley KG, Holmes C, Josse RG, Leiter LA, Connelly PW, Singer W. <u>Effect of plant sterols in combination with other cholesterol-lowering foods.</u> *Metabolism.* 2008 Jan; 57(1): 130-139. PMID: 18078870.	Focus on plant sterols.

243

Jones PJ, Raeini-Sarjaz M, Jenkins DJ, Kendall CW, Vidgen E, Trautwein EA, Lapsley KG, Marchie A, Cunnane SC, Connelly PW. <u>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.</u> *Lipids.* 2005 Feb; 40(2): 169-174. PMID: 15884765.	Outcome measures were serum sterols (e.g., campesterol and sitosterol) and RBC fragility.
Katz DL, Evans MA, Nawaz H, Njike VY, Chan W, Comerford BP, Hoxley ML. <u>Egg consumption and endothelial function: a randomized controlled crossover trial.</u> *Int J Cardiol.* 2005 Mar 10; 99(1): 65-70. PMID: 15721501.	More appropriate for Question 3.3 on cholesterol.
Khoury J, Haugen G, Tonstad S, Frøslie KF, Henriksen T. <u>Effect of a cholesterol-lowering diet during pregnancy on maternal and fetal Doppler velocimetry: The CARRDIP study.</u> *Am J Obstet Gynecol.* 2007 Jun; 196(6): 549.e1-549.37.PMID: 17547890.	Pregnancy not is inclusion criteria.
Krauss RM, Blanche PJ, Rawlings RS, Fernstrom HS, Williams PT. <u>Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia.</u> *Am J Clin Nutr.* 2006 May; 83(5): 1, 025-1, 031; quiz 1205. Erratum in: *Am J Clin Nutr.* 2006 Sep; 84(3): 668. PMID: 16685042.	Low CHO diet issue.
Related to Type 2 Diabetes	
Barnard ND, Katcher HI, Jenkins DJ, Cohen J, Turner-McGrievy G. <u>Vegetarian and vegan diets in type 2 diabetes management.</u> *Nutr Rev.* 2009 May; 67(5): 255-263. Review. PMID: 19386029.	Narrative review.

244

Bisschop PH, de Metz J, Ackermans MT, Endert E, Pijl H, Kuipers F, Meijer AJ, Sauerwein HP, Romijn JA. Dietary fat content alters insulin-mediated glucose metabolism in healthy men. *Am J Clin Nutr.* 2001 Mar; 73(3): 554-559. PMID: 11237931.	N=6 per group in random crossover design.
Bo S, Ciccone G, Baldi C, Benini L, Dusio F, Forastiere G, Lucia C, Nuti C, Durazzo M, Cassader M, Gentile L, Pagano G. Effectiveness of a lifestyle intervention on metabolic syndrome. A randomized controlled trial. *J Gen Intern Med.* 2007 Dec; 22(12): 1, 695-1, 703. Epub 2007 Oct 6. PMID: 17922167.	Behavioral.
Bray GA, Lovejoy JC, Smith SR, DeLany JP, Lefevre M, Hwang D, Ryan DH, York DA. The influence of different fats and fatty acids on obesity, insulin resistance and inflammation. *J Nutr.* 2002 Sep; 132(9): 2, 488-2, 491. Review. PMID: 12221198.	Narrative review.
Browning LM, Jebb SA. Nutritional influences on inflammation and type 2 diabetes risk. *Diabetes Technol Ther.* 2006 Feb; 8(1): 45-54. Review. PMID: 16472050.	Narrative review; covers animal and human studies.
Corcoran MP, Lamon-Fava S, Fielding RA. Skeletal muscle lipid deposition and insulin resistance: Effect of dietary fatty acids and exercise. *Am J Clin Nutr.* 2007 Mar; 85(3): 662-677. Review.	Narrative review; covers animal and human studies.
Corpeleijn E, Feskens EJ, Jansen EH, Mensink M, Saris WH, de Bruin TW, Blaak EE. Improvements in glucose tolerance and insulin sensitivity after lifestyle intervention are related to changes in serum fatty acid profile and desaturase activities: the SLIM study. *Diabetologia.* 2006 Oct; 49(10): 2, 392-2, 401. Epub 2006 Aug 3. PMID: 16896932.	Behavioral.

245

Dai J, Su YX, Bartell S, Le NA, Ling WH, Liang YQ, Gao L, Wu HY, Veledar E, Vaccarino V. <u>Beneficial effects of designed dietary fatty acid compositions on lipids in triacylglycerol-rich lipoproteins among Chinese patients with type 2 diabetes mellitus.</u> *Metabolism.* 2009 Apr; 58(4): 510-518. PMID: 19303972.	Lipid profile of post-prandial TG rich lipoproteins in Chinese T2D patients after high PUFA or MUFA meals. Does not address effect of dietary fat on risk of T2D.
Dekker MJ, Wright AJ, Mazurak VC, Graham TE, Marangoni AG, Robinson LE. <u>New oral fat tolerance tests feature tailoring of the polyunsaturated/saturated fatty acid ratio to elicit a specific postprandial response.</u> *Appl Physiol Nutr Metab.* 2007 Dec; 32(6): 1, 073-1, 081. PMID: 18059580.	Methods paper; subject number less than 10.
Ebbesson SO, Ebbesson LO, Swenson M, Kennish JM, Robbins DC. <u>A successful diabetes prevention study in Eskimos: The Alaska Siberia project.</u> *Int J Circumpolar Health.* 2005 Sep; 64(4): 409-424. PMID: 16277124.	Intervention was not dietary; intervention was only dietary counseling provided one time per year for three years in small villages in Alaska.
Eckel RH, Hanson AS, Chen AY, Berman JN, Yost TJ, Brass EP. <u>Dietary substitution of medium-chain triglycerides improves insulin-mediated glucose metabolism in NIDDM subjects.</u> *Diabetes.* 1992 May; 41(5): 641-647. PMID: 1568535.	Date of publication prior to 2000.
Grundy SM, Abate N, Chandalia M. <u>Diet composition and the metabolic syndrome: what is the optimal fat intake?</u> *Am J Med.* 2002 Dec 30; 113 Suppl 9B: 25S-29S. Review. PMID: 12566135.	Narrative review.
Haag M, Dippenaar NG. <u>Dietary fats, fatty acids and insulin resistance: Short review of a multifaceted connection.</u> *Med Sci Monit.* 2005 Dec; 11(12): RA359-RA367. Epub 2005 Nov 24. Review. PMID: 16319806.	Narrative review; covers in vivo and in vitro studies.

Harding AH, Sargeant LA, Welch A, Oakes S, Luben RN, Bingham S, Day NE, Khaw KT, Wareham NJ; EPIC-Norfolk Study. <u>Fat consumption and HbA(1c) levels: The EPIC-Norfolk study.</u> *Diabetes Care.* 2001 Nov; 24(11): 1, 911-1, 916. PMID: 11679456.	Cross-sectional study.
Howard BV. <u>Dietary fat as a risk factor for type 2 diabetes.</u> *Ann N Y Acad Sci.* 2002 Jun; 967:324-328. Review. PMID: 12079859.	Narrative review.
Related to Cardiovascular Disease	
Li D, Siriamornpun S, Wahlqvist ML, Mann NJ, Sinclair AJ. <u>Lean meat and heart health.</u> *Asia Pac J Clin Nutr.* 2005; 14(2): 113-119. Review. PMID: 15927927.	Narrative review. Reviewed 54 studies on lean red meat consumption and increased risk of CVD.
Lindi V, Schwab U, Louheranta A, Vessby B, Hermansen K, Tapsell L, Riccardi G, Rivellese AA, Laakso M, Uusitupa MI; KANWU Study Group. <u>The G-250A polymorphism in the hepatic lipase gene promoter is associated with changes in hepatic lipase activity and LDL cholesterol: The KANWU Study.</u> *Nutr Metab Cardiovasc Dis.* 2008 Feb; 18(2): 88-95 PMID: 17327141.	Paper on hepatic lipase (HL) gene polymorphism that affects LDL-C. Addresses Question 3.1 on genetic polymorphisms.
Manning PJ, Sutherland WH, McGrath MM, de Jong SA, Walker RJ, Williams MJ. <u>Postprandial cytokine concentrations and meal composition in obese and lean women.</u> *Obesity (Silver Spring).* 2008 Sep; 16(9): 2, 046-2, 052. PMID: 19186329	Postprandial.
Margioris AN. <u>Fatty acids and postprandial inflammation.</u> *Curr Opin Clin Nutr Metab Care.* 2009 Mar; 12(2): 129-137. Review. PMID: 19202384.	Addresses PUFA question.

247

Mauler B, Dubben S, Pawelzik M, Pawelzik D, Weigle DS, Kratz M. <u>Hypercaloric diets differing in fat composition have similar effects on serum leptin and weight gain in female subjects with anorexia nervosa.</u>*Nutr Res.* 2009 Jan; 29(1): 1-7. PMID: 19185771.	Does not address question. Focus is on weight gain after anorexia nervosa and effects on leptin.
McAuley KA, Hopkins CM, Smith KJ, McLay RT, Williams SM, Taylor RW, Mann JI. <u>Comparison of high-fat and high-protein diets with a high-carbohydrate diet in insulin-resistant obese women.</u> *Diabetologia.* 2005 Jan; 48(1): 8-16. PMID: 15616799.	Does not address question. Focus is on the difference between high fat (Atkins) vs. high protein (Zone diet) replacement of CHO in overweight insulin resistant women.
McDonald BE. <u>The Canadian experience: why Canada decided against an upper limit for cholesterol.</u> *J Am Coll Nutr.* 2004 Dec; 23(6 Suppl): 616S-620S. Review. PMID: 15640515.	Narrative review of the literature that formed the background for the Candian decision not to limit dietary cholesterol in their recommendations.
Miller ER 3rd, Erlinger TP, Sacks FM, Svetkey LP, Charleston J, Lin PH, Appel LJ. <u>A dietary pattern that lowers oxidative stress increases antibodies to oxidized LDL: Results from a randomized controlled feeding study.</u>*Atherosclerosis.* 2005 Nov; 183(1): 175-182. PMID: 16216596.	Health outcome measure was antibodies to oxidized LDL as an indicator of oxidative stress.
Miller M, Beach V, Sorkin JD, Mangano C, Dobmeier C, Novacic D, Rhyne J, Vogel RA. <u>Comparative effects of three popular diets on lipids, endothelial function, and C-reactive protein during weight maintenance.</u> *J Am Diet Assoc.* 2009 Apr; 109(4): 713-717. PMID: 19328268.	Does not address question. Study reports effects of three popular diets (Atkins, South Beach and Ornish) on lipid profiles, and so on, during weight maintenance.
Moreno JA, Pérez-Jiménez F, Marín C, Gómez P, Pérez-Martínez P, Moreno R, Bellido C, Fuentes F, López-Miranda J. <u>Apolipoprotein E gene promoter -219G-T polymorphism increases LDL-cholesterol concentrations and susceptibility to oxidation in response to a diet rich in saturated fat.</u> *Am J Clin Nutr.* 2004 Nov; 80(5): 1, 404-1, 409. PMID: 15531693.	ApoE genetic polymorphism question.

248

Nestel PJ, Chronopulos A, Cehun M. <u>Dairy fat in cheese raises LDL cholesterol less than that in butter in mildly hyper- cholesterolaemic subjects.</u> *Eur J Clin Nutr.* 2005 Sep; 59(9): 1, 059-1, 063. PMID: 16015270.	RCT testing high SFA in cheese vs butter. Both test diets had the same amount of total and SFA.
Nicholls SJ, Lundman P, Harmer JA, Cutri B, Griffiths KA, Rye KA, Barter PJ, Celermajer DS. <u>Consumption of saturated fat impairs the anti-inflammatory properties of high-density lipoproteins and endothelial function.</u> *J Am Coll Cardiol.* 2006 Aug 15; 48(4): 715-720. PMID: 16904539.	Postprandial.
Ordovas JM, Kaput J, Corella D. <u>Nutrition in the genomics era: cardiovascular disease risk and the Mediterranean diet.</u> *Mol Nutr Food Res.* 2007 Oct; 51(10): 1, 293-1, 299. Review. PMID: 17879995	Addresses Question 3.1 on genetic polymorphisms.
Perez-Martinez P, Perez-Jimenez F, Ordovas JM, Bellido C, Moreno JA, Gomez P, Marin C, Fernandez de la Puebla RA, Paniagua JA, Lopez-Miranda J. <u>The APOB -516C/T polymorphism has no effect on lipid and apolipoprotein response following changes in dietary fat intake in a healthy population.</u> *Nutr Metab Cardiovasc Dis.* 2007 Mar; 17(3): 224-229. PMID: 17367707.	Addresses Question 3.1 on genetic polymorphisms.
Pirro M, Schillaci G, Savarese G, Gemelli F, Mannarino MR, Siepi D, Bagaglia F, Mannarino E. <u>Attenuation of inflammation with short-term dietary intervention is associated with a reduction of arterial stiffness in subjects with hyper cholesterol-aemia.</u> *Eur J Cardiovasc Prev Rehabil.* 2004 Dec; 11(6): 497-502. PMID: 15580061.	Case control study.
Pittaway JK, Robertson IK, Ball MJ. <u>Chickpeas may influence fatty acid and fiber intake in an ad libitum diet, leading to small improvements in serum lipid profile and glycemic control.</u> *J Am Diet Assoc.* 2008 Jun; 108(6): 1, 009-1, 013. PMID: 18502235.	Weak intervention trial with the addition of 728g chickpeas per week to an ad libitum diet. No other controls on dietary intake of subjects.

Raitakari OT, Rönnemaa T, Järvisalo MJ, Kaitosaari T, Volanen I, Kallio K, Lagström H, Jokinen E, Niinikoski H, Viikari JS, Simell O. Endothelial function in healthy 11-year-old children after dietary intervention with onset in infancy: The Special Turku Coronary Risk Factor Intervention Project for children (STRIP). *Circulation.* 2005 Dec 13; 112(24): 3, 786-3, 794. PMID:16330680.	Low-saturated fat diet introduced during infancy (seven months) and followed for first decade of life. Infancy not in inclusion criteria.
Riccardi G, Giacco R, Rivellese AA. Dietary fat, insulin sensitivity and the metabolic syndrome. *Clin Nutr.* 2004 Aug; 23(4): 447-456. Review. PMID: 15297079.	Narrative review. Health outcome is metabolic syndrome.
Related to Type 2 Diabetes	
Lithander FE, Keogh GF, Wang Y, Cooper GJ, Mulvey TB, Chan YK, McArdle BH, Poppitt SD. No evidence of an effect of alterations in dietary fatty acids on fasting adiponectin over 3 weeks. *Obesity (Silver Spring).* 2008 Mar; 16(3): 592-599. PMID: 18239552.	Adiponectin (or other adipokines) not included in health outcomes of question.
Louheranta AM, Turpeinen AK, Schwab US, Vidgren HM, Parviainen MT, Uusitupa MI. A high-stearic acid diet does not impair glucose tolerance and insulin sensitivity in healthy women. *Metabolism.* 1998 May; 47(5): 529-534. PMID: 9591742,	Date of publication prior to 2000.
Lovejoy JC, Smith SR, Champagne CM, Most MM, Lefevre M, DeLany JP, Denkins YM, Rood JC, Veldhuis J, Bray GA. Effects of diets enriched in saturated (palmitic), monounsaturated (oleic), or trans (elaidic) fatty acids on insulin sensitivity and substrate oxidation in healthy adults. *Diabetes Care.* 2002 Aug; 25(8): 1, 283-1, 288. PMID: 12145222.	Covered in Galgani review.
Lovejoy JC. The influence of dietary fat on insulin resistance. *Curr Diab Rep.* 2002 Oct; 2(5): 435-440. Review. PMID: 12643169.	Narrative review.

Manco M, Calvani M, Mingrone G. <u>Effects of dietary fatty acids on insulin sensitivity and secretion.</u> *Diabetes Obes Metab.* 2004 Nov; 6(6): 402-413. Review. PMID: 15479216.	Narrative review; covers animal and human studies.
McAuley K, Mann J. <u>Thematic review series: Patient-oriented research. Nutritional determinants of insulin resistance.</u> *J Lipid Res.* 2006 Aug; 47(8): 1, 668-1, 676. Review. PMID: 16720893.	Narrative review; covers animal and human studies.
Risérus U. <u>Fatty acids and insulin sensitivity.</u> *Curr Opin Clin Nutr Metab Care.* 2008 Mar; 11(2): 100-105. Review. PMID: 18301083.	Narrative review.
Rivellese AA, Giacco R, Annuzzi G, De Natale C, Patti L, Di Marino L, Minerva V, Costabile G, Santangelo C, Masella R, Riccardi G. <u>Effects of monounsaturated vs. saturated fat on postprandial lipemia and adipose tissue lipases in type 2 diabetes.</u> *Clin Nutr.* 2008 Feb; 27(1): 133-141. PMID: 17765364.	Study done in diabetics and health outcomes are related to lipid profile and CVD parameters, not T2D risk.
Rivellese AA, Lilli S. Quality of dietary fatty acids, insulin sensitivity and type 2 diabetes. *Biomed Pharmacother.* 2003 Mar; 57(2): 84-87. Review. PMID: 12842493.	Narrative review.
Robertson MD, Jackson KG, Fielding BA, Williams CM, Frayn KN. <u>Acute effects of meal fatty acid composition on insulin sensitivity in healthy post-menopausal women.</u> *Br J Nutr.* 2002 Dec; 88(6): 635-640. PMID: 12493085.	Postprandial; N=10.
Related to Cardiovascular Disease	
Seidel C, Deufel T, Jahreis G. <u>Effects of fat-modified dairy products on blood lipids in humans in comparison with other fats.</u> *Ann Nutr Metab.* 2005 Jan-Feb;49(1):42-8. PMID: 15761214	Milk fat was modified by feeding cows rapeseed oil; this decreased SFA and increased PUFAs. More of a functional food report.

251

Sheridan MJ, Cooper JN, Erario M, Cheifetz CE. <u>Pistachio nut consumption and serum lipid levels.</u> *J Am Coll Nutr.* 2007 Apr;26(2):141-8. PMID: 17536125	Subjects per intervention group less than 10.
Skeaff CM, Thoma C, Mann J, Chisholm A, Williams S, Richmond K. <u>Isocaloric substitution of plant sterol-enriched fat spread for carbohydrate-rich foods in a low-fat, fibre-rich diet decreases plasma low-density lipoprotein cholesterol and increases high-density lipoprotein concentrations.</u>*Nutr Metab Cardiovasc Dis.* 2005 Oct;15(5):337-44. PMID: 16216719	Plant sterol enriched fat substituted for CHO, both on low fat diet but compared to control, higher SFA diet.
Solà R, Godàs G, Ribalta J, Vallvé JC, Girona J, Anguera A, Ostos M, Recalde D, Salazar J, Caslake M, Martín-Luján F, Salas-Salvadó J, Masana L. <u>Effects of soluble fiber (Plantago ovata husk) on plasma lipids, lipoproteins, and apolipoproteins in men with ischemic heart disease.</u> *Am J Clin Nutr.* 2007 Apr; 85(4): 1, 157-1, 163. PMID: 17413119.	Fiber intervention trial.
Spiteller G. <u>The relation of lipid peroxidation processes with atherogenesis: a new theory on atherogenesis.</u> *Mol Nutr Food Res.* 2005 Nov; 49(11): 999-1, 013. Review. PMID: 16270286.	Narrative review. Theory that cholesterol-n-3PUFAesters are atherogenic and it is furan fatty acids that are protective in fish oils.
St-Onge MP, Aban I, Bosarge A, Gower B, Hecker KD, Allison DB. <u>Snack chips fried in corn oil alleviate cardiovascular disease risk factors when substituted for low-fat or high-fat snacks.</u> *Am J Clin Nutr.* 2007 Jun; 85(6): 1, 503-1, 510.PMID: 17556685.	The test diet was low in both saturated and TFAs and high in PUFAs; the effects of each were not determined.
St-Onge MP, Zhang S, Darnell B, Allison DB. <u>Baseline serum C-reactive protein is associated with lipid responses to low-fat and high-polyunsaturated fat diets.</u> *J Nutr.* 2009 Apr; 139(4): 680-683. PMID: 19297430.	Does not address question. Report on CRP and diet interactions to affect changes in LDL-C.

Stoernell CK, Tangney CC, Rockway SW. <u>Short-term changes in lipoprotein subclasses and C-reactive protein levels of hypertriglyceridemic adults on low-carbohydrate and low-fat diets.</u> *Nutr Res.* 2008 Jul; 28(7): 443-449. PMID: 19083444.	Low-CHO vs. low-fat issue.
Tapsell LC, Gillen LJ, Patch CS, Batterham M, Owen A, Baré M, Kennedy M. <u>Including walnuts in a low-fat/modified-fat diet improves HDL cholesterol-to-total cholesterol ratios in patients with type 2 diabetes.</u> *Diabetes Care.* 2004 Dec; 27(12): 2, 777-2, 783. PMID: 15562184.	More appropriate for Question 2.4 on PUFAs.
Theuwissen E, Mensink RP. <u>Water-soluble dietary fibers and cardiovascular disease.</u> *Physiol Behav.* 2008 May 23; 94(2): 285-292. Epub 2008 Jan 5. Review. PMID: 18302966.	Narrative review on dietary fiber.
Thijssen MA, Mensink RP. <u>Fatty acids and atherosclerotic risk.</u> *Handb Exp Pharmacol.* 2005; (170): 165-194. Review. PMID: 16596799.	Narrative review.
Tholstrup T, Samman S. <u>Postprandial lipoprotein(a) is affected differently by specific individual dietary fatty acids in healthy young men.</u> *J Nutr.* 2004 Oct; 134(10): 2, 550-2, 555. PMID: 15465746.	Does not address the question. Health outcome measure was lipoprotein(a) [Lp(a)].
Thompson JL, Allen P, Helitzer DL, Qualls C, Whyte AN, Wolfe VK, Herman CJ. <u>Reducing diabetes risk in American Indian women.</u> *Am J Prev Med.* 2008 Mar; 34(3): 192-201. PMID: 18312806.	Behavioral study in American Indian women with T2D.
Tonstad S, Sundfør T, Seljeflot I. <u>Effect of lifestyle changes on atherogenic lipids and endothelial cell adhesion molecules in young adults with familial premature coronary heart disease.</u> *Am J Cardiol.* 2005 May 15; 95(10): 1, 187-1, 191. PMID: 15877991.	Subjects with familial premature CHD not on inclusion list.

253

Upritchard JE, Zeelenberg MJ, Huizinga H, Verschuren PM, Trautwein EA. <u>Modern fat technology: What is the potential for heart health?</u> *Proc Nutr Soc.* 2005 Aug; 64(3): 379-386. Review. PMID: 16048672.	Functional foods paper.
Van Horn L, Obarzanek E, Friedman LA, Gernhofer N, Barton B. <u>Children's adaptations to a fat-reduced diet: The Dietary Intervention Study in Children (DISC).</u> *Pediatrics.* 2005 Jun; 115(6): 1, 723-1, 733. PMID: 15930237.	An ancillary study from DISC. Behavioral study on childrens' food choices from "go" and "whoa" food groups.
Viikari J, Niinikoski H, Raitakari OT, Simell O. <u>The initiatives and outcomes for cardiovascular risks that can be achieved through paediatric counselling.</u> *Curr Opin Lipidol.* 2009 Feb; 20(1): 17-23. Review. PMID: 19106707.	Behavioral study on pediatric counselling.
Volek JS, Phinney SD, Forsythe CE, Quann EE, Wood RJ, Puglisi MJ, Kraemer WJ, Bibus DM, Fernandez ML, Feinman RD. <u>Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet.</u> *Lipids.* 2009 Apr; 44(4): 297-309. PMID: 19082851.	Low-CHO diet paper.
Willett WC. <u>Trans fatty acids and cardiovascular disease-epidemiological data.</u> *Atheroscler Suppl.* 2006 May; 7(2): 5-8. Epub 2006 May 19. Review. PMID: 16713753.	More appropriate for Question 3.5 on TFAs.
Williams PT, Blanche PJ, Rawlings R, Krauss RM. <u>Concordant lipoprotein and weight responses to dietary fat change in identical twins with divergent exercise levels 1.</u> *Am J Clin Nutr.* 2005 Jul; 82(1): 181-187. PMID: 16002817.	Subjects not on inclusion list; identical twins with divergent exercise levels.
Zern TL, Fernandez ML. <u>Cardioprotective effects of dietary polyphenols.</u> *J Nutr.* 2005 Oct; 135(10): 2, 291-2, 294. Review. PMID: 16177184.	Narrative review.
Related to Type 2 Diabetes	

254

Archived from www.NEL.gov on March 21, 2017

Schulze MB, Hu FB. <u>Primary prevention of diabetes: what can be done and how much can be prevented?</u> *Annu Rev Public Health.* 2005; 26: 445-467. Review. PMID: 15760297.	Narrative review; broad dietary coverage, includes SFA.
Segal-Isaacson CJ, Carello E, Wylie-Rosett J. <u>Dietary fats and diabetes mellitus: Is there a good fat?</u> *Curr Diab Rep.* 2001 Oct; 1(2): 161-169. Review.	Narrative review.
Summers LK, Fielding BA, Bradshaw HA, Ilic V, Beysen C, Clark ML, Moore NR, Frayn KN. <u>Substituting dietary saturated fat with polyunsaturated fat changes abdominal fat distribution and improves insulin sensitivity.</u> *Diabetologia.* 2002 Mar; 45(3): 369-377. PMID: 11914742.	N less than 10 per group.
Thomsen C, Storm H, Holst JJ, Hermansen K. <u>Differential effects of saturated and monounsaturated fats on postprandial lipemia and glucagon-like peptide 1 responses in patients with type 2 diabetes.</u> *Am J Clin Nutr.* 2003 Mar; 77(3): 605-611.PMID: 12600850.	Postprandial response; measured glucagon like peptide (GLP-1) and gastric inhibitory polypeptids (GIP) after a meal.
Vessby B. <u>Dietary fat and insulin action in humans.</u> *Br J Nutr.* 2000 Mar; 83 Suppl 1: S91-S96.	Narrative review.
Yost TJ, Erskine JM, Gregg TS, Podlecki DL, Brass EP, Eckel RH. <u>Dietary substitution of medium chain triglycerides in subjects with non-insulin-dependent diabetes mellitus in an ambulatory setting: Impact on glycemic control and insulin-mediated glucose metabolism.</u> *J Am Coll Nutr.* 1994 Dec; 13(6): 615-622. PMID: 7706596.	Date of publication prior to 2000

255

CHAPTER 10. SPECIFIC FATS, FATTY ACIDS, AND CHOLESTEROL – DIETARY STEARIC ACID AND LDL CHOLESTEROL

WHAT IS THE ASSOCIATION BETWEEN DIETARY STEARIC ACID AND LDL CHOLESTEROL?

Conclusion statement

Moderate evidence from a systematic review indicates that when stearic acid is substituted for other saturated fatty acids (SFA) or trans fatty acids, plasma LDL cholesterol (LDL-C) levels are decreased; when substituted for carbohydrates, LDL-C levels are unchanged; and when substituted for monounsaturated fatty acids (MUFA) or polyunsaturated fatty acids (PUFA), LDL-C levels are increased. Therefore, the impact of stearic acid replacement of other energy sources is variable regarding LDL-C, and the potential impact of changes in stearic acid intake on cardiovascular disease risk remains unclear.

Grade

Moderate

Evidence summary overview

A review of the evidence since 2000 resulted in one systematic review that covered all selected primary studies. This review was focused on the effect of stearic acid on cardiovascular disease (CVD) risks when substituted for saturated fat(SFA), trans fatty acids (TFA), monounsaturated fat (MUFA), polyunsaturated fat (PUFA) or carbohydrates (CHO) and provided the evidence to address this question (Hunter, 2010).

This systematic review covered 21 epidemiologic studies (three that assessed stearic acid specifically) and 22 randomized controlled trials (RCTs). Overall, the results showed that in comparison with SFA, stearic acid lowered LDL cholesterol(LDL-C), was neutral with respect to HDL cholesterol (HDL-C) and lowered the ratio of total to HDL-C. In comparison with unsaturated fatty acids, MUFA and PUFA, stearic acid tended to raise LDL-C, lower HDL-C and increase the ratio of total cholesterol (TC) to HDL-C. Replacing industrial trans fatty acids (iTFA) with stearic acid may increase stearic acid intake from 3% to 4-5% of energy in the US population.

Evidence summary paragraphs

Hunter et al, 2010 (neutral quality) This was a systematic review that examined the effect of stearic acid on blood LDL-C when substituted for SFA, MUFA, PUFA, CHO or TFA. This systematic review covered three epidemiologic studies that examined stearic acid specifically, and 20 RCTs that examined high stearic acid intake as a replacement of other dietary fats or CHO. The RCTs were grouped according to comparisons with:

1. High SFA (palmitic acid, myristic acid, or butterfat)
2. High CHO

256

3. High unsaturated fat (oleic acid or linoleic acid)
4. Baseline (or habitual) diet.

Four studies assessed the effect of substituting stearic acid for TFA in the diet. Both univariate and multivariate regression analysis was conducted with all selected studies. Overall, the results showed that in comparison with other SFA, stearic acid lowered LDL-C, was neutral with respect to HDL-C and lowered the ratio of TC to HDL-C. In comparison with unsaturated fatty acids (MUFA or PUFA) stearic acid tended to raise LDL-C, lower HDL-C and increase the ratio of TC to HDL-C. Univariate regression analysis of the data substituting stearic acid for cholesterol-raising SFA showed that the LDL-C concentration decreased as dietary stearic acid increased. The univariate regression coefficient for this relation was -0.036 (P=0.034). The regression coefficient suggests that for each 1% of energy increase in stearic acid, when substituted for cholesterol-raising SFA, the LDL-C concentration could decrease by 0.036mmol per L. When multivariate regression analysis was done, with adjustments for both between-study, and within-study, variation, the multivariate regression coefficient for this relation was 0.043 (<0.001), suggesting that for each 1% energy increase in cholesterol-raising SFA, when substituted for stearic acid, the LDL-C concentration would increase by 0.043mmol per L. Additionally, a one-to-one substitution of stearic acid for trans fatty acids showed a decrease or no effect on LDL-C, an increase or no effect on HDL-C and a decrease in the ratio of total to HDL-C. Replacing iTFA with stearic acid could increase stearic acid intake from 3% to 4-5% of energy in the US population. This systematic review provided broad qualitative and quantitative analysis, however, it was scored as methodologically neutral based on one limitation: The selected studies included in the review were not individually graded. Overall, this review provided the most updated evidence and covered all aspects of stearic acid replacements and risk/benefit outcomes related to LDL-C and CVD risk.

Overview table

Author, Year, Study Design, Class, Rating	Study Population/ Location	Intervention, Protocol/ Exposure Levels	Significant Results	Limitations
Hunter JE, Zhang J et al, 2010 Study Design: Meta-analysis or Systematic Review Class: M Rating: Neutral quality	International epidemiologic studies and RCTs.	Stearic acid and blood LDL-HDL-C and non HDL-C Reviewed epidemiologic studies investigating stearic acid when substituted for SFA, MUFA, PUFA, CHO or TFA. Conducted univariate and multivariate regression analysis with all selected studies. Three epidemiologic studies that examined stearic acid specifically. 20 RCT that examined high stearic acid intake as a replacement of other dietary fats or CHO. Four studies assessed effect of substituting stearic acid for TFAs in the diet.	Comparison with other SFA, stearic acid: ↓ LDL-C Neutral with respect to HDL-C ↓ TC: HDL-C ratio. Comparison with unsaturated FAs (MUFA or PUFA) stearic acid: Tended to ↑ LDL-C ↓ HDL-C ↑ TC: HDL-C ratio. Univariate regression analysis of the data substituting stearic acid for cholesterol-raising SFA: LDL-C concentration ↓ as dietary stearic acid ↑ (univariate regression coefficient= -0.036 (P=0.034) When multivariate regression (between- and within-study) multivariate regression coefficient=0.043 (<0.001) One-to-one substitution of stearic acid for TFAs showed: ↓ or no effect on LDL-C ↑ or no effect on HDL-C ↓ in the ratio of TC to HDL-C.	Included studies were not graded.

258

Research recommendations

Examine stearic acid for its benefits as a solid fat, in contrast to liquid oils high in MUFA and PUFA; include other potential metabolic effects of stearic acid, such as inflammation and coagulation.

Search plan and results

Inclusion Criteria

Subjects/Population

- *Age*: Two years through adult
- *Setting*: US and International
- *Health status*: Healthy and those with elevated chronic disease risk (CHD/CVD, type 2 diabetes, metabolic syndrome and obesity).

Nutrition Related Problem/Condition

Search criteria:

- *Study design preferences*: RCT or Clinical Controlled Studies, Large nonrandomized observational studies, Met-analysis and Systematic reviews.
- *Size of study groups*: Sample size >10 subjects per study group.
- *Study drop out rate*: Less than 20%; preference for smaller dropout rates
- *Year Range*: 2000 - April 2010
- *Languages*: Limited to articles in English
- *Other*: Article must be published in peer-reviewed journal
- *Diet*: Experimental fat from natural sources; feeding period greater than 4 weeks

Exclusion Criteria

Subjects/Population

- *Age*: Infants or children less than two years
- *Setting*: Inpatients
- *Health status*: None.

Search criteria:

- *Study Designs*: Cross sectional; Feeding periods less than 4 weeks.
- *Diet*: Experimental fat must be from natural sources
- *Size of study groups*: Sample sizes < 10
- *Study Drop out rate*: If the dropout rate in a study is 20% or greater, the study will be rejected.
- *Year Range*: Prior to January 2000
- *Authorship*: Studies by same author similar in content.
- *Languages*: Articles not in English
- *Other*: Animal studies; Abstracts or presentations

Search Terms and Electronic Databases Used

- PubMed: dietary stearic acid and: LDL; HDL; blood; dosage; metabolism; ldl:hdl

259

ratio; intake; cardiovascular disease; thrombosis; hemostasis; serum lipoproteins; cholesterol

Date Searched: 05/05/2009 to 05/12/-2009

Summary of Articles Identified to Review

- Total hits from all electronic database searches: 140
- Total articles identified to review from electronic databases: 41
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 0
- Number of Review Articles Identified: 1
- Total Number of Articles Identified: 1
- Number of Articles Reviewed but Excluded: 40

Included Article

Systematic Reviews/Meta-analyses

1. Hunter JE, Zhang J, Kris-Etherton PM. Cardiovascular disease risk of dietary stearic acid compared with trans, other saturated, and unsaturated fatty acids: a systematic review.Am J Clin Nutr. 2010 Jan;91(1):46-63. Epub 2009 Nov 25. Review.PMID: 19939984

Excluded Articles

Article	Reason for exclusion
Abia R, Pacheco YM, Montero E, Ruiz-Gutierrez V, Muriana FJ.Distribution of fatty acids from dietary oils into phospholipid classes of triacylglycerol-rich lipoproteins in healthy subjects. Life Sci. 2003 Feb 21;72(14):1643-54. PubMedPMID: 12551753.	Variable studied does not address question
Baer DJ, Judd JT, Clevidence BA, Tracy RP. Dietary fatty acids affect plasma markers of inflammation in healthy men fed controlled diets: a randomized crossover study. Am J Clin Nutr. 2004 Jun;79(6):969-73. PubMed PMID: 15159225. Excluded from previously approved list.	Does not address question specifically. Measures markers of inflammation.
Baer DJ, Judd JT, Kris-Etherton PM, Zhao G, Emken EA. Stearic acid absorption and its metabolizable energy value are minimally lower than those of other fatty acids in healthy men fed mixed diets.J Nutr. 2003 Dec;133(12):4129-34. PubMed PMID: 14652360.	Does not address question. Reports on absorption of Stearic acid.

260

Berry SE, Tucker S, Banerji R, Jiang B, Chowienczyk PJ, Charles SM, Sanders TA. <u>Impaired postprandial endothelial function depends on the type of fat consumed by healthy men.</u> J Nutr. 2008 Oct;138(10):1910-4. PubMed PMID: 18806100.	Does not address question. Investigates effect on lipemia (TG).
Berry SE, Miller GJ, Sanders TA. <u>The solid fat content of stearic acid-rich fats determines their postprandial effects.</u> Am J Clin Nutr. 2007Jun;85(6):1486-94. PubMed PMID: 17556683.	Study involves other risk factors that do not address the question.
Burdge GC, Wootton SA. <u>Conversion of alpha-linolenic acid to palmitic, palmitoleic, stearic and oleic acids in men and women.</u> Prostaglandins Leukot Essent Fatty Acids. 2003 Oct;69(4):283-90. PubMed PMID: 12907139.	Studies ALA conversion and does not address question.
Bysted A, Hølmer G, Lund P, Sandström B, Tholstrup T. <u>Effect of dietary fatty acids on the postprandial fatty acid composition of triacylglycerol-rich lipoproteins in healthy male subjects.</u> Eur J Clin Nutr. 2005 Jan;59(1):24-34. PubMed PMID: 15305178**.**	Does not address question. Investigates effect of trans fatty acid on postprandial lipemia.
Cheng HH, Wen YY, Chen C. <u>Serum fatty acid composition in primary school children is associated with serum cholesterol levels and dietary fat intake.</u> Eur J Clin Nutr. 2003 Dec;57(12):1613-20. PubMed PMID: 14647227.	Does not address question. Examines serum fatty acid composition.
Ding EL, Hutfless SM, Ding X, Girotra S. <u>Chocolate and prevention of</u> <u>cardiovascular disease: a systematic review.</u> Nutr Metab (Lond). 2006 Jan 3;3:2.PubMed PMID: 16390538; PubMed Central PMCID: PMC1360667.	Does not address questions. Emphasis on beneficial effect of Chocolate
DiRienzo MA, Lemke SL, Petersen BJ, Smith KM. <u>Effect of substitution of high stearic low linolenic acid soybean oil for hydrogenated soybean oil on fatty acid intake.</u> Lipids. 2008 May;43(5):451-6. Epub 2008 Mar 26. PubMed PMID: 18365266.	Involves substitution studies that do not address question.
Edionwe AO, Kies C. <u>Comparison of palm and mixtures of refined palm and soybean oils on serum lipids and fecal fat and fatty acid excretions of adult humans.</u> Plant Foods Hum Nutr. 2001;56(2):157-65. PubMed PMID: 11318504.	Excretion studies that do not address question.

Habán P, Zideková E, Klvanová J. Oleic acid serum phospholipid content is linked with the serum total- and LDL-cholesterol in elderly subjects. Med Sci Monit. 2000 Nov-Dec;6(6):1093-7. PubMed PMID: 11208461.	Studies oleaic acid and PI and does not address question
Hac-Wydro K, Wydro P.The influence of fatty acids on model cholesterol/phospholipid membranes. Chem Phys Lipids. 2007 Nov;150(1):66-81. Epub 2007 Jun 21. PubMed PMID: 17651712.	Does not address question.
Hodge AM, English DR, O'Dea K, Sinclair AJ, Makrides M, Gibson RA, Giles GG. Plasma phospholipid and dietary fatty acids as predictors of type 2 diabetes: interpreting the role of linoleic acid. Am J Clin Nutr. 2007 Jul;86(1):189-97.PubMed PMID: 17616780.	Studies plasma PL and does not address question.
Hunter KA, Crosbie LC, Horgan GW, Miller GJ, Dutta-Roy AK.Effect of diets rich in oleic acid, stearic acid and linoleic acid on postprandial haemostatic factors in young healthy men. Br J Nutr. 2001 Aug;86(2):207-15. PubMed PMID:11502234.	Does not address question. Investigated effect on postprandial haemostasis.
Jensen J, Bysted A, Dawids S, Hermansen K, Hølmer G. The effect of palm oil, lard, and puff-pastry margarine on postprandial lipid and hormone responses in normal-weight and obese young women. Br J Nutr. 1999 Dec;82(6):469-79. PubMedPMID: 10690162.	Does not study stearic acid.
Judd JT, Baer DJ, Clevidence BA, Kris-Etherton P, Muesing RA, Iwane M. Dietary cis and trans monounsaturated and saturated FA and plasma lipids and lipoproteins in men. Lipids. 2002 Feb;37(2):123-31. PubMed PMID: 11908904.	Captured by Hunter et al 2010 - Review.
Kabagambe EK, Baylin A, Siles X, Campos H. Individual saturated fatty acids and nonfatal acute myocardial infarction in Costa Rica. Eur J Clin Nutr. 2003Nov;57(11):1447-57. PubMed PMID: 14576758**.**	Does not address question. Studies effect on MI.
Kelly FD, Sinclair AJ, Mann NJ, Turner AH, Raffin FL, Blandford MV, Pike MJ. Short-term diets enriched in stearic or palmitic acids do not alter plasma lipids, platelet aggregation or platelet activation status. Eur J Clin Nutr. 2002Jun;56(6):490-9. PubMed PMID: 12032647.	Studies outcomes not of interest and do not address the question

262

Kelly FD, Sinclair AJ, Mann NJ, Turner AH, Abedin L, Li D. A stearic acid-rich diet improves thrombogenic and atherogenic risk factor profiles in healthy males. Eur J Clin Nutr. 2001 Feb;55(2):88-96. PubMed PMID: 11305631.	Studies outcomes not of interest and do not address the question
Li D. Relationship between the concentrations of plasma phospholipid stearic acid and plasma lipoprotein lipids in healthy men.Clin Sci (Lond). 2001 Jan;100(1):25-32. PubMed PMID: 11115414.	Does not meet inclusion criteria. Cross sectional study
Mensink RP. Effects of stearic acid on plasma lipid and lipoproteins in humans.2005 Dec;40(12):1201-5. REVIEW PubMed PMID: 16477803. Excluded from previously approved list.	No new data. Cites data already cited and addressed in the larger 2002 review.
Mensink RP. Effects of products made from a high-palmitic acid, trans-free semiliquid fat or a high-oleic acid, low-trans semiliquid fat on the serum lipoprotein profile and on C-reactive protein concentrations in humans. Eur J Clin Nutr. 2008 May;62(5):617-24. Epub 2007 Apr 18. PubMed PMID: 17440525.	Studies variables not normally consumed. Does not address question
Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr. 2003 May;77(5):1146-55. PubMed PMID: 12716665	Captured by Hunter et al 2010 - Review
Müller H, Kirkhus B, Pedersen JI. Serum cholesterol predictive equations with special emphasis on trans and saturated fatty acids. an analysis from designed controlled studies. Lipids. 2001 Aug;36(8):783-91. PubMed PMID: 11592728.	Study invoves predictive equations and do not address question
Nydahl MC, Smith RD, Kelly CN, Fielding BA, Williams CM.Achievement of dietary fatty acid intakes in long-term controlled intervention studies: approach and methodology. Public Health Nutr. 2003 Feb;6(1):31-40. PubMed PMID: 12581463.	Outcomes studied do not address question
Robinson DM, Martin NC, Robinson LE, Ahmadi L, Marangoni AG, Wright AJ. Influence of interesterification of a stearic Acid-rich spreadable fat on acute metabolic risk factors. Lipids. 2009 Jan;44(1):17-26. Epub 2008 Nov 4. PubMedPMID: 18982377.	Variable studied not consumed normally. Does not address question.

263

Sacks FM, Katan M. <u>Randomized clinical trials on the effects of dietary fat and carbohydrate on plasma lipoproteins and cardiovascular disease.</u> Am J Med. 2002 Dec 30;113 Suppl 9B:13S-24S. Review. PMID: 12566134 Excluded from previously approved list.	Does not address question. Not a systematic review and emphasizes is on clinical outcomes
Sanders TA, Berry SE. <u>Influence of stearic acid on postprandial lipemia and hemostatic function.</u> Lipids. 2005 Dec;40(12):1221-7. PubMed PMID: 16477806.	Does not address question. Looks at postprandial lipemia and hemostatic function.
Sanders TA, Berry SE, Miller GJ. <u>Influence of triacylglycerol structure on the postprandial response of factor VII to stearic acid-rich fats.</u> Am J ClinNutr. 2003 Apr;77(4):777-82. PubMed PMID: 12663272.	Studies postprandial lipemia. Does not address question.
Sanders TA, Oakley FR, Cooper JA, Miller GJ. <u>Influence of a stearic acid-rich structured triacylglycerol on postprandial lipemia, factor VII concentrations, and fibrinolytic activity in healthy subjects.</u> Am J Clin Nutr. 2001Apr;73(4):715-21. PubMed PMID: 11273845.	Studied structured fats not normally consumed. Experiment fats.
Sundram K, Karupaiah T, Hayes KC. <u>Stearic acid-rich interesterified fat and trans-rich fat raise the LDL/HDL ratio and plasma glucose relative to palm olein in humans.</u> Nutr Metab (Lond). 2007 Jan 15;4:3. PubMed PMID: 17224066; PubMed Central PMCID: PMC1783656.	Structured fatty acids used, not natural. Experimental fats/diets
Thijssen MA, Hornstra G, Mensink RP. <u>Stearic, oleic, and linoleic acids have comparable effects on markers of thrombotic tendency in healthy human subjects.</u> JNutr. 2005 Dec;135(12):2805-11. PubMed PMID: 16317124.	Does not address question. Studied thrombogenic effects.
Thijssen MA, Mensink RP. <u>Small differences in the effects of stearic acid, oleic acid, and linoleic acid on the serum lipoprotein profile of humans.</u>Am J Clin Nutr. 2005 Sep;82(3):510-6. PubMed PMID: 16155261	Captured by Hunter et al 2010. - Review
Tholstrup T. <u>Influence of stearic acid on hemostatic risk factors in humans.</u> Lipids. 2005 Dec;40(12):1229-35. PubMed PMID: 16477807.	Does not address question. Study looks at thrombogenic effects.

Tholstrup T, Samman S. <u>Postprandial lipoprotein(a) is affected differently by specific individual dietary fatty acids in healthy young men.</u> J Nutr. 2004 Oct;134(10):2550-5. PubMed PMID: 15465746.	Does not address question. Study looks at thrombogenic effects.
Tholstrup T, Vessby B, Sandstrom B. <u>Difference in effect of myristic and stearic acid on plasma HDL cholesterol within 24 h in young men.</u>Eur J Clin Nutr. 2003 Jun;57(6):735-42. PubMed PMID: 12792657.	Intervention was less than 4 weeks.
Tholstrup T, Sandström B, Bysted A, Hølmer G. <u>Effect of 6 dietary fatty acids on the postprandial lipid profile, plasma fatty acids, lipoprotein lipase, and cholesterol ester transfer activities in healthy young men.</u> Am J Clin Nutr. 2001 Feb;73(2):198-208. PubMed PMID: 11157314.	Variables studied do not address question.
Wang L, Folsom AR, Eckfeldt JH. <u>Plasma fatty acid composition and incidence of diabetes in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study.</u> Nutr Metab Cardiovasc Dis. 2003 Oct;13(5):256-66. PubMed PMID: 14717057.	Variables studied do not not address question.
Wang L, Folsom AR, Zheng ZJ, Pankow JS, Eckfeldt JH; ARIC Study Investigators. <u>Plasma fatty acid composition and incidence of coronary heart disease in middle aged adults: the Atherosclerosis Risk in Communities (ARIC) Study.</u> Am J Clin Nutr. 2003 Jul;78(1):91-8.	Variables studied do not address question.

265

CHAPTER 11. SPECIFIC FATS, FATTY ACIDS, AND CHOLESTEROL – EFFECT OF NATURAL VS. SYNTHETIC TRANS FATTY ACIDS ON LDL, HDL AND NON-HDL CHOLESTEROL

WHAT EFFECT DOES CONSUMING NATURAL (RUMINANT) VS. SYNTHETIC (INDUSTRIALLY HYDROGENATED) TRANS FATTY ACIDS HAVE ON LDL-, HDL- AND NON-HDL CHOLESTEROL?

Conclusion statement

Limited evidence is available to support a substantial biological difference in the detrimental effects of industrial trans fatty acids (iTFA) and ruminant trans fatty acids (rTFA) on health when rTFA is consumed at seven to ten times the normal level of consumption..

Grade

Limited

Evidence summary overview

Three studies were reviewed to determine the effect of ruminant (rTFA) vs. industrially-produced trans fatty acids (iTFA) on low-density lipoprotein cholesterol, (LDL-C), high-density lipoprotein cholesterol (HDL-C) and nonHDL-C: One non-systematic reviews and two randomized controlled trials (RCTs).

It is well-documented that synthetic iTFA adversely effects LDL-C, HDL-C and non-HDL-C, but evidence is very limited that natural ocurring rTFA at levels typically consumed have any effect on cardiovascular disease(CVD) or coronary heart disease (CHD) risks. Based upon the results of two, small, well-designed crossover studies (Chardigny et al, 2008; Motard-Belanger et al, 2008), high intakes of rTFA (10.2g-12g per day) do not show consistent and different effects from synthesized iTFAs. One small RCT (Chardigny et al, 2008) found rTFA intake compared to iTFA intake increased both LDL-C and HDL-C in women, but not in men. This finding does not allow for a conclusion that there is any change in risk between iTFA and rTFA, since these lipid changes should not change the CVD risk appreciably.

Jakobsen et al, 2006 reviewed three prospective cohort studies, one case-control study and one descriptive study using CHD end-points and reported no significant (NS) difference in associations between rTFA and iTFA, corroborating the studies evaluating their effect on lipids and lipoproteins. Omen et al, 2001 confirmed these findings in a cohort of 667 Dutch men.

These data taken together, based upon very limited studies, indicate that there is insufficient evidence to suggest rTFA and iTFA be considered differentially in their metabolic effect. Total TFA intake should be considered the target for dietary change.

Evidence summary paragraphs

Chardigny JM et al 2008, in a positive quality randomized, double-blind, controlled, cross-over trial that compared the effects of TFAs from industrially-produced and

266

natural sources on HDL-C and LDL-C, lipoprotein particle size and distribution, apolipoproteins and other lipids in 40 (21 women, 19 men) healthy, normolipidemic subjects in France. The eight-week intervention consisted of two, three-week experimental periods and a one-week run-in and one-week wash-out period. The experimental diet incorporated either rTFAor iTFA (11-12g per day, representing approximately 5% of daily energy) consumed daily in form of 20g butter, 100g cheese and 22g cookies. Compliance was assessed via questionnaire and plasma assay for TFA in plasma cholesteryl-esters. Compared with TFAs from industrially produced sources, TFAs from natural sources significantly increased HDL-C (P<0.012) and LDL-C (P<0.001) in women, but not in men. In women, an increased concentration of large LDL-C particles was significant (P=0.009). Plasma concentrations of total cholesterol (TC) and triacylglycerol (TG) were also significant higher (<0.001 and P=0.001, respectively) in women consuming TFAs from natural vs. industrial sources. The TC to HDL-C ratio was NS increased.

Jakobsen et al, 2006, in a negative quality narrative reviewed the findings of five epidemiological studies that investigated the effects of different quintiles of intake of rTFA and iTFA on CHD risk factors. Three prospective cohort studies, one case-control and one descriptive study were reviewed. Two of the three prospective cohort studies found an inverse association between energy-adjusted rTFA intake and risk of CHD. Willett WC et al, 1993, found that the relative risk (RR) of CHD for the highest vs. the lowest quintile of energy adjusted rTFA was 0.59 (95% CI 0.30-1.17) and Pietinen P et al, 1997, found that the relative risk of coronary death for the highest vs. the lowest quintile of energy adjusted rTFA was 0.83 (95% CI 0.62-1.11); and a case-control study (Ascherio A et al, 1994) found that the RR of myocardial infarction (MI) for the higher vs. lowest quintile of energy-adjusted rTFA intake was 1.02 (95% CI 0.43-2.41). Those findings might imply that intake of rTFA, as C18:1,t11 (vaccenic acid) is innocuous or even protective against CHD. One prospective cohort study (Oomen CM et al, 2001) found NS direct associations between intake of rTFA and iTFA and risk of CHD; i.e., for 0.5% higher level of energy intake from rTFA, the RR of CHD was 1.17 (95% CI 0.69-1.98) and, for iTFA, the RR was 1.05 (95% CI 0.94-1.17). Authors recommended that more controlled metabolic studies on the effect of intake of total and specific rTFA on CHD risk factors and more epidemiological studies of intake of rTFA and risk of CHD, assessing association for both absolute and energy-adjusted intake, be conducted. Method of selection of articles reviewed was not defined.

Motard-Bélanger A et al, 2008, in a positive quality double-blind, randomized, crossover controlled feeding trial that compared the effects of rTFA and iTFA on plasma LDL-C concentrations and other CVD risk factors. Thirty-eight male normolipidemic Canadian subjects (36 white and two black) were fed four experimental isoenergetic diets each lasting four weeks. The following diets were tested:

1. High rTFA (10.2g per 2,500kcal)
2. Moderate rTFA (4.2g per 2,500kcal), high iTFA (10.2g per 2,500 kcal) and low in TFA from any source (2.2g per 2,500kcal) (control diet).

Each diet was separated by a wash-out period of three to 12 weeks. All diets were identical in terms of menus, calories and macronutrient composition. Ruminant TFA and iTFA provided 3.6% of daily energy intake in the high TFA diets and

267

the rTFA provided 1.5% of daily energy intake in the moderate rTFA diet. Finally, the control diet provided 0.8% of daily energy intake from rTFA and 0% from iTFA. Results showed that plasma LDL-Cconcentrations were significantly higher after the high-rTFA diet than after the control (P<0.03) or the moderate- rTFA diet (P<0.002). Plasma LDL-C concentrations were significantly higher (P<0.02) after the iTFA diet than after the moderate-rTFA diet. Plasma HDL-C concentrations were significantly lower (P<0.02) after the high rTFA diet than after the moderate-rTFA diet. All risk factors were comparable between the control and the moderate-rTFA diets.

Overview table

Author, Year, Study Design, Class, Rating	Study Population and Location	Intervention	Significant Results	Limitations
Chardigny J, Destaillats F et al, 2008 Study Design: Randomized, double-blind, controlled, cross-over trial Class: A Rating: Positive quality	N=40 normolipidemic French subjects (21 women, 19 men). Mean age: 27.6±7.1 years. Attrition: 9%. Location: France.	rTFA vs. iTFA One week run-in period; two, three-week experimental periods; one-week wash-out period. rTFA and iTFA fed (11-12g per day, ~5% of daily energy) daily in the form of 20g butter,100g cheese and 22g cookies. Compliance assessed via questionnaire and plasma assay for TFA in cholesteryl-esters.	Compared with iTFAs, rTFAs ↑ HDL-C (P<0.012) and LDL-C(P<0.001) in women, but not in men.	Limited generalizability. Limited to young and healthy people with good lipid profile only and no good controls were used.

268

| Jakobsen M, Bysted A et al, 2006 Study Design: Narrative Review Class: R Rating: Neutral quality | Not applicable. | Reviewed findings: Three prospective cohort studies One case control One descriptive study. Studies examined the effects of different quintiles of intake of rTFA and iTFA on CHD risk factors. | Two prospective cohort studies found: Inverse association between energy-adjusted rTFA intake and risk of CHD: Willett WC et al, 1993 reported RR of CHD for the highest vs. the lowest quintile of energy adjusted rTFA to be 0.59 (95% CI 0.30-1.17). Pietinen P et al, 1997 reported that the RR of coronary death for the highest vs. the lowest quintile of energy adjusted rTFA was 0.83 (95% CI 0.62-1.11). Ascherio A et al, 1994 (case-control study) reported that the RR of MI for the higher vs. lowest quintile of energy-adjusted rTFA intake was 1.02 (95% CI 0.43-2.41). Findings imply that intake of rTFA, as C18:1,t11 (vaccenic acid) is innocuous or even protective against CHD. Oomen CM et al, 2001 (prospective cohort) found NS direct associations between intake of rTFA and iTFA and risk of CHD; i.e., for 0.5% higher level of energy intake from rTFA, RR of CHD was 1.17 (95% CI 0.69-1.98) and, for iTFA, RR was 1.05 (95% CI 0.94-1.17). | Not a systematic review. Article selection methods not described. |

Motard-Belanger A, Charest A et al, 2008 Study Design: Double-blind, randomized, crossover controlled trial Class: A Rating: Positive quality	N=38 normolipidemic Canadian men. Mean age: 32.8±15.0 years. Attrition: 20%.	rTFA vs. iTFA: High and Moderate concentrations. Four isocaloric experimental diets: High in rTFA (10.2g per 2,500kcal) Moderate rTFA (4.2g per 2,500kcal) High in iTFA (10.2g per 2,500kcal) Low in iTFA (2.2g per 2,500kcal) (control diet). All meals were provided to participants. Based upon checklist provided, 99.9% of food provided was consumed.	High-rTFA: Plasma LDL-C significantly higher after the high- rTFA diet than after the control (P<0.03) or the moderate- rTFA (P<0.002) diet. Plasma LDL-C concentrations significantly higher (P<0.02) after the iTFA diet than after the moderate-rTFA diet. Plasma HDL-C significantly lower (P<0.02) after the high rTFA diet than after the moderate-rTFA diet.	Funded in part by the dairy industry. No mention of intent to treat statistics analysis. Study involved only healthy males. Small sample size.

Research recommendations

Characterize the difference in metabolic effects and intermediate markers between industrial and ruminant trans fatty acids.

Search plan and results

Inclusion Criteria

- *Age*: Two years to adult.
- *Setting*: US and International.
- *Health Status*: Healthy and those with elevated chronic risk (CHD/CVD, type 2 diabetes, metabolic syndrome, and obesity).

Nutrition Related Problem/Condition:

Search Criteria

- *Study Design Preferences*: Randomized controlled trial (RCT) or clinical controlled studies, large non-randomized observational studies, cohort, meta-analysis and systematic reviews.
- *Size of Study Groups:* The sample size must be equal to 10 adults for each study group. (For example, this would include 10 patients in the Intervention group and 10 patients in the control or comparison group).
- *Study Dropout Rate:* Less than 20%; preference for smaller dropout rates.
- *Year Range:* January 2004 to May 2009.

270

- *Authorship:* If an author is included on more than one review article or primary research article that is similar in content, the most recent review or article will be accepted and earlier versions will be rejected.
- *Languages:* Limited to articles in English.
- *Other:* Article must be published in peer-review journal.

Exclusion Criteria

Subjects/Population

- *Age***:** Infants less than two years.
- *Setting***:** Inpatients.
- *Health Status***:** None.
- *Nutrition Related Problem/Condition***:** Eating disorders.

Search Criteria

- *Study Design Preferences***:** Not applicable.
- *Size of Study Groups***:** <10.
- *Study Dropout Rate***:** If the dropout rate in a study is 20% or greater, the study will be rejected.
- *Year Range***:** Prior to 2000.
- *Authorship***:** Studies by same author similar in content.
- *Languages***:** Articles in English.
- *Other***:** Animal studies; abstracts or presentations.

Search Terms and Electronic Databases Used

PubMed

Date Searched: 05/06/2009

Summary of Articles Identified to Review

- Total hits from all electronic database searches: 62
- Total articles identified to review from electronic databases: 20
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 2
- Number of Review Articles Identified: 1
- Total Number of Articles Identified: 3
- Number of Articles Reviewed but Excluded: 17

Included Articles (References)

Review Articles:

1. Jakobsen MU, Bysted A, Andersen NL, Heitmann BL, Hartkopp HB, Leth T, Overvad K, Dyerberg J. Intake of ruminant trans fatty acids and risk of coronary heart disease-an overview. Atheroscler Suppl. 2006 May; 7 (2): 9-11. Epub 2006 May 18. *Review.* PMID:16713389.

Research Articles:

271

1. Motard-Bélanger A, Charest A, Grenier G, Paquin P, Chouinard Y, Lemieux S, Couture P, Lamarche B. <u>Study of the effect of trans fatty acids from ruminants on blood lipids and other risk factors for cardiovascular disease.</u> *Am J Clin Nutr.* 2008 Mar; 87 (3): 593-599. PMID:18326596.

2. Chardigny JM, Destaillats F, Malpuech-Brugère C, Moulin J, Bauman DE, Lock AL, Barbano DM, Mensink RP, Bezelgues JB, Chaumont P, Combe N, Cristiani I, Joffre F, German JB, Dionisi F, Boirie Y, Sébédio JL. <u>Do Trans fatty acids from industrially produced sources and from natural sources have the same effect on cardiovascular disease risk factors in healthy subjects? Results of the Trans Fatty Acids Collaboration (TRANSFACT) study.</u> *Am J Clin Nutr.* 2008 Mar; 87 (3): 558-566. PMID: 18326592.

Excluded Articles

Articles	Reason for Exclusion
Baer DJ, Judd JT, Clevidence BA, Tracy RP. Dietary fatty acids affect plasma <u>Markers of inflammation in healthy men fed controlled diets: A randomized crossover study.</u> *Am J Clin Nutr.* 2004 Jun; 79 (6): 969-973. PMID: 15159225.	Does not address variables of interest. No direct comparisons
Chardigny JM, Malpuech-Brugère C, Dionisi F, Bauman DE, German B, Mensink RP, Combe N, Chaumont P, Barbano DM, Enjalbert F, Bezelgues JB, Cristiani I, Moulin J, Boirie Y, Golay PA, Giuffrida F, Sébédio JL, Destaillats F. <u>Rationale and design of the TRANSFACT project phase I: A study to assess the effect of the two different dietary sources of trans fatty acids on cardiovascular risk factors in humans.</u> *Contemp Clin Trials.* 2006 Aug; 27 (4): 364-373. Epub 2006 Apr 24. PMID: 16632411.	Does not address question. Describes the rationale and design of the TRANSFACT project phase I.
Clifton PM, Keogh JB, Noakes M. <u>Trans fatty acids in adipose tissue and the food supply are associated with myocardial infarction.</u> *J Nutr.* 2004 Apr; 134 (4): 874-879. Erratum in: *J Nutr.* 2004 Jul; 134 (7): 1, 848. PMID: 15051840.	Does not address question. Examines both adipose tissue levels and dietary intake.
de Roos NM, Schouten EG, Katan MB. <u>Trans fatty acids, HDL-cholesterol and cardiovascular disease. Effects of dietary changes on vascular reactivity.</u> *Eur J Med Res.*2003 Aug 20; 8 (8): 355-357. PMID: 12915329.	Does not address variables in question. No direct comparison

de Roos NM, Schouten EG, Scheek LM, van Tol A, Katan MB. <u>Replacement of dietary saturated fat with trans fat reduces serum paraoxonase activity in healthy men and women.</u> *Metabolism.* 2002 Dec; 51 (12): 1, 534-1, 537. PMID: 12489064.	Does not address question. Studies replacing saturated fat with TFA on PON1 activity and HDL.
Dyerberg J, Eskesen DC, Andersen PW, Astrup A, Buemann B, Christensen JH, Clausen P, Rasmussen BF, Schmidt EB, Tholstrup T, Toft E, Toubro S, Stender S. <u>Effects of trans- and n-3 unsaturated fatty acids on cardiovascular risk markers in healthy males. An eight-week dietary intervention study.</u> *Eur J Clin Nutr.* 2004 Jul; 58 (7): 1, 062-1, 070. PMID: 15220949	Does not address question. Examines cardiovascular risk markers of dietary enrichment with TFA or n-3 PUFA.
Jakobsen MU, Overvad K, Dyerberg J, Heitmann BL. <u>Intake of ruminant trans fatty acids and risk of coronary heart disease.</u> *Int J Epidemiol.* 2008 Feb; 37 (1): 173-182. Epub 2007 Dec 12. PMID: 18077475.	Does not address questions. No direct comparisons with iTrans.
Judd JT, Baer DJ, Clevidence BA, Kris-Etherton P, Muesing RA, Iwane M. <u>Dietary cis and trans monounsaturated and saturated FA and plasma lipids and lipoproteins in men.</u> *Lipids.* 2002 Feb; 37 (2): 123-131. PMID: 11908904.	Does not address question. Investigate post-prandialhaemostasis.
Lichtenstein AH, Matthan NR, Jalbert SM, Resteghini NA, Schaefer EJ, AusmanLM. <u>Novel soybean oils with different fatty acid profiles alter cardiovascular disease risk factors in moderately hyperlipidemic subjects.</u> *Am J Clin Nutr.* 2006 Sep; 84 (3): 497-504. PMID: 16960162	Does not address question. Studies effect of selectively modified soybean oils.
Mensink RP. <u>Effects of products made from a high-palmitic acid, trans-free semi-liquid fat or a high-oleic acid, low-trans semiliquid fat on the serum lipoprotein profile and on C-reactive protein concentrations in humans.</u> *Eur J Clin Nutr.* 2008 May; 62 (5): 617-624. Epub 2007 Apr 18. PMID: 17440525	Does not address question or compare variables head to head in questions.

273

Mozaffarian D, Abdollahi M, Campos H, Houshiarrad A, Willett WC. Consumption of trans fats and estimated effects on coronary heart disease in Iran. *Eur J Clin Nutr.* 2007 Aug; 61 (8): 1, 004-1, 010. Epub 2007 Jan 31. PMID: 17268422.	Does not address question. Investigates intake of industrial TFA in Iranian homes.
Mozaffarian D, Clarke R. Quantitative effects on cardiovascular risk factors and coronary heart disease risk of replacing partially hydrogenated vegetable oils with other fats and oils. *Eur J Clin Nutr.* 2009 May; 63 Suppl 2: S22-S33 PMID: 19424216. Hand search.	Does not address question. Investigates exchange of trans fatfor SFA, MUFA and PUFA
Müller H, Kirkhus B, Pedersen JI. Serum cholesterol predictive equations with special emphasis on trans and saturated fatty acids. An analysis from designed controlled studies. *Lipids.* 2001 Aug; 36 (8): 783-791. PMID: 11592728 Hand Search 05/30/09	Does not address question. Compares results of predictive equations.
Oomen CM, Ocké MC, Feskens EJ, van Erp-Baart MA, Kok FJ, Kromhout D. Association between trans fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: A prospective population-based study. *Lancet.* 2001 Mar 10; 357(9258): 746-751. PMID:11253967	Overlap. Cited in review article by Jakobsen et al, 2006.
Sun Q, Ma J, Campos H, Hankinson SE, Manson JE, Stampfer MJ, Rexrode KM, Willett WC, Hu FB. A prospective study of trans fatty acids in erythrocytes and risk of coronary heart disease. *Circulation.* 2007 Apr 10; 115 (14): 1, 858-1, 865. Epub 2007 Mar 26. PMID: 17389261.	Does not address question. Studies the TFA contents in erythrocytes.
St-Onge MP, Aban I, Bosarge A, Gower B, Hecker KD, Allison DB. Snack chips fried in corn oil alleviate cardiovascular disease risk factors when substituted for low-fat or high-fat snacks. *Am J Clin Nutr.* 2007 Jun; 85 (6): 1, 503-1, 510. PMID: 17556685.	Does not address question. Did not compare variables in question.

Archived from www.NEL.gov on March 21, 2017

Tholstrup T, Raff M, Basu S, Nonboe P, Sejrsen K, Straarup EM. Effects of butter high in ruminant trans and monounsaturated fatty acids on lipoproteins, incorporation of fatty acids into lipid classes, plasma C-reactive protein, oxidative stress, hemostatic variables and insulin in healthy young men. *Am J Clin Nutr.* 2006 Feb; 83 (2): 237-243. PMID: 16469980.	Does not address question, but studies effects of rTFA alone

CHAPTER 12. SPECIFIC FOODS, FATTY ACIDS AND CHOLESTEROL – HEALTH EFFECTS RELATED TO CHOCOLATE CONSUMPTION

WHAT ARE THE HEALTH EFFECTS RELATED TO THE CONSUMPTION OF CHOCOLATE?

Conclusion statement

Moderate evidence suggests that modest consumption of dark chocolate or cocoa is associated with health benefits in the form of reduced cardiovascular disease risk. Potential health benefits need to be balanced with caloric intake.

Grade

Moderate

Evidence summary overview

The current evidence regarding chocolate and health outcomes primarily focuses on flavonoids as bioactive constituents of chocolate and their relation to cardiovascular disease (CVD) risk. Flavonoids are a subgroup of polyphenols, and within the flavonoid chemical hierarchy the flavan-3-ols (flavanols) are particularly high in dark chocolate and cocoa. The flavan-3-ols in dark chocolate and cocoa are primarily catechins, epicatechins (monomers) and procyanidins (polymers).

A Nutrition Evidence Library (NEL) search of the literature since 2000 identified a total of 13 studies that addressed the question on health effects of chocolate consumption. Three methodologically strong systematic reviews of international randomized controlled trials (RCTs) and prospective cohort studies (Desch, 2010; Ding, 2006; Hooper, 2008) were identified. Eight RCTs conducted in the US, Europe, Australia and Japan, covering from 25 to 297 subjects, that were methodologically strong (Allen, 2008) and methodologically neutral (Baba, 2007; Crews, 2008; Davidson, 2008; Farouque, 2006; Kurlandsky and Stote, 2006; Monagas, 2009; Tuabert, 2007) were identified. One methodologically strong prospective cohort study of 876 males in the Netherlands (Buijsse, 2006) and one methodologically neutral population-based case-control study conducted in Sweden (Janszky, 2009) were included to address this question.

The systematic review and meta-analysis by Desch et al (2010) covered 10 randomized controlled trials and showed that high-flavanol chocolate or cocoa significantly lowered systolic blood pressure (SBP) and diastolic blood pressure(DBP) (Desch, 2010). Hooper et al (2008) included six RCTs in their meta-analysis and showed that dark chocolate or cocoa improved flow mediated dilation both acutely and chronically. Ding et al (2006) included 21 RCTs and 11 prospective cohort studies and both flavonoids and stearic acid were examined for association with intermediate markers and CVD outcomes. Overall, the RCTs suggested that cocoa and chocolate have beneficial effects on blood pressure (BP), inflammatory markers, anti-platelet function, serum high-density lipoprotein (HDL) and low-density lipoprotein (LDL) oxidation. The prospective cohort studies showed that flavonoids in chocolate were

276

positively associated with decreased risk of CHD and myocardial infarction (MI) mortality. Overall, the evidence from these systematic reviews and meta-analyses was strengthened by the consistency of findings across studies.

The RCTs in this evidence analysis were focused on flavonoids and intermediate markers of CVD risk. Studies showed that dark chocolate or cocoa consumption decreased serum total cholesterol (TC) and LDL-C, increased HDL-C, delayed LDL oxidation (Baba, 2007), decreased serum triglycerides (TG) and improved inflammation markers (Kurlandsky and Stote, 2006). However, one study found no effect of dark chocolate consumption on serum cholesterol levels (Kurlandsky and Stote, 2006). Regarding BP, dark chocolate or cocoa consumption decreased SBP (Allen, 2008; Tuabert, 2007), DBP(Davidson, 2008) and decreased prevalence of hypertension (HTN) (Tuabert, 2007). One RCT found no effect of dark chocolate or cocoa consumption on BP (Crews, 2008). A more detailed analysis of inflammation markers showed that cocoa consumption decreased monocyte expression of numerous cell adhesion molecules (Monagas, 2009). Additionally, high-flavonol cocoa (vs. low flavonol cocoa) increased flow-mediated dilation, both acutely and chronically and reduced insulin resistance (Davidson, 2008). High-flavonol cocoa was also tested in subjects with coronary artery disease(CAD) and did not improve any markers of arterial blood flow or inflammation (Farouque, 2006).

The evidence regarding chocolate and CVD health outcomes contains relatively few epidemiologic studies. Overall, this evidence included populations in the US, Europe, Japan and Australia, participating in both primary prevention and, to a lesser extent, secondary prevention studies. Subject sample sizes ranged from relatively small randomized controlled trials to 470 subjects in the Zutphen Elderly Study and 1,169 subjects in the SHEEP study.

A prospective cohort study in the Netherlands examined cocoa intake and found it inversely associated with BP and CVDmortality in male subjects from the Zutphen Elderly Study (Buijsse, 2006). A population-based case-control study assessed the effects of chocolate consumption in patients with established CHD in the Stockholm Heart Epidemiology Program (SHEEP) where people who had had MIs were followed for eight years. In this study, chocolate consumption had a significant inverse association with cardiac mortality (Janszky, 2009).

Evidence summary paragraphs

Systematic Reviews/Meta-analyses

Desch et al, 2010 (positive) This was systematic review with meta-analysis covering 10 selected RCTs with 297 subjects to investigate the effects of cocoa products (dark chocolate and cocoa beverages) on BP, due to their high content of flavanols. Subjects were healthy adults or with pre-hypertension (PHTN) and treatment duration ranged from two to 18 weeks. The mean BP change across all trials was -4.5mmHg (95% CI: -5.9 to -3.2, P<0.001) for SBP and -2.5mmHg (95% CI: -3.9 to -1.2, P<0.001) for DBP. The meta-analysis confirms the BP-lowering effects of flavanol-rich cocoa products in a larger, updated set of trials than previously reported. Limitations included statistical heterogeneity across studies.

Ding et al, 2006 (positive) This was a systematic review that covered MEDLINE publications from 1966 to 2005 on experimental, observational and clinical studies of the association between cocoa, cacao, chocolate, stearic acid, flavonoids and risk of CVD (CHD and stroke). In addition, an updated meta-analysis was done on flavonoid intake and CHD mortality. Overall, RCTs measured intermediate markers of CVD risk and showed cocoa and chocolate have beneficial effects by lowering blood pressure, decreasing inflammation markers, increasing HDL and decreasing LDLoxidation. Stearic acid, on the other hand, did not affect serum cholesterol and lipoprotein levels. Epidemiological studies on the association of stearic acid and CVD risk were considered inconclusive with methodological limitation. There was a large body of prospective cohort studies on flavonoids that showed chocolate reduced risk of CVD mortality. The updated meta-analysis indicated that intake of flavonoids lowered risk of CHD mortality, RR=0.81 (95% CI: 0.71 to 0.92) comparing highest and lowest tertiles.

Hooper et al, 2008 (positive) This was a meta-analysis of RCTs on flavonoid-rich foods and CVD risk. For the purposes of question 5.3 on chocolate, the meta-analysis of the effects of chocolate or cocoa on the percentage of FMD is relevant (Figure 3). The authors showed that chocolate increased FMD after acute (3.99%; 95% CI: 2.86%, 5.12%) and chronic (1.45%; 0.62%, 2.28%) intake. The time-course suggested a peak effect at approximately two hours, but subgrouping by epicatechin dose did not suggest a strong epicatechin dose effect. The authors note that more studies of the effects of chronic intake are necessary to confirm a clinically significant effect on FMD.

Primary Articles

Allen et al, 2008 (positive) This was a randomized crossover trial conducted in the US to examine the effect of daily consumption of a flavanol-containing chocolate bar with added phytosterols on cardiovascular risk factors in normotensive subjects with elevated cholesterol. After a two-week lead-in diet based on the American Heart Association (AHA) "An Eating Plan for Healthy Americans," subjects consumed two cocoa flavanol-containing dark chocolate bars per day, with or without 1.1g sterol esters per bar, for a period of four weeks and then were switched to the other chocolate bar for an additional four weeks. Out of 650 recruited subjects, 49 entered the study, and 44 subjects completed the study, 24 initially receiving the phytosterol-containing bars (66% male, mean age 45.9±8.1 years) and 20 initially receiving the control bars (64% male, mean age 43.5±8.9 years). Regular consumption of the phytosterol-containing chocolate bars resulted in reductions of 2.0% in serum TC and 5.3% in LDL-C (both P<0.05). In addition, consumption of cocoa flavanols reduced SBP after eight weeks (-5.8mmHg, P<0.05). Limitations include the lack of a washout period between interventions, as well as the lack of comparison to diet-only controls. Baseline comparison with flavonol-containing dark chocolate bar.

Baba et al, 2007 (neutral) This was an RCT conducted in Japan to test whether long-term intake of cocoa powder altered plasma lipid profiles in normocholesterolemic and mildly hypercholesterolemic human subjects. Twenty-five male subjects (mean age 38±1 years) were randomized to consume either 12g sugar a day (control group) or 26g cocoa powder and 12g sugar a day (cocoa group) for 12 weeks; all 25 completed the trial. Plasma HDL-C was significantly increased in the cocoa group compared with

the control group (24% vs. 5%, P<0.05). In addition, the prolongation from baseline levels in the lag time of LDL oxidation in the cocoa group was significantly greater than the reduction measured in the control group (9% vs. -13%, P<0.05). Limitations include the small sample size consisting of only male subjects, limiting generalizability.

Buijsse et al, 2006 (positive) This was a cohort study conducted in the Netherlands to examine whether habitual cocoa intake was inversely related to BP and cardiovascular mortality in elderly male participants from the Zutphen Elderly Study. Cocoa intake was estimated in 1985, 1990 and 1995 by dietitians through the cross-check dietary history; causes of death were ascertained during 15 years of follow-up. Out of 876 men (aged 65 to 84 years at baseline) with dietary intake estimations, chronic disease prevalence was available for 790 men; 470 were included in the analysis. During the 15-year follow-up, 314 men died (66.8%), 152 from CVD. Median cocoa intake was 2.11g per day in 1985, 2.30g per day in 1990 and 2.36g per day in 1995. After multivariate adjustment, compared to the lowest tertile of cocoa intake, the mean SBP in the highest tertile of cocoa intake was 3.7mmHg lower (95% CI: -7.1 to -0.3mmHg, P=0.03) and the mean DBP was 2.1mmHg lower (95% CI: -4.0 to -0.2mmHg, P=0.03). Compared with the lowest tertile of cocoa intake, the adjusted relative risk (RR) for men in the highest tertile of cocoa intake was 0.50 (95% CI: 0.32 to 0.78, P=0.004) for cardiovascular mortality and 0.53 (95% CI: 0.39 to 0.72, P<0.001) for all-cause mortality. No limitations were noted.

Crews et al, 2008 (neutral) This was an RCT conducted in the US to examine the short-term effects of dark chocolate and cocoa on variables associated with neuropsychological functioning and cardiovascular health in healthy, cognitively intact older adults. Participants were randomly assigned to receive a 37g dark chocolate bar and 237ml of an artificially sweetened cocoa beverage, or similar placebo products, each day for six weeks. Of 101 subjects aged 60 years or older initially randomized, 90 completed the trial (38 males and 52 females), 45 in each group. No significant (NS) group-by-trial interactions were found for any of the neuropsychological variables, hematologic tests or BP variables examined. However, the mean pulse rate after three and six weeks of treatment was significantly higher in the dark chocolate and cocoa group than at baseline (P<0.01) and when compared with the placebo group at three and six weeks (P<0.01). Authors note the relatively short duration of the treatment phase and the small quantity of dark chocolate and cocoa may have contributed to the null findings.

Davison et al, 2008 (neutral) This was an RCT conducted in Australia to investigate the effect of cocoa flavanols and exercise on cardio-metabolic risk factors in overweight and obese subjects. Subjects were randomized to one of four groups for 12 weeks: High-flavanol cocoa (902mg flavanols), high-flavanol cocoa and exercise, low-flavanol cocoa (36mg flavanols) or low-flavanol cocoa and exercise; exercise duration was 45 minutes, three times per week, at 75% of age-predicted maximum heart rate. Of 98 screened subjects, 65 subjects were enrolled and 49 completed the 12-week trial: 12 in the high-flavanol cocoa group (four males, eight females; mean age 45.3±4.4 years), 13 in the high-flavanol cocoa and exercise group (six males, seven females; mean age 45.5±4.0 years), 11 in the low-flavanol cocoa group (three males, eight females, mean age 44.4±4.4 years) and 13 in the low-flavanol cocoa and

exercise group (four males, nine females, mean age 45.2±3.0 years). Compared to the low-flavanol cocoa, high-flavanol cocoa increased flow-mediated dilatation acutely (two-hour post-dose) by 2.4% (P<0.01) and chronically (over 12 weeks) by 1.6% (P<0.01), and reduced insulin resistance by 0.31% (P<0.05), DBP by 1.6mmHg (P<0.05) and mean arterial pressure (MAP) by 1.2mmHg (P<0.05), independent of exercise. Limitations include the small numbers of subjects in groups, and differences between groups.

Farouque et al, 2006 (neutral) This was an RCT conducted in Australia to determine the acute and chronic effects of flavanol-rich cocoa on endothelial and vascular function in subjects with CAD. Subjects were randomized to receive either a flavanol-rich chocolate bar and cocoa beverage (444mg flavanols, 170mg epicatechin monomer) or matching isocaloric placebo (19.6mg flavanols, 4.7mg epicatechin monomer) daily for six weeks. Of 40 subjects initially enrolled (30 males, mean age 61±8 years), 38 subjects completed the trial. No acute or chronic changes in flow-mediated dilatation or systemic arterial compliance were seen in either group, and there were no differences in soluble cellular adhesion molecules or forearm blood flow responses to ischemia, exercise, acetylcholine chloride or sodium nitroprusside. Limitations include the relatively short intervention duration and baseline differences between groups; authors note that the age of the subjects and their burden of cardiovascular risk factors may have been too great for flavanol-rich cocoa to exert a positive effect over the time frame of the study.

Janszky et al, 2009 (neutral) This was a population-based, case-control study conducted in Sweden, to assess the long-term effects of chocolate consumption in patients with established CHD in the Stockholm Heart Epidemiology Program (SHEEP). Male cases were identified during 1992 and 1993 and female cases during 1992 and 1994. Questionnaires about chocolate consumption were completed a few days after the acute MI and patients underwent a health examination three months after discharge; patients were followed for eight years. Of 1,381 identified, 1,169 subjects aged 45 to 70 years were included in the analysis. Chocolate consumption had a strong inverse association with cardiac mortality; when compared to those never eating chocolate, the multivariable-adjusted hazard ratios were 0.73 (95% CI: 0.41 to 1.31) for those consuming chocolate less than once per month, 0.56 (95% CI: 0.32 to 0.99) for those consuming chocolate up to once per week and 0.34 (95% CI: 0.17 to 0.70) for those consuming chocolate twice or more per week. There was an inverse but weak association between chocolate consumption and total mortality. Authors note that it is possible that some patients ceased chocolate consumption prior to hospitalization due to poor health, and that patients were not queried regarding dark vs. milk chocolate.

Kurlandsky and Stote, 2006 (neutral) This was an RCT conducted in the US to evaluate the cardioprotective effects of chocolate and almond consumption in healthy women. Subjects were randomized to one of four interventions for six weeks: 41g dark chocolate per day, 60g almonds per day, both 41g dark chocolate and 60g almonds per day or a control diet without nuts and chocolate; all subjects consumed a self-selected diet based on the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC). Of 52 women (mean age 43.7 years)

Archived from www.NEL.gov on March 21, 2017

initially enrolled, 47 completed the trial. During the study period, all subjects improved dietary intakes and no subjects gained or lost weight. While serum cholesterol concentrations did not change during the study period, triacylglycerol levels were reduced by 21% in the chocolate group, 13% in the almond group, 19% in the chocolate and almond group and 11% in the control group (P<0.05). In addition, circulating intercellular adhesion molecule (ICAM) levels decreased by 10% in the chocolate group (P=0.027). No significant changes were observed in any group for vascular adhesion molecule and high-sensitivity C-reactive protein (CRP) levels. Limitations include small numbers of subjects in groups and baseline differences between groups; only women were studied.

Monagas et al, 2009 (neutral) This was a randomized crossover trial conducted in Spain to evaluate the effects of chronic cocoa consumption on cellular and serum biomarkers related to atherosclerosis in high-risk patients. All participants followed an isocaloric Mediterranean-type diet throughout the study period; for four weeks, subjects were randomized to consume either 40g cocoa powder with 500ml skim milk per day or only 500ml skim milk per day, and then consumed the opposite diet for an additional four weeks. Of 47 subjects initially enrolled, 42 completed the study (19 men, 23 women; mean age, 69.7±11.5 years). There were NS changes in the expression of adhesion molecules on T-lymphocyte surfaces between groups. However, in monocytes, the expression of VLA-4 (P=0.005), CD40 (P=0.028) and CD36 (P=0.001) was significantly lower after cocoa powder and milk intake compared with milk intake alone. In addition, serum concentrations of P-selectin and intercellular adhesion molecule-1 were significantly lower (both P=0.007) after cocoa powder and milk intake compared with milk intake alone. Limitations include the short intervention duration and the lack of washout period between interventions.

Taubert, 2007 (neutral) This was an RCT conducted in Germany to assess the effect of consumption of cocoa on BPreduction, as well as plasma markers of vasodilative nitric oxide (S-nitrosoglutathione) and oxidative stress (8-isoprostane). Older subjects (56 to 73 years) with PHTN or stage 1 hypertension (24 women, 20 men) were assigned to a receive either 6.3g per day of commercially available polyphenol-rich dark chocolate containing 3.1g of cacao (30mgpolyphenols and 30 Cal) for 18 weeks or a matching 5.6g per day of polyphenol-free white chocolate. Subjects in the dark chocolate group had a significant decrease in mean SBP at 18 weeks; however, those in the white chocolate group did not. From baseline to 18 weeks, dark chocolate intake reduced mean SBP by −2.9 (1.6)mmHg (P<0.001) and DBP by −1.9 (1.0)mmHg (P<0.001) without changes in weight gain, plasma lipids, glucose, or 8-isoprostane. Hypertension prevalence declined from 86% to 68% and there was an increase in S-nitrosoglutathione by 0.23nmol per L (P<0.001) in the dark chocolate group. White chocolate consumption did not cause any change in BP or plasma biomarkers.

Overview table

Author, Year, Study Design, Class, Rating	Study Description, Duration	Study Population, Demographics	Intervention	Significant Outcomes	Limitations
Allen et al 2008 Study Design: Randomized Crossover Trial Class: A Rating: Positive Quality	Examined the effect of daily consumption of a flavanol-containing chocolate bar with added phytosterols on CVD risk factors. Four weeks, with two-week lead-in.	Normotensive population with elevated cholesterol. Out of 650 recruited subjects, 49 entered the study and 44 subjects completed the study. 24 initially received the phytosterol-containing bars (66% male, mean age 45.9±8.1 years). 20 initially received the control bars (64% male, mean age 43.5±8.9 years). Location: United States.	After a two-week lead-in diet based on the AHA "An Eating Plan for Healthy Americans," subjects consumed two cocoa flavanol-containing dark chocolate bars per day, with or without 1.1g sterol esters per bar, for a period of four weeks and then were switched to the other chocolate bar for an additional four weeks.	Regular consumption of the phytosterol-containing chocolate bars resulted in ↓ of 2.0% in serum TC and 5.3% in LDL-C (both $P<0.05$). Consumption of cocoa flavanols reduced SBP after eight weeks (-5.8mmHg, $P<0.05$).	Studies varied in sample sizes and infant ages.
Baba et al 2007 Study Design: Randomized Controlled Trial Class: A Rating: Neutral	Tested whether long-term intake of cocoa powder altered plasma lipid profiles. 12-week diet periods.	25 normo-cholesterolemic and mildly hypercholesterol-emic male subjects completed the trial. Mean age: 38±1 years. Location: Japan.	Subjects randomized to consume either 12g sugar a day (control group) or 26g cocoa powder and 12g sugar a day (cocoa group) for 12 weeks.	Plasma HDL-C was significantly ↑ in the cocoa group compared with the control group (24% vs. 5%, $P<0.05$). The prolongation from baseline levels in the lag time of LDL oxidation in the cocoa group was significantly > the ↓ measured in the control group (9% vs. -13%, $P<0.05$).	Relatively small sample size. DHA supplement did not affect maternal DHA levels in previous trial.

Buijsse B, Feskens EJM et al, 2006 Study Design: Cohort study Class: B Rating: Positive Quality	To determine whether habitual cocoa intake was inversely related to BP and CVD mortality. 15-year follow-up.	Elderly male participants from the Zutphen Elderly Study. Out of 876 men with dietary intake estimations, chronic disease prevalence was available for 790 men; 470 were included in analysis. Age at baseline: 65 to 84 years.	Cocoa intake was estimated in 1985, 1990 and 1995 by cross-check dietary history; causes of death ascertained during 15-year follow-up.	During the 15-year follow-up, 314 men died (66.8%), 152 from CVD. Median cocoa intake was 2.11g per day in 1985, 2.30g per day in 1990 and 2.36g per day in 1995. After multivariate adjustment, compared to the lowest tertile of cocoa intake, the mean systolic SBP in the highest tertile of cocoa intake was 3.7mmHg ↓ (95% CI: -7.1 to -0.3mmHg, P=0.03) and the mean DBP was 2.1mmHg ↓ (95% CI: -4.0 to -0.2mmHg, P=0.03). Compared with the lowest tertile cocoa intake, the adjusted RR for men in the highest tertile of cocoa intake was 0.50 (95% CI: 0.32 to 0.78, P=0.004) for cardiovascular mortality and 0.53 (95% CI: 0.39 to 0.72, P<0.001) for all-cause mortality.	None.

Crews, Harrison and Wright 2008 Study Design: Randomized Controlled Trial Class: A Rating: Neutral	Examined the short-term effects of dark chocolate and cocoa on variables associated with neuro-psychological functioning and cardiovascular health. Six-week diet period.	Healthy, cognitively intact older adults. Of 101 subjects aged 60 years or older initially randomized, 90 completed the trial (38 males and 52 females), 45 in each group. Location: United States.	Participants were randomly assigned to receive a 37g dark chocolate bar and 237ml of an artificially sweetened cocoa beverage, or similar placebo products, each day for six weeks.	NS group-by-trial interactions were found for any of the neuropsychological variables, hematologic tests or BP variables examined. However, the mean pulse rate after three and six weeks of treatment was significantly higher in the dark chocolate and cocoa group than at baseline (P<0.01) and when compared with the placebo group at three and six weeks (P<0.01).	Maternal report of child development and behavior are prone to reporting bias. Disproportionate attrition of socially disadvantaged subjects.

284

Davison et al 2008 Study Design: Randomized Controlled Trial Class: A Rating: Neutral	Investigated the effect of cocoa flavanols and exercise on cardiometabolic risk factors. 12-week diet period.	Overweight and obese subjects. Of 98 screened subjects, 65 subjects were enrolled and 49 completed the 12-week trial: 12 in the high-flavanol cocoa group (four males, eight females; mean age 45.3±4.4 years) 13 in the high-flavanol cocoa + exercise group (six males, seven females; mean age 45.5±4.0 years) 11 in the low-flavanol cocoa group (three males, eight females; mean age 44.4±4.4 years) 13 in the low-flavanol cocoa + exercise group (four males, nine females; mean age 45.2±3.0 years). Location: Australia.	Subjects were randomized to one of four groups for 12 weeks: High-flavanol cocoa (902mg flavanols) High-flavanol cocoa and exercise Low-flavanol cocoa (36mg flavanols) Low-flavanol cocoa and exercise.* *Exercise duration was 45 minutes, three times per week, at 75% of age-predicted maximum heart rate.	Compared to the low-flavanol cocoa, high-flavanol cocoa ↑ flow-mediated dilatation acutely (two hours post-dose) by 2.4% ($P<0.01$) and chronically (over 12 weeks) by 1.6% ($P<0.01$) and ↓ insulin resistance by 0.31% ($P<0.05$), DBP by 1.6mmHg ($P<0.05$) and MAP by 1.2mmHg ($P<0.05$), independent of exercise.	Small sample size and dropout of subjects throughout the study. Measurements not made in all subjects at all time points.

Desch S, Schmidt J et al, 2010 Study Design: Meta-analysis or Systematic Review Class: M Rating: Positive Quality		MEDLINE publications from 1966 to 2009, EMBASE, Central Cochrane and ClinicalTrials.gov. Examined association between dark chocolate and cocoa-containing beverages on arterial BP.	10 RCTs with 297 subjects. Subjects were either healthy adults or patients with PHTN or stage 1 HTN. Treatment duration was two to 18 weeks. Meta-analysis of cocoa product intake and change in SDP and DBP.	Mean BP Δ across trials: SBP: -4.5mmHg (95% CI: -5.9 to -3.2, P<0.001). DBP: -2.5mmHg (95% CI: -3.9 to -1.2 P<0.001). Meta-analysis showed BP-lowering effects of cocoa-rich products.	None.
Ding EL, Hutfless SM et al, 2006 Study Design: Meta-analysis or Systematic Review Class: M Rating: Positive Quality		MEDLINE publications from 1966 to 2005 reviewed for experimental, observational and clinical studies. Examined association between cocoa, cacao, chocolate, stearic acid, flavonoids and risk of CVD.	21 RCTs measured intermediate markers of CVD risk. 11 prospective cohort studies examined CVD outcomes. Updated meta-analysis on flavonoid intake and CHD mortality.	RCTs showed that cocoa and chocolate have beneficial effects on BP, inflammatory markers, anti-platelet function, serum HDL and LDL oxidation. Prospective cohort studies showed that flavonoids in chocolate were positively associated with ↓ risk of CVD mortality. RCTs that examined stearic acid showed it had no effect on serum cholesterol and lipoprotein levels.	Study population contained a high proportion of women who were educated, white and from a higher socioeconomic class.

Farouque et al 2006 Study Design: Randomized Controlled Trial Class: A Rating: Neutral	To determine the acute and chronic effects of flavanol-rich cocoa on endothelial and vascular function. Six-week diet period.	Subjects with CAD. Of 40 subjects initially enrolled (30 males, mean age 61±8 years), 38 subjects completed the trial. Location: Australia.	Subjects were randomized to receive either a flavanol-rich chocolate bar and cocoa beverage (444mg flavanols, 170mg epicatechin monomer) or matching isocaloric placebo (19.6mg flavanols, 4.7mg epicatechin monomer) daily for six weeks.	No acute or chronic Δ in flow-mediated dilatation or systemic arterial compliance were seen in either group, and there were no differences in soluble cellular adhesion molecules or forearm blood flow responses to ischemia, exercise, acetylcholine chloride or sodium nitroprusside.	Subjects were not a representative sample; women included in data analysis differed from those not included with respect to breastfeeding duration, marital status and smoking during pregnancy.
Hooper L, Kroon PA et al, 2008 Study Design: Meta-analysis or Systematic Review Class: M Rating: Positive Quality		MEDLINE, EMBASE, Cochrane Library to June 2007 publications. Examined association between flavonoid-rich foods and CVD risk.	Six RCTs used for meta-analysis of effects of chocolate or cocoa on %FMD.	Chocolate ↑ FMD: ↑ 3.99% after acute intake (95% CI: 2.86% to 5.12%) ↑ 1.45% after chronic intake (95% CI: 0.62% to 2.28%). Time-course showed peak effect at two hours. No strong epicatechin dose effect.	None.

| Janszky et al 2009

Study Design: Population-based Case-Control Study

Class: C

Rating: Neutral | To assess the long-term effects of chocolate consumption.

Eight-year follow-up. | Patients with established CHD in the Stockholm Heart Epidemiology Program (SHEEP).

Male cases were identified during 1992 and 1993 and female cases during 1992 and 1994.

Of 1,381 identified, 1,169 subjects aged 45 to 70 years were included in the analysis.

Location: Sweden. | Questionnaires about chocolate consumption were completed a few days after acute MI.

Patients underwent health examination three months after discharge.

Patients followed for eight years. | Chocolate consumption had strong inverse association with cardiac mortality; when compared to those never eating chocolate, the multivariable-adjusted HRs were 0.73 (95% CI: 0.41 to 1.31) for those consuming chocolate <one time a month, 0.56 (95% CI: 0.32 to 0.99) for those consuming chocolate up to one time a week and 0.34 (95% CI: 0.17 to 0.70) for those consuming chocolate ≥twice per week.

There was an inverse, but weak association between chocolate consumption and total mortality. | Authors note that it is possible that some patients ceased chocolate consumption prior to hospitalization due to poor health, and that patients were not queried regarding dark vs. milk chocolate. |

Kurlandsky and Stote, 2006 Study Design: Randomized controlled parallel trial. Class: A Rating: Neutral	Evaluated the cardioprotective effects of chocolate and almond consumption. Six-week diet period.	52 healthy women initially enrolled; 47 completed the trial. Mean age: 43.7 years. Location: United States.	Subjects randomized to one of four interventions for six weeks: 41g dark chocolate per day, 60g almonds per day, both 41g dark chocolate and 60g almonds per day, or a control diet without nuts and chocolate. All subjects consumed a self-selected diet based on the NCEP Therapeutic Lifestyle Changes.	During the study period, all subjects improved dietary intakes and no subjects gained or lost weight. No Δ in serum cholesterol concentrations during the study period. TG levels ↓ by 21% in chocolate group, 13% in almond group, 19% in chocolate and almond group and 11% in control group (P<0.05). Circulating intercellular adhesion molecule (ICAM) levels ↓ by 10% in the chocolate group (P=0.027). NS Δ observed in any group for vascular adhesion molecule and high-sensitivity CRP levels.	Limitations include small numbers of subjects in groups and baseline differences between groups; only women were studied.

Monagas et al 2009

Study Design: Randomized Crossover Trial

Class: A

Rating:

Neutral | To evaluate the effects of chronic cocoa consumption on cellular and serum biomarkers related to atherosclerosis.

Four-week diet period. | High-risk patients.

Of 47 subjects initially enrolled; 42 completed the study (19 men, 23 women).

Mean age: 69.7±11.5 years.

Location: Spain. | All participants followed an isocaloric Mediterranean-type diet throughout the study period

For four weeks, subjects were randomized to consume either 40g cocoa powder with 500ml skim milk per day or only 500ml skim milk per day.

Participants consumed the opposite diet for an additional four weeks. | NS Δ in expression of adhesion molecules on T-lymphocyte surfaces between groups.

In monocytes, the expression of VLA-4 (P=0.005), CD40 (P=0.028) and CD36 (P=0.001) was significantly ↓ after cocoa powder and milk intake, compared with milk intake alone.

P-selectin and intercellular adhesion molecule-1 were significantly ↓ (both P=0.007) after cocoa powder and milk intake, compared with milk intake alone. | Lack of washout period between interventions. |

290

Taubert D, Roesen R et al, 2007 Study Design: Randomized controlled parallel-group trial Class: A Rating: Neutral	To assess the effect of cocoa consumption on BP, plasma markers of vasodilation and oxidative stress. 18-week diet period.	Older subjects with pre- or stage 1 HTN (24 women, 20 men) Age: 56 to 73 years. Location: Germany.	Subjects were assigned to dark chocolate group (6.3g per day polyphenol-rich dark chocolate with 3.1g cacao (30mg polyphenols) for 18 weeks or matching polyphenol-free white chocolate group.	Dark chocolate group had significant ↓ in mean SBP at 18 weeks; white chocolate group did not. Dark chocolate intake ↓ mean SBP by -2.9 (1.6)mmHg (P<0.001) and DBP by -1.9 (1.0)mmHg (P<0.001). No Δ in weight gain, plasma lipids, glucose, or 8-isoprostane in dark chocolate group. HTN prevalence ↓ from 86% to 68% and S-nitroso-glutathione ↑ by 0.23nmol per L (P<0.001) in dark chocolate group. White chocolate consumption did not cause any Δ in BP or plasma biomarkers.	None.

Research recommendations

Elucidate further the role of polyphenolic compounds as major active ingredients in the health benefits of chocolate. Test different chocolate formulations that are commonly consumed by the general public.

Search plan and results

Inclusion criteria

- 2 years through adult
- US and International
- Healthy and those with elevated chronic disease risk (CHD/CVD, T2D, Metabolic Syndrome, and Obesity)
- RCT or Clinical Controlled Studies, large nonrandomized observational studies, meta-analysis and systematic reviews.

- Feeding period >4 wks
- Sample size >10 subjects for each study group.
- Less than 20% drop-out; preference for smaller dropout rates
- 2000 - Present
- Limited to articles in English

Exclusion criteria

- Infants/children less than 2 yrs
- Inpatients
- Medical treatment/therapy, Diseased subjects
- Malnourished third-world populations
- Sample sizes <10
- Cross sectionals; Feeding periods <4 wks
- Dropout rate is >20%
- Prior to January 2000
- Articles not in English
- Narrative reviews, Animal studies, *In vitro* studies, Abstracts or presentations, Articles not peer reviewed

Search terms and electronic databases used

- Pubmed: "Cacao"[Mesh] AND (chocolate OR cocoa OR "Flavonoids"[Mesh]) ("Cacao" OR chocolate OR cocoa) AND (coronary OR cardiovascular OR heart OR diabetes OR "blood pressure" OR hypertension OR "weight gain" OR "insulin sensitivity" OR cholesterol OR "glucose tolerance" OR hypercholesterolemia OR Dyslipidemia OR hyperlipidemia OR markers of inflammation)

Date searched: 10/13/2009 and 12/16/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 790
- Total articles identified to review from electronic databases: 45
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 10
- Number of Review Articles Identified: 3
- Total Number of Articles Identified: 13
- Number of Articles Reviewed but Excluded: 32

Included articles (References)

Systematic Reviews/Meta-analysis:

1. Ding EL, Hutfless SM, Ding X, Girotra S. <u>Chocolate and prevention of cardiovascular disease: a systematic review.</u> Nutr Metab (Lond). 2006 Jan 3;3:2. PMID: 16390538. Systematic review [Medline publications: 1966 through 2005]
2. Desch S, Schmidt J, Kobler D, Sonnabend M, Eitel I, Sareban M, Rahimi K, Schuler G, Thiele H. <u>Effect of cocoa products on blood pressure: systematic review and meta-analysis.</u> Am J Hypertens. 2010 Jan;23(1):97-103. Epub 2009 Nov 12.

292

Review.PMID: 19910929

3. Hooper L, Kroon PA, Rimm EB, Cohn JS, Harvey I, Le Cornu KA, Ryder JJ, Hall WL, Cassidy A. <u>Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials.</u> Am J Clin Nutr. 2008 Jul;88(1):38-50. PMID: 18614722

Primary Articles:

1. Allen RR, Carson L, Kwik-Uribe C, Evans EM, Erdman JW Jr. <u>Daily consumption of a dark chocolate containing flavanols and added sterol esters affects cardiovascular risk factors in a normotensive population with elevated cholesterol.</u> J Nutr. 2008 Apr;138(4):725-31. PMID: 18356327
2. Baba S, Osakabe N, Kato Y, Natsume M, Yasuda A, Kido T, Fukuda K, Muto Y, Kondo K. <u>Continuous intake of polyphenolic compounds containing cocoa powder reduces LDL oxidative susceptibility and has beneficial effects on plasma HDL-cholesterol concentrations in humans.</u> Am J Clin Nutr. 2007 Mar;85(3):709-17. PMID: 17344491. [n=160)
3. Buijsse B, Feskens EJ, Kok FJ, Kromhout D. <u>Cocoa intake, blood pressure, and cardiovascular mortality: the Zutphen Elderly Study.</u> Arch Intern Med. 2006 Feb 27;166(4):411-7. PMID: 16505260.
4. Crews WD Jr, Harrison DW, Wright JW. <u>A double-blind, placebo-controlled, randomized trial of the effects of dark chocolate and cocoa on variables associated with neuropsychological functioning and cardiovascular health: clinical findings from a sample of healthy, cognitively intact older adults.</u> Am J Clin Nutr. 2008 Apr;87(4):872-80. PMID: 18400709.
5. Davison K, Coates AM, Buckley JD, Howe PR. <u>Effect of cocoa flavanols and exercise on cardiometabolic risk factors in overweight and obese subjects.</u> Int J Obes (Lond). 2008 Aug;32(8):1289-96. Epub 2008 May 27. PMID: 18504447.
6. Farouque HM, Leung M, Hope SA, Baldi M, Schechter C, Cameron JD, Meredith IT. <u>Acute and chronic effects of flavanol-rich cocoa on vascular function in subjects with coronary artery disease: a randomized double-blind placebo-controlled study.</u> Clin Sci (Lond). 2006 Jul;111(1):71-80. PMID: 16551272.
7. Janszky I, Mukamal KJ, Ljung R, Ahnve S, Ahlbom A, Hallqvist J. <u>Chocolate consumption and mortality following a first acute myocardial infarction: the Stockholm Heart Epidemiology Program.</u> J Intern Med. 2009 Sep;266(3):248-57. PMID: 19711504.
8. Kurlandsky, SB, Stote, KS. Cardioprotective effects of chocolate and almond consumption in healthy women. Nutrition Research 2006;26:509–516. (No PubMed ID)
9. Monagas M, Khan N, Andres-Lacueva C, Casas R, Urpí-Sardà M, Llorach R, Lamuela-Raventós RM, Estruch R. <u>Effect of cocoa powder on the modulation of inflammatory biomarkers in patients at high risk of cardiovascular disease.</u> Am J Clin Nutr 2009 90: 1144-1150. PMID: 19776136
10. Taubert D, Roesen R, Lehmann C, Jung N, Schomig E. <u>Effects of low habitual cocoa intake on blood pressure and bioactive nitric oxide: a randomized controlled trial.</u> JAMA 2007;298(1):49–60. PMID: 17609490

Excluded articles

Articles	Reason for Exclusion
Balzer J, Rassaf T, Heiss C, Kleinbongard P, Lauer T, Merx M, et al. Sustained benefits in vascular function through flavanol-containing cocoa in medicated diabetic patients a double-masked, randomized, controlled trial. J Am Coll Cardiol 2008;51(22):2141-9. PMID: 18510961.	Single-dose ingestion of cocoa, containing increasing concentrations of flavanols
Bordeaux B, Yanek LR, Moy TF, White LW, Becker LC, Faraday N, Becker DM. Casual chocolate consumption and inhibition of platelet function. Prev Cardiol. 2007 Fall;10(4):175-80. PMID: 17917513	Cross sectional Study
Cienfuegos-Jovellanos E, Quiñones Mdel M, Muguerza B, Moulay L, Miguel M, Aleixandre A. Antihypertensive effect of a polyphenol-rich cocoa powder industrially processed to preserve the original flavonoids of the cocoa beans. J Agric Food Chem. 2009 Jul 22;57(14):6156-62. PMID: 19537788	Intervention was a single oral dose
Corder R. Red wine, chocolate and vascular health: developing the evidence base. Heart. 2008 Jul;94(7):821-3. No abstract available. PMID: 18552215	Narrative review
Corti R, Flammer AJ, Hollenberg NK, Lüscher TF. Cocoa and cardiovascular health. Circulation. 2009 Mar 17;119(10):1433-41. PMID: 19289648.	Narrative review. Used for references
di Giuseppe R, Di Castelnuovo A, Centritto F, Zito F, De Curtis A, Costanzo S, Vohnout B, Sieri S, Krogh V, Donati MB, de Gaetano G, Iacoviello L. Regular consumption of dark chocolate is associated with low serum concentrations of C-reactive protein in a healthy Italian population. J Nutr. 2008 Oct;138(10):1939-45. PMID: 18806104.	Only measured CRP
Faridi Z, Njike VY, Dutta S, Ali A, Katz DL. Acute dark chocolate and cocoa ingestion and endothelial function: a randomized controlled crossover trial. Am J Clin Nutr. 2008 Jul;88(1):58-63. PMID: 18614724	Intervention was a single oral dose
Fisher ND, Hughes M, Gerhard-Herman M, Hollenberg NK. Flavanol-rich cocoa induces nitric-oxide-dependent vasodilation in healthy humans. J Hypertens. 2003 Dec;21(12):2281-6. PMID: 14654748.	Four day intervention +infusion

294

Flammer AJ, Hermann F, Sudano I, Spieker L, Hermann M, Cooper KA, Serafini M, Lüscher TF, Ruschitzka F, Noll G, Corti R. <u>Dark chocolate improves coronary vasomotion and reduces platelet reactivity.</u> Circulation. 2007 Nov 20;116(21):2376-82. Epub 2007 Nov 5. PMID: 17984375	Intervention was a single oral dose – 2 hours. Variable studied not of included
Galleano M, Oteiza PI, Fraga CG. <u>Cocoa, chocolate and cardiovascular disease.</u> J Cardiovasc Pharmacol. 2009 Aug 20. [Epub ahead of print] PMID: 19701098	Narrative review
Giannandrea F. <u>Correlation analysis of cocoa consumption data with worldwide incidence rates of testicular cancer and hypospadias.</u> Int J Environ Res Public Health. 2009 Feb;6(2):568-78. Epub 2009 Feb 5. PMID: 19440400	Epi study, correlation analyses
Heiss C, Kleinbongard P, Dejam A, Perré S, Schroeter H, Sies H, Kelm M. <u>Acute consumption of flavanol-rich cocoa and the reversal of endothelial dysfunction in smokers.</u> J Am Coll Cardiol. 2005 Oct 4;46(7):1276-83. PMID: 16198843.	2 day intervention; n =4 in one arm
Hirano R, Osakabe N, Iwamoto A, Matsumoto A, Natsume M, Takizawa T, Igarashi O, Itakura H, Kondo K. <u>Antioxidant effects of polyphenols in chocolate on low-density lipoprotein both in vitro and ex vivo.</u> J Nutr Sci Vitaminol (Tokyo). 2000 Aug;46(4):199-204. PMID: 11185658.	Acute study; 2h and 4 h after ingestion; n=3 males
Hodgson JM, Devine A, Burke V, Dick IM, Prince RL. <u>Chocolate consumption and bone density in older women.</u> Am J Clin Nutr. 2008 Jan;87(1):175-80. PMID: 18175753.	Cross sectional study
Hooper L, Kroon PA, Rimm EB, Cohn JS, Harvey I, Le Cornu KA, Ryder JJ, Hall WL, Cassidy A. <u>Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials.</u> Am J Clin Nutr. 2008 Jul;88(1):38-50.PMID: 18614722.	Studying flavonoids in acute studies and not chocolate
Jourdain C, Tenca G, Deguercy A, Troplin P, Poelman D. <u>In-vitro effects of polyphenols from cocoa and beta-sitosterol on the growth of human prostate cancer and normal cells.</u> Eur J Cancer Prev. 2006 Aug;15(4):353-61. PMID: 16835506.	In vitro study
K Hollenberg N <u>Vascular action of cocoa flavanols in humans: the roots of the story.</u> J Cardiovasc Pharmacol. 2006;47 Suppl 2:S99-102; discussion S119-21. PMID: 16794463.	Narrative review

Kenny TP, Shu SA, Moritoki Y, Keen CL, Gershwin ME. <u>Cocoa flavanols and procyanidins can modulate the lipopolysaccharide activation of polymorphonuclear cells in vitro.</u> J Med Food. 2009 Feb;12(1):1-7. PMID: 19298189.	In vitro study
Matsumoto M, Tsuji M, Okuda J, Sasaki H, Nakano K, Osawa K, Shimura S, Ooshima T. <u>Inhibitory effects of cacao bean husk extract on plaque formation in vitro and in vivo.</u> Eur J Oral Sci. 2004 Jun;112(3):249-52. PMID: 15154923 .	Intervention cocoa bean husk extract
McCarty MF, Barroso-Aranda J, Contreras F. <u>Potential complementarity of high-flavanol cocoa powder and spirulina for health protection.</u> Med Hypotheses. 2009 Jul 2. [Epub ahead of print] PMID: 19577379	Narrative review
McCullough ML, Chevaux K, Jackson L, Preston M, Martinez G, Schmitz HH, Coletti C, Campos H, Hollenberg NK. <u>Hypertension, the Kuna, and the epidemiology of flavanols.</u> J Cardiovasc Pharmacol. 2006;47 Suppl 2:S103-9; discussion 119-21. PMID: 16794446.	Variables measured not included
Nahas R. <u>Complementary and alternative medicine approaches to blood pressure reduction: An evidence-based review.</u> Can Fam Physician. 2008 Nov;54(11):1529-33. Review. No abstract available. PMID: 19005120.	Review, used as a source for references
Oba S, Nagata C, Nakamura K, Fujii K, Kawachi T, Takatsuka N, Shimizu H. <u>Consumption of coffee, green tea, oolong tea, black tea, chocolate snacks and the caffeine content in relation to risk of diabetes in Japanese men and women.</u> Br J Nutr. 2009 Oct 12:1-7. [Epub ahead of print] PMID: 19818197.	Study based on effect of caffeine
Osakabe N, Baba S, Yasuda A, Iwamoto T, Kamiyama M, Takizawa T, Itakura H, Kondo K. <u>Daily cocoa intake reduces the susceptibility of low-density lipoprotein to oxidation as demonstrated in healthy human volunteers.</u> Free Radic Res. 2001 Jan;34(1):93-9. PMID: 11235000.	N=9 intervention group; n=6 control group; 2 week
Patanè S, Marte F, La Rosa FC, Rocca RL. <u>Atrial fibrillation associated with chocolate intake abuse and chronic salbutamol inhalation abuse.</u> Int J Cardiol. 2009 Jan 24. [Epub ahead of print] PMID: 19171401.	Case control study; n=1
Patel AK, Rogers JT, Huang X. <u>Flavanols, mild cognitive impairment, and Alzheimer's dementia.</u> Int J Clin Exp Med. 2008;1(2):181-91. Epub 2008 Apr 15. PMID: 19079672.	Narrative review

Polagruto JA, Wang-Polagruto JF, Braun MM, Lee L, Kwik-Uribe C, Keen CL. <u>Cocoa flavanol-enriched snack bars containing phytosterols effectively lower total and low-density lipoprotein cholesterol levels.</u> J Am Diet Assoc. 2006 Nov;106(11):1804-13. PMID: 17081832.	Study effect of phytosterols
Rein D, Paglieroni TG, Wun T, Pearson DA, Schmitz HH, Gosselin R, Keen CL. <u>Cocoa inhibits platelet activation and function.</u> Am J Clin Nutr. 2000 Jul;72(1):30-5. PMID: 10871557	Acute ingestion; single dose, 2h and 6h analyses
Ried K, Frank OR, Stocks NP. <u>Dark chocolate or tomato extract for prehypertension: a randomised controlled trial.</u> BMC Complement Altern Med. 2009 Jul 8;9:22. PMID: 19583878 .	In vitro study
Schnorr O, Brossette T, Momma TY, Kleinbongard P, Keen CL, Schroeter H, Sies H. <u>Cocoa flavanols lower vascular arginase activity in human endothelial cells in vitro and in erythrocytes in vivo.</u> Arch Biochem Biophys. 2008 Aug 15;476(2):211-5. Epub 2008 Mar 6. PMID: 18348861.	In vitro study
Schramm DD, Wang JF, Holt RR, Ensunsa JL, Gonsalves JL, Lazarus SA, Schmitz HH, German JB, Keen CL <u>Chocolate procyanidins decrease the leukotriene-prostacyclin ratio in humans and human aortic endothelial cells.</u> Am J Clin Nutr. 2001 Jan;73(1):36-40. PMID: 11124747.	In vitro study
Strandberg TE, Strandberg AY, Pitkälä K, Salomaa VV, Tilvis RS, Miettinen TA. <u>Chocolate, well-being and health among elderly men.</u> Eur J Clin Nutr. 2008 Feb;62(2):247-53. Epub 2007 Feb 28. PMID: 17327862.	Does not address health outcomes of the question.

CHAPTER 13. SPECIFIC FOODS, FATTY ACIDS AND CHOLESTEROL – HEALTH EFFECTS RELATED TO CONSUMPTION OF NUTS

WHAT ARE THE HEALTH EFFECTS RELATED TO THE CONSUMPTION OF NUTS?

Conclusion statement

There is moderate evidence that consumption of unsalted peanuts and tree nuts, specifically walnuts, almonds and pistachios, in the context of a nutritionally adequate diet and when total calorie intake is held constant, has a favorable impact on cardiovascular disease risk factors, particularly serum lipid levels.

Grade

Moderate

Evidence summary overview

Review of seventeen studies [five cohort (positive quality), nine randomized controlled trials (RCTs) (five positive, four neutral quality) and three positive quality reviews (two systematic reviews and one meta-analysis)] provided evidence that consumption of nuts collectively and walnuts, almonds and pistachio nuts individually, in the context of a healthy diet when total calorie intake is held constant, has a favorable impact on cardiovascular risk factors, particularly serum lipid levels. The evidence was strongest for walnuts. Insufficient evidence was available to address the health effects of macadamia nuts.

Nuts (Including Peanuts) and Health Effects

Seven studies were reviewed to determine the health benefits related to consumption of nuts, five prospective cohort studies (all positive), one randomized crossover trial (positive) and one systematic review (positive quality).

One systematic review, Mukuddem-Petersen et al, 2005 (positive quality), investigated the effect of nuts on lipid profiles in 185 men and women (23 studies) and reported results of three almond (50 to 100g per day), two peanut (35 to 68g per day), one pecan nut (72g per day) and four walnut (40 to 84g per day) studies showing decreases in total cholesterol(TC) between 2% and 16%, low-density lipoprotein cholesterol (LDL-C) between 2% and 19% compared with subjects consuming control diets, and not so convincing results for studies consuming macadamia nuts (50 to 100g per day).

Two positive quality prospective cohort studies (Bes-Rastrollo et al, 2007; Bes-Rastrollo et al, 2009) assessed the associations between nut (including peanut butter) consumption and changes in body weight in cohorts of free-living adults (SUN study), the Nurses' Health study and in the Physician Health Study I and body mass index (BMI), reporting that increased frequency of nut consumption (two or more times per week) is associated with lower risk of weight gain or obesity. Djousse et al, 2009 (positive quality), as part of the Physician Health Study I (N=15,966) found an inverse relationship between nut intake and hypertension (HTN) in lean subjects, but not

Archived from www.NEL.gov on March 21, 2017

in overweight or obese subjects.

Two positive quality cohort studies assessed the association of nut consumption with cardiac-related outcomes in high-risk populations. Li et al, 2009, in a positive quality prospective cohort study (N=6,309 diabetic women), found consumption of at least five servings a week of nuts or peanut butter [serving size, 28g (1oz) for nuts and 16g (one tablespoon) for peanut butter] was significantly associated with a lower risk of cardiovascular disease (CVD) (RR=0.56; 95% CI: 0.36 to 0.89). Increasing nut consumption was significantly associated with a more favorable plasma lipid profile, including lower LDL-C, non-high density lipoprotein cholesterol (non-HDL-C), TC and apolipoprotein-B-100 concentrations. Salas-Salvado et al, 2008 (positive quality), in a three-arm randomized controlled trial (RCT) conducted in among 1,224 Spanish subjects with type 2 diabetes (T2D) or three or more CVD risk factors, assessed the effect of a Mediterranean diet high in olive oil (MedDiet + VOO) or nuts (MedDiet + 30g per day of mixed nuts) and a low-fat diet (control diet) and found one-year prevalence of metabolic syndrome was reduced by 6.7% (MedDiet + VOO), 13.7% (MedDiet + nuts) and 2.0% (control diet), respectively (MedDiet + nuts vs. control groups, P=0.01; MedDiet + VOO vs. control group, P=0.18). This researcher also found diets high in nuts and virgin olive oil was associated with lower serum concentrations of inflammatory markers, especially those related to endothelial function.

Almonds and Health Effects

To assess the health benefits related to consumption of almonds, the US Department of Agriculture Nutrition Evidence Library (USDA-NEL) updated the American Dietetic Association (ADA) reviews, pulling in two small RCTs [Kurlandsky S, Stote K. 2006 (neutral quality); Wien et al, 2003 (positive quality)] and reviewed one meta-analysis [Phung et al, 2009 (positive quality)].

Phung et al, 2009 analyzed five RCTs totaling 142 participants and reported that consumption of almonds (25 to 168gper day) decreases TC, does not affect LDL-C or HDL-C, triglycerides (TG), or the LDL:HDL ratio, concluding that the current body of randomized trials does not support the ingestion of almonds solely for their lipid-modifying effects.

One neutral quality study (Kurlandsky S, Stote K, 2006) assessed the effect of combining chocolate and almonds as part of the Therapeutic Lifestyle Changes (TLC) diet in 47 normolipidemic women and reported that intake of almonds reduced serum TG by 13% but had no effect on serum cholesterol level.

Wien et al, 2003 reported that HDL-C decreased with consumption of 85g per day of almonds (-6%, P=0.05) compared to complex carbohydrates (CHO) (provided as a part of a formula diet), but TC, TG, LDL-C and LDL-C:HDL-C ratio decreased significantly to a similar extent in both almond and complex CHO interventions. There was a significantly greater percent change in body weight among the almond group (-18% vs. -11%).

Walnuts and Health Effects

Four studies evaluated the effects of walnuts on health outcomes, one positive quality systematic review and meta-analysis and three RCTs (one positive and two

neutral quality).

In one systematic review and meta-analysis, Banel and Hu, 2009 (positive quality), reviewed 13 studies (12 RCTs) with walnuts providing 10% to 24% of calories, representing 365 participants and found that compared with control diets, diets supplemented with walnuts resulted in a significantly greater decrease in TC and LDL-C. Triglycerides and HDL-Cwere not affected by walnuts.

Two small RCTs (both neutral), reported that a walnut diet containing 42.5g (1.5oz) walnuts per 10.1mJ (2,400kcal) (Rajaram et al, 2009), or consumption of a meat product with walnuts (19.4g per day) five times per week for five weeks (Olmedilla-Alonso et al, 2008) resulted in a decrease in TC at four weeks when compared to baseline (P<0.002) and at five weeks compared to four weeks (P=0.027). LDL-cholesterol was also decreased at four weeks when compared to baseline (P<0.007), but no further changes occurred by five weeks compared to four weeks (P=0.303). Rajaram et al, 2009 found that the ratios of TC:HDL-C, LDL-C:HDL-C and apoB:apoA-I were lower in those who followed the walnut diet. Olmedilla-Alonso et al, 2008, found that compared to baseline, meat products with walnuts decreased body weight.

One randomized crossover trial, Sabate et al, 2005 (positive-quality), found that a walnut-supplemented diet (28 to 56gper day, 12% energy from walnuts) provided approximately 133 more calories per day than the control diet and increased the weight, BMI, fat mass and lean mass of the subjects. Energy-adjusted results were not significant, indicating that care must be taken to accommodate the caloric content of nuts in the diet.

Macadamia and Health Effects

One RCT was reviewed for macadamia nuts. Griel et al, 2008 (neutral quality), report that serum concentrations of TCand LDL-C were lower after consumption of macadamia nut-rich diet than the average American diet. Serum TG and serum non-HDL-C concentrations were not affected.

Pistachios and Health Effects

Two studies (Sheridan et al, 2007; Gebauer et al, 2008) assessed the effects of pistachio nuts on serum lipid response. Sheridan et al, 2007, in a randomized crossover trail, found two to three ounces a day of pistachio nuts (15% of daily calorie intake), when substituted for high-fat snacks by free living subjects over a four-week period, significantly decreased saturated fatty acid (SFA) intake and increased polyunsaturated fatty acid (PUFA) and fiber intake, resulting in a significant reduction in TC/HDL-C, LDL-C/HDL-C and HDL-C. The pistachio diet had no effect on blood pressure (BP) in the 15 subjects. Gebauer et al, 2008, in a four-week randomized crossover trail, found a dose-dependent response (P<0.05) on TC, HDL-C, LDL-C:HDL-C and non-HDL-C:HDL-C in 28 hyperlipidemic adults consuming an isocaloricdiet (SFA and cholesterol-controlled) with either 10% or 20% of total energy (from 32 to 63g per day and from 63 to 126g per day, respectively) from pistachio nuts.

Evidence summary paragraphs

Nuts and Health (Including Peanuts)

Bes-Rastrollo et al, 2007 (positive quality), a prospective cohort study conducted in Spain, assessed the association between nut consumption and risk of weight gain or the risk of becoming overweight or obese in the Mediterranean dynamic Seguimiento Universidad de Navarra (SUN) cohort of free-living adults. Of 11,714 eligible adults, a total of 8,865 adults completed a follow-up questionnaire after a median of 28 months and were included in the analysis. Participants were classified based on their baseline frequency of nut consumption (in 50g servings): Never/almost never (33.1% male, mean age 35.6 years); one to three times per month (40.8% male, mean age 36.7 years); once per week (46.9% male, mean age 37.6 years); or at least twice per week (51.0% male, mean age 41.5 years). Walnuts were found to be the most frequently consumed nut, followed by hazelnuts, almonds and peanuts, respectively. At the 28-month follow-up, 937 participants reported a weight gain of at least 5kg. After adjustment for confounding variables, participants who ate nuts two or more times per week had a significantly lower risk of weight gain (OR=0.69, 95% CI: 0.53 to 0.90, P=0.006) than those who never or almost never ate nuts; participants who never or almost never consumed nuts gained an average of 424g (95% CI: 102 to 746) more than frequent nut consumers. Nut consumption was not significantly associated with incident overweight or obesity. Authors note that the participants were not representative of the general population; in addition, dietary habits were only measured at baseline and body weight was based on self-report.

Bes-Rastrollo et al, 2009 (positive quality), a prospective cohort study conducted in the US, assessed the long-term relation between nut or peanut butter consumption and weight change in participants of the Nurses' Health Study II. Of 116,671 female nurses aged 24 to 44 years at baseline in 1989, 51,188 were included in the 1991 to 1999 analysis. A semi-quantitative food frequency questionnaire (FFQ) was administered originally in 1991 that included 133 items to obtain dietary information about their average consumption of a commonly used unit or portion size of each food during the previous year. Similar questionnaires were used to update information on the subject's diet in 1995 and 1999. Participants were asked about their average consumption of peanut butter [one tablespoon equivalent to 1oz of peanuts (1oz=28.35g)], peanuts [1oz (28.35g) of peanuts] and tree nuts [1oz (28.35g) of nuts] during the previous year. In 1999 "tree nuts" was subdivided into two separate items, walnuts and other nuts. Over eight years of follow-up, women who reported eating nuts more than two times per week had slightly less mean weight gain than women who rarely ate nuts (5.04±0.12kg vs. 5.55±0.04kg, P<0.001); the results were similar when total nut consumption was subdivided by peanuts and tree nuts and when subjects were subdivided by normal weight, overweight and obese. After adjustment for confounding variables, greater nut consumption (more than two times per week) was associated with a slightly lower risk of obesity compared with never/almost never consuming nuts (HR=0.77, 95% CI: 0.57 to 1.02, P=0.003). Authors note that there were a small percentage of women in the cohort with high levels of nut consumption. In addition, weight was based on self-report.

Djousse et al, 2009 (positive quality), a prospective cohort study conducted in the US, examined the association between nut consumption and lower risk of incident HTN in participants of the Physician's Health Study I. Of 22,071 male physicians aged 40 to 84 years (mean age 52.3±8.9 years) at baseline in 1981, 15,966 were included in the

301

analysis. During the 237,585 person-years of follow-up, there were 8,423 new cases of HTN. Compared to subjects who did not consume nuts, multivariable adjusted hazard ratios (HR) for HTN were 0.97 (95% CI: 0.91 to 1.03) for nut consumption of one to two times per month, 0.98 (95% CI: 0.92 to 1.05) for nut consumption of once per week, 0.96 (95% CI: 0.89 to 1.03) for nut consumption of two to six times per week, and 0.82 (95% CI: 0.71 to 0.94) for nut consumption of seven or more times per week. In analyses stratified by BMI, there was an inverse relation between nut intake and HTN in lean subjects (P=0.0019) but not in overweight or obese subjects (P for interaction = 0.0037). Authors note that participants were male physicians who may have different behaviors or lifestyles than the general population, limiting the generalizability of findings; in addition, incidence of HTN was based on self-report.

Li et al 2009 (positive quality), a prospective cohort study, assessed the association between intake of nuts and incident CVD in a cohort of women with T2D. For the primary analysis, there were 6,309 women with T2D who completed a validated FFQ every two to four years between 1980 and 2002 and were without CVD or cancer at study entry. Major CVD events included incident myocardial infarction (MI), revascularization and stroke. During 54,656 person-years of follow-up, there were 452 coronary heart disease (CHD) events (including MI and revascularization) and 182 incident stroke cases. Frequent nut and peanut butter consumption was inversely associated with total CVD (P-trend = 0.015) and MI (P-trend = 0.05) risk in age-adjusted analyses. After adjustment for conventional CVD risk factors, consumption of at least five servings a week of nuts or peanut butter [serving size, 28g (1oz) for nuts and 16g (one tablespoon) for peanut butter] was significantly associated with a lower risk of CVD (RR=0.56; 95% CI: 0.36 to 0.89). Increasing nut consumption was significantly associated with a more favorable plasma lipid profile, including lower LDL-C (P=0.008), non-HDL cholesterol (P=0.014), TC (P=0.007), and apolipoprotein-B-100 concentrations (P=0.016). No significant (NS) associations for HDL-C or inflammatory markers were observed. Authors conclude that frequent nut and peanut butter consumption is associated with a significantly lower CVD risk in women with T2D.

Salas-Salvadó J et al, 2008 (positive quality), a cross-sectional study of subjects within cohort previously subjected to a randomized controlled study (Estruch et al 2006) in Spain. The study assessed the associations between components of the Mediterranean diet and circulating markers of inflammation in a large cohort of asymptomatic subjects, 339 men and 433 women aged between 55 and 80 years at high cardiovascular risk because of the presence of diabetes, or at least three classical cardiovascular risk factors at high risk for CVD. Food consumption was determined by a semi-quantitative FFQ. Serum concentrations of high-sensitivity C-reactive protein (CRP) were measured by immunonephelometry and those of interleukin-6 (IL-6), intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). After adjusting for age, gender, BMI, diabetes, smoking, use of statins, non-steroidal anti-inflammatory drugs and aspirin, a higher consumption of fruits and cereals was associated with lower concentrations of IL-6 (P for trend = 0.005). Subjects with the highest consumption of nuts and virgin olive oil showed the lowest concentrations of VCAM-1, ICAM-1, IL-6 and CRP; albeit only for ICAM-1 was this difference statistically significant in the case of nuts (P for trend = 0.003) and for VCAM-1 in the case of virgin olive oil (P for trend = 0.02). Participants with higher

302

adherence to the Mediterranean-type diet did not show significantly lower concentrations of inflammatory markers (P<0.1 for VCAM-1 and ICAM-1). Authors conclude that consumption of some typical Mediterranean foods (fruits, cereals, virgin olive oil and nuts) was associated with lower serum concentrations of inflammatory markers, especially those related to endothelial function, in subjects with high cardiovascular risk living in a Mediterranean country.

Salas-Salvadó J et al, 2008 (positive study), a multicenter, three-arm, RCT conducted in Spain. The study compared the one-year effect of two behavioral interventions to implement the Mediterranean diet (MedDiet) vs. advice on a low-fat diet on metabolic syndrome (MetS) status. One thousand two hundred twenty-four participants (presence of T2Dmellitus and three or more CVD risk factors) recruited from the PREDIMED (Prevención con Dieta Mediterránea) Study to determine the efficacy of the MedDiet on the primary prevention of CVD. Participants were older subjects (55 and 80 years) at high risk for CVD. Interventions included: 1) Quarterly education about the MedDiet; 2) Provision of either 1Lper week of virgin olive oil (MedDiet + VOO); or 3) 30g per day of mixed nuts (MedDiet + nuts), and advice on a low-fat diet (control diet ad libitum. and there was no increase in physical activity for any of the interventions. Lifestyle variables and MetS features as defined by the National Cholesterol Education Program Adult Treatment Panel III criteria were assessed. 61.4% of participants met criteria for the MetS at baseline. One-year prevalence of MetS was reduced by 6.7% (MedDiet + VOO), 13.7% (MedDiet + nuts) and 2.0% (control diet), respectively (MedDiet + nuts vs. control groups, P=0.01; MedDiet + VOO vs. control group, P=0.18). Incident rates of the MetS were not different among groups (22.9%, 17.9% and 23.4%, respectively). After adjustment for sex, age, baseline obesity status and weight changes, the odds ratios for reversion of MetS were 1.3 (95% CI, 0.8 to 2.1) for the MedDiet + VOO group and 1.7 (1.1 to 2.6) for the MedDiet + nuts group compared with the control diet group. Authors conclude that a traditional MedDiet enriched with nuts could be a useful tool in the management of the MetS. The authors also made note of the age of the participants.

Mukuddem-Petersen et al, 2005 (positive quality) conducted a systematic review to investigate the effects of nuts on the lipid profile searching the MEDLINE and Web of Science databases from the start of the database to August 2004. Four-hundred fifteen publications were screened and 23 intervention studies (16 RCTs and seven non-RCTs) were included. Dietary intervention studies with 186 healthy or diseased (216 hypercholesterolemic, 66 hyperlipidemic, 30 T2D) or mixed (95) subjects (312 men and 281 women) were included in this systematic review. The results of three almond (50 to 100g per day), two peanut (35 to 68g per day), one pecan nut (72g per day), and four walnut (40 to 84g per day) studies showed decreases in TC between 2% and 16% and LDL-C between 2% and 19% compared with subjects consuming control diets. Consumption of macadamia nuts (50 to 100g per day) produced less convincing results. The authors concluded that, consumption of 50 to 100g (1.5 to 3.5 servings) of nuts five times a week as part of a heart-healthy diet with total fat content (high in mono- or polyunsaturated fatty acids) of 35% of energy may significantly decrease TC and LDL-C in normo- and hyperlipidemic individuals.

Almonds (including ADA update)

303

Kurlandsky S, Stote K. 2006 (neutral quality), in a six week four-armed randomized parallel trial assessed the effect on selected CVD factors of combining chocolate and almonds as part of a low-fat diet on circulating levels of serum lipids and inflammatory markers: Intercellular adhesion molecule (ICAM), vascular adhesion molecule, and high-sensitivity CRPin 47 normolipidemic women. All subjects followed the NCEPT Lifestyle Changes diet. The intervention involved four diets: 1) 60g almonds with a self-selected diet; 2) 41g dark chocolate with a self-selected diet; 3) Almonds (60g) and chocolate (41g) with a self-selected diet; 4) Control diet which was a self-selected diet avoiding nuts and chocolate. All subjects improved dietary intakes in accordance with guidelines, and no subjects gained or lost weight. Serum cholesterol concentrations showed no changes after six weeks; however, triacylglycerol levels were reduced by approximately 21%, 13%, 19% and 11% (P<0.05), in the chocolate, almond, chocolate and almond and control groups, respectively. Circulating ICAM levels decreased significantly by 10% in the treatment group consuming chocolate only (P=0.027). No significant changes were observed for vascular adhesion molecule and high-sensitivity CRP levels in any treatment group. No synergistic or additive effects were observed when both products were consumed. In conclusion, consumption of chocolate and almonds as part of the TLC diet for six weeks showed no harmful effects in healthy women; all dietary modifications improved serum triacylglycerol levels and consumption of chocolate reduced levels of circulating ICAM.

Phung et al, 2009 (positive quality), a meta-analysis of five international RCTs totaling 142 participants, evaluated the influence of almonds on lipid parameters. Almond consumption ranging from 25 to 168g per day significantly lowered TC [weighted mean difference = -6.95mg per dL (95% CI: -13.12 to -0.772mg per dL)] and showed a strong trend toward reducing LDL-C [weighted mean difference = -5.79mg per dL (95% CI: -11.2 to 0.00)]. There were no significant effects on HDL-C, TG, or LDL:HDL ratio. Authors note that the meta-analysis may have been underpowered to demonstrate statistical significance for some endpoints or subgroups. In addition, different background diets may have resulted in weight loss, potentially confounding the results.

Wien et al, 2003 (positive quality), in a randomized, prospective 24-week trial evaluated the effect of an almond-enriched or complex carbohydrate-enriched formula-based low-calorie diet on anthropometric, body composition and metabolic parameters in 65 overweight or obese subjects (age: 27 to 79 years, BMI: 27 to 55kg/m2) enrolled in a weight-reduction program. The intervention involved a formula-based LCD enriched with 84g per day of almonds (almond-LCD; 39% total fat, 25% MUFA and 32% carbohydrate as percent of dietary energy) or self-selected complex carbohydrates (CHO-LCD; 18% total fat, 5% MUFA and 53% CHO as percent of dietary energy) featuring equivalent calories and protein. Intake of almonds in the LCD, in contrast to complex CHO, was associated with greater reductions in weight/BMI (-18 vs. -11%), waist circumference (WC) (-14 vs. -9%), fat mass (FM) (-30 vs. -20%), total body water (-8 vs. -1%) and systolic blood pressure (SBP) (-11 vs. 0%), P=0.0001-0.05. A 62% greater reduction in weight/BMI, 50% greater reduction in WC and 56% greater reduction in fat mass were observed in the almond-LCD as compared to the CHO-LCD intervention. Ketone levels increased only in the almond-LCD group (+260 vs. 0%, P<0.02). Baseline TC level in the almond vs. CHO group was close to normal (198±8 and 216±7mg per dL). HDL-cholesterol increased in the CHO group and

304

decreased in the almond groups (+15% vs. -6%, P=0.05). Glucose, insulin, diastolic blood pressure (DBP), TC, TG, LDL-C and LDL-C to HDL-C ratio decreased significantly to a similar extent in both dietary interventions. Homeostasis model analysis of insulin resistance (HOMA-IR) decreased in both study groups over time (almond-LCD: -66% and CHO-LCD: -35%, P<0.0001). Homeostasis model analysis of insulin resistance (HOMA-IR) decreased in both study groups over time (almond-LCD: -66% and CHO-LCD: -35%, P<0.0001). Among subjects with T2D, diabetes medication reductions were sustained or further reduced in a greater proportion of almond-LCD as compared to CHO-LCD subjects (96 vs. 50%, respectively). Intake of almonds was associated with greater reduction in weight/BMI (-18% vs. -11%, P<0.0001), WC (-14% -9%, P<0.05), fat mass (-30% vs. -20%, P<0.05). Subjects self-reported evaluation of almond and complex CHO diet acceptability, satiety, palatability and texture did not differ over time or between groups. Both dietary interventions were effective in decreasing body weight beyond the weight loss recorded during long-term pharmacological interventions, but the almond-LCD group experienced a sustained and greater weight reduction during the 24 weeks of intervention. Authors conclude that an almond-enriched LCD improves a preponderance of the abnormalities associated with the metabolic syndrome.

Walnuts and Health Effects

Banel and Hu, 2009 (positive quality), in a systematic review and meta-analysis of 13 international studies, examined the changes in lipid concentrations induced by a walnut-enhanced diet. Of the 13 studies, 12 were randomized trials, 10 of which had a crossover design; 365 participants were included in the analysis. When compared with control diets, diets supplemented with walnuts (10% to 24% of total calories) resulted in a significantly greater decrease in TC (weighted mean difference = -10.3mg per dL, P<0.001) and LDL-C (weighted mean difference = -9.2mg per dL, P<0.001) concentrations, while HDL-C concentrations, TG levels and body weight were not significantly affected. Some trials reported that walnuts provided significant benefits for antioxidant capacity and inflammatory markers. Authors noted that studies had relatively small sample sizes and short durations of follow-up; the longest follow-up time was six months.

Olmedilla-Alonso et al, 2008 (neutral quality), a randomized crossover trial conducted in Spain, assessed the potential effect of regular consumption of walnut-enriched restructured meat products on biomarkers of coronary heart disease in subjects at risk for CVD. Subjects consumed a meat product, with or without walnuts, five times per week for five weeks with a one-month washout period in between diets. From 144 respondents, 25 were selected to participate and all completed the study (15 men, 10 women, mean age 54.4±8.1 years). Compared to the meat products without walnuts, consumption of the meat products with walnuts resulted in a decrease in TC of 6.8mg per dL (95% CI: -12.8 to -0.85mg per dL), P=0.02. Compared to baseline, consumption of the meat products with walnuts resulted in a decrease in TC of -10.7mg per dL (95% CI: -17.1 to -4.2mg per dL) P=0.002, LDL-C of -7.6mg per dL (95% CI: -2.2 to -13.0mg per dL), P=0.007 and body weight of -0.5kg (95% CI: -0.1 to -0.9kg), P=0.032, as well as an increase in g-tocopherol of 8.9mg per dL (95% CI: 1.0 to 16.8mg per dL), P=0.029. Enrollment of subjects may have led to selection bias,

and certain factors were not controlled for in the analysis.

Rajaram et al, 2009 (neutral quality), a randomized crossover trial conducted in the US, investigated whether walnuts and fatty fish have similar effects on serum lipid markers. Subjects consumed three isoenergetic diets (30% total fat, less than 10% saturated fat) for four weeks each, with a weekend break between diets: A control diet containing no nuts or fish, a walnut diet containing 42.5g walnuts per 10.1mJ and a fish diet containing 113g salmon twice per week. Of 27 subjects initially enrolled, 25 completed the study (14 males, 11 females, aged 23 to 65 years). Serum total cholesterol and LDL-C concentrations were lower when following the walnut diet (4.87±0.18 and 2.77±0.15mmol per L, respectively, $P<0.0001$) than when following the control diet (5.14±0.18 and 3.06±0.15mmol per L, respectively) and the fish diet (5.33±0.18 and 3.2±0.15mmol per L, respectively). However, the fish diet resulted in decreased serum TG ($P<0.05$) and increased HDL-C concentrations ($P<0.001$) compared with the control diet and walnut diet. In addition, the ratios of TC:HDL-C, LDL-C:HDL-C, and apolipoprotein B:apolipoprotein A-I were lower ($P<0.05$) in those after consumption of the walnut diet compared with the control and fish diets. Authors note that the sample was relatively small in size, and that the washout period between treatments was short.

Sabate et al, 2005 (positive quality), a randomized crossover trial conducted in the US, determined the potential changes in body weight and body composition related to walnut consumption. Subjects were randomly assigned to two diets for six months: A walnut-supplemented diet (28 to 56g per day, 12% of energy) and a control diet, then switched diets for another six months. Of 94 subjects randomized, 90 completed the trial, 50 females and 40 males aged 30 to 72 years (mean 54.3; SD, 10.6) years. The walnut supplementation resulted in greater daily energy intake of 133kcal. For all participants, walnut supplementation increased weight (0.4±0.1kg, $P<0.01$), BMI (0.2±0.1kg/m^2, $P<0.05$), fat mass (0.2±0.1kg, $P<0.05$) and lean mass (0.2±0.1kg, $P<0.05$); however, after adjusting for energy differences between diets, no significant differences were observed in body weight or body composition parameters except for BMI (0.1±0.1kg/m^2, $P<0.05$). Authors conclude that regular walnut intake results in weight gain much lower than expected was not significant after adjustment for differences in energy intake. No limitations were noted.

Macadamia Nuts and Health Effects

Griel et al, 2008 (neutral quality), a randomized crossover trial conducted in the US, evaluated the lipid and lipoprotein responses of a blood cholesterol-lowering diet that contained macadamia (MAC) nuts when substituted for saturated fat content of the average American diet. Subjects were randomly assigned to two diets for five weeks each: A macadamia nut-rich diet (1.5oz per 2,100kcal, 33% total fat, 7% SFA) and the average American diet (13% SFA and matched for total fat, protein and carbohydrate). Of 25 mildly hypercholesterolemic subjects randomized (10 men and 15 women, mean age 50.2±8.4 years), 24 completed the trial. Compliance was confirmed by serum fatty acid analysis, serum MUFAincreased while SFA decreased with intake of MAC ($P<0.05$). Serum concentrations of TC and LDL-C were lower following the macadamia nut-rich diet than the average American diet (4.94±0.17mmol per L vs. 5.45±0.17mmol per L for TC, 3.14±0.14mmol per L vs. 3.44±0.14mmol per L for LDL-C, both $P<0.05$).

306

While there was no change in serum TGconcentrations, the serum non-HDL cholesterol concentration was reduced following consumption of the macadamia nut-rich diet compared to the average American diet (P<0.05). The study was based on relatively small sample size; difficult to define the average American diet.

Pistachios Nuts and Health Effects

Gebauer et al, 2008 (neutral quality), a randomized crossover trial conducted in the US, assessed potential mechanisms that may account for the lipid and lipoprotein responses to a cholesterol-lowering diet with varying levels of pistachios. After a two-week run-in period, subjects were randomly assigned to three treatment diets for four weeks each, with two-week compliance breaks between diets: A lower-fat control diet with no pistachios (25% total fat), one serving per day of pistachios (10% of energy from pistachios, 30% total fat) and two servings per day of pistachios (20% of energy from pistachios, 34% total fat). Twenty-eight subjects completed the trial (10 men, 18 women, mean age 48±1.5 years). Compared with the control diet, the diet with two servings per day of pistachios decreased TC (-8%), LDL-C (-11.6%), non-HDL cholesterol (-11%), apo B (-4%), apo B/apo A-I (-4%) and plasma stearoyl-CoA desaturase activity (-1%, all P<0.05). Both pistachio-based diets elicited a dose-dependent lowering of TC/HDL-C, LDL-C/HDL-C, and non-HDL cholesterol/HDL-C (all P<0.05). Recruitment methods were not described and the original number of subjects enrolled was unclear; each dietary period only lasted four weeks.

Sheridan et al, 2007 (neutral quality), a prospective randomized cross-over trial, investigated the effects of consuming 15% of the daily caloric intake in the form of pistachio nuts on the lipid profiles of 15 free-living subjects, average (mean±SEM) age of 60±3 years with primary, moderate hypercholesterolemia (serum cholesterol higher than 210mg per dL) in the US. The intervention involved consumption of two to three ounces per day of Pistachio nut over a four-week period. Seven subjects were randomized to the pistachio diet for four weeks followed by four weeks on their regular diet, while eight subjects followed these diets in reverse order. The control diet was not defined. Outpatient dietary counseling and blood analysis were conducted and no differences were observed for total energy or percent of energy from protein, carbohydrate or fat. A significant decrease in percent energy from saturated fat was observed (mean difference, -2.7%; 95% CI: -5.4% to -0.08%; P=0.04) on the pistachio nut diet. Significant increases were seen for percent energy from polyunsaturated fat (mean difference, 6.5%; 95% CI: 4.2% to 8.9%; P<0.0001) and fiber intake (mean difference, 15g; 95% CI, 8.4g to 22g; P=0.0003) on the pistachio nut diet. There was a significant reductions in TC/HDL-C(mean difference, -0.38; 95% CI: -0.57 to -0.19; P=0.001), LDL-C/HDL-C (mean difference, -0.40; 95% CI: -0.66 to -0.15; P=0.004), B-100/A-1 (mean difference, -0.11; 95% CI: -0.19 to -0.03; P=0.009) and a significant increase in HDL-C (mean difference, 2.3; 95% CI: 0.48 to 4.0; P=0.02) on the pistachio diet. Total cholesterol, triglycerides, LDL-C, VLDL-C, apolipoprotein A-1 or apolipoprotein B-100 were not different. Body mass index or blood pressure did not change. Authors conclude that a diet consisting of 15% of calories as pistachio nuts can favorably improve some lipid profiles in subjects with moderate hypercholesterolemia and may reduce risk of coronary disease. Note that the study had design flaws such as a lack of proper controls, and used the experimental diet

(pistachio nut) as a source of fat calories for subjects not used to high fat snacks. There was also no definitive compliance measure of pistachio consumption. The study was industry funded.

Overview table

Author, Year, Study Design, Class, Rating	Study Duration	Study Population /Location	Intervention Protocol/ Exposure levels	Significant Results	Limitations; Funding Source
Banel DK and Hu FB 2009 Study Design: Systematic Review/Meta-analysis Class: M Rating: Positive Quality	Minimum four to 24 weeks.	N=365 participants. 13 international studies. 12 were RCTs (10 crossover design). Location: International.	Walnuts and Blood Lipid Literature data bases. Diets lasting four to 24 weeks. Walnut providing 10% to 24% of calories. Jadad rating used to score RCTs (one to five points).	Compared with control diets, diets supplemented with walnuts (10% to 24% of total calories) resulted in a significantly greater ↓ in TC (weighted mean difference = -10.3mg per dL, P<0.001) and LDL-C (weighted mean difference = -9.2mg per dL, P<0.001) concentrations. HDL-C, TG levels and body weight were NS affected. Some trials reported that walnuts provided significant benefits for antioxidant capacity and inflammatory markers.	Authors noted that studies had relatively small sample sizes and short durations of follow-up; the longest follow-up time was six months.

309

Bes-Rastrollo M et al 2007 Study Design: Prospective Cohort Study Class: B Rating: Neutral	28 months follow-up.	N=8,865 of 11,714 participants of the Mediterranean dynamic Seguimiento Universidad de Navarra (SUN) cohort of free-living adults. Age based on frequency of nut consumption (mean and SD): Never/almost never: 35.6 (11.9) years. One to three times a month: 36.7 (11.8) years. Once a week: 37.6 (12.0) years. At least two times per week: 41.5 (13.1) years. Location: Spain.	Nut Consumption and Risk of Weight Gain Follow-up questionnaire after a median of 28 months. Participants were grouped based on baseline frequency of nut consumption (50g servings): Never/almost never (33.1% male, mean age 35.6 years) One to three times a month (40.8% male, mean age 36.7 years) One time a week (46.9% male, mean age 37.6 years) At least twice per week (51.0% male, mean age 41.5 years).	At the 28-month follow-up, 937 participants reported a weight gain of at least 5kg. After adjustment for confounding variables, participants who ate nuts two or more times a week had a ↓ risk of weight gain (OR=0.69, 95% CI: 0.53 to 0.90, P=0.006), than those never or almost never ate nuts. Participants who never or almost never consumed nuts gained an average of 424g (95% CI: 102 to 746) more than frequent nut consumers. Nut consumption was not associated with incident overweight or obesity.	Authors note that the participants were not representative of the general population. Dietary habits were only measured at baseline. Body weight based on self-report.

310

Bes-Rastrollo M et al 2009 Study Design: Prospective Cohort Study Class: B Rating: Neutral	Eight years of follow-up.	Participants of the Nurses' Health Study II. Of 116,671 female nurses aged 24 to 44 years at baseline in 1989, 51,188 were included in the 1991 to 1999 analysis. Location: United States.	Long-term Relation Between Nut or Peanut Butter Intake and Weight Δ Semi-quantitative FFQ at baseline (1991) included 133 items to obtain dietary information. Participants asked to report their average consumption of a commonly used unit or portion size of each food during the previous year. Nine possible responses, ranging from never to more than six times a day. Average intake of peanut butter [one Tbsp equivalent to one ounce of peanuts (28.35g)], peanuts [1oz (28.35g) of peanuts] and tree nuts [1oz (28.35g) of nuts] during the previous year.	Women who ate nuts more than two times a week had slightly less mean weight gain than women who rarely ate nuts (5.04±0.12kg vs. 5.55±0.04kg, P<0.001). Results were similar when total nut intake was subdivided by peanuts and tree nuts and when subjects were subdivided by normal weight, overweight and obese. After adjustment for confounding variables, greater nut consumption (more than two times a week) was associated with a slightly ↓ risk of obesity compared with never or almost never consuming nuts (HR = 0.77, 95% CI: 0.57 to 1.02, P=0.003).	Authors note that there were a small percentage of women in the cohort with high levels of nut consumption, in addition. Weight was self-reported.

311

Djousse L, Rudich T and Gaziano JM 2009 Study Design: Prospective Cohort Study Class: B Rating: Positive Quality	237,585 person-years follow-up.	Participants of the Physician's Health Study I. Of 22,071 male physicians aged 40 to 84 years (mean age 52.3±8.9 years) at baseline in 1981, 15,966 were included in the analysis. Location: United States.	Nut Intake and Risk of Incident HTN Nut consumption was self-reported on a simple abbreviated semi-quantitative FFQ at 12 months post-randomization (1983–1985). Possible response categories were: "Rarely/never," "one to three times a month," "once a week," "two to four times a week," "five to six times a week," "daily," and "two times a day." Diagnosis of hypertension was made based on self-reported treatment.	During 237,585 person-years of follow-up, there were 8,423 new cases of hypertension. Compared to subjects who did not consume nuts, multivariable adjusted HR for hypertension were 0.97 (95% CI: 0.91 to 1.03) for nut consumption of one to times a month; HR=0.98 (95% CI: 0.92 to 1.05) for nut consumption of once a week; HR=0.96 (95% CI: 0.89 to 1.03) for nut consumption of two to six times a week; and HR= 0.82 (95% CI: 0.71 to 0.94, for nut consumption seven or more times per week. In analyses stratified by BMI, there was an inverse relation between nut intake and hypertension in lean subjects (P for trend = 0.0019) but not in overweight or obese subjects (P for interaction = 0.0037).	Authors note that participants were male physicians who may have different behaviors or lifestyle habits than the general population, limiting the generalizability of findings. Incidence of hypertension was based on self-reports.

Gebauer SK et al 2008 Study Design: Randomized Crossover Trial Class: A Rating: Neutral	Four weeks.	N=28 (10 men, 18 women) with hyperlipidemia. Mean age: 48±1.5 years. Location: United States.	Pistachios and Lipid- and Lipoproteins-lowering Two-week run-in period. Three diets for four weeks each, with two-week compliance breaks between diets: 1. Lower-fat control diet with no pistachios (25% total fat) 2. One serving per day of pistachios (10% of energy from pistachios, 30% total fat). 3. Two servings per day of pistachios (20% of energy from pistachios, 34% total fat).	Compared with the control diet, diet with two servings per day of pistachios lowered TC (-8%), LDL-C (-11.6%), non-HDL-C (-11%), apo B (-4%), apo B/apo A-I (-4%) and plasma stearoyl-CoA desaturase activity (-1%, all P<0.05). Both pistachio-based diets elicited dose-dependent lowering TC/HDL-C, LDL-C/HDL-C, and non-HDL-C/HDL-C (all P<0.05).	Recruitment methods were not described. The original number of subjects enrolled was unclear. Each dietary period only lasted four weeks.

313

Griel AE, Cao Y et al, 2008 Study Design: Randomized crossover trial Class: A Rating: Neutral	Five weeks.	N=24 (10 men and 15 women), mildly hypercholesterolemic. Attrition: 0.4%. Mean age: 50.2±8.4 years. Location: United States.	Macadamia Nuts and Lipid and Lipoprotein Responses Two diets for five weeks each: Macadamia (MAC) nut-rich diet [1.5oz per 2,100kcal, 33% total fat (7% SFA, 18% MUFA, 5% PUFA), 17% protein and 52% CHO]. The average American diet (AAD) [matched for total fat, 33% (13% SFA, 11% MUFA, 5% PUFA), 19% protein and 50% CHO].	Serum SFA lowered and MUFA rose after MAC diet compared to AAD (P<0.05) and no Δs in PUFA, indicating compliance. Serum TC and LDL-C lowered following MAC nut-rich diet than the AAD (4.94±0.17mmol per L vs. 5.45±0.17mmol per L for TC, 3.14±0.14mmol per L vs. 3.44±0.14mmol per L for LDL-C, both P<0.05). Serum TG remained unchanged. Serum non-HDL-C concentration lowered following the MAC nut-rich diet (3.83±0.14mmol per L vs. 4.60±0.24mmol per L for TC, 2.91±0.17mmol per L compared to the AAD (4.26±0.17mmol per L vs. 4.89±0.24mmol per L for TC, 3.09±0.18mmol per L (P<0.05).	Study based on relatively small sample size. Supported by The Hershey Company.

Kurlandsky and Stote, 2006 Study Design: Randomized controlled parallel trial. Class: A Rating: Neutral	Six weeks.	N=47 normolipidemic women. Mean age: 36.5 years. Location: United States.	Almonds and Cholesterol Diets: 1) 60g almonds with a self-selected diet; 2) 41g dark chocolate with a self-selected diet; 3) Chocolate (41g) and almonds (60g) with a self-selected diet; and 4) A self-selected diet avoiding nuts and chocolate (Control). Self-selected diet was based on the NCEP ATP III TLC diet.	NS Δ in cholesterol level over the six-week trial. TG levels ↓ in all treatment groups, and by 21 % with chocolate, 13% with almonds, 19% with almonds and chocolate combined and 11% in controls.	Small sample size. Limiting to measures of markers of inflammation due to loss of sample. Bias in the recruitment of only healthy subjects with good blood lipid.

Li TY, Brennan AM et al, 2009 Study Design: Prospective cohort study. Class: B Rating: Positive Quality		N=6309 women with T2D, without CVD or cancer at study entry. Location: United States.	Nuts, Peanut Butter and Incidents of CVD. Frequency of nut intake. Validated FFQ every two to four years between 1980 and 2002. A semi-quantitative FFQ included 61 foods in 1980. Later revised and expanded. Participants report their average frequency of consumption of selected foods and beverages with a specified commonly used unit or portion size . In 1980 and 1984 dietary questionnaires, participants were asked how often, on average, they consumed nuts [serving size, 28g (1oz)] according to categories: never/ almost never, one to three servings a month, one serving a week, two to four servings a week, five to six servings a week, one serving a day, two to three servings a day, four to six servings a day or six servings a day. In the 1986, 1990, 1994, and 1998 dietary questionnaires, the question for nuts was divided into two separate questions: peanuts and other nuts.	During 54,656 person-years of follow-up: 452 CHD events (MI and revascularization) 182 incident stroke cases. Intake of at least five servings a week of nuts or peanut butter [28g (1oz.) for nuts and 16g (one tablespoon) for peanut butter]: Significantly associated with ↓ risk of CVD (RR=0.56; 95% CI: 0.36 to 0.89) and more favorable plasma lipid profile, lower LDL, non-HDL-C, TC and apo-B100 conc. NS associations for HDL-C or inflammatory markers were observed.	Very well conducted prospective cohort study. Authors note the small sample size effect on power to conduct detailed analyses for biomarker. Method of handling withdrawals was not described. Authors presented results based on the total initial sample size. Characteristics of withdrawals, if any, were not described. Power calculation and intent to treat analysis were not described.

Mukuddem-Petersen J, Oosthuizen W et al, 2005 Study Design: Narrative Review Class: R Rating: Positive Quality	Minimum four to 24 weeks of intake.	N=186 healthy or diseased (216 hyper-cholesterolemic, 66 hyperlipidemic, 30 T2D) or mixed (95) subjects (312 men and 281 women). 23 international studies. Location: International.	Nuts and Blood Lipid Studies were included if objective was to investigate the independent effect of nuts on lipid concentrations and study was conducted among humans. Trials were excluded when these independent effects could not be assessed and had incomplete or missing data. 23 original research papers were identified that were suitable for inclusion. Main outcome measures percentage differences between treatment and control for blood TC, LDL-C, HDL-C, and TG.	Most of the studies (12 of 16) included more than 20 subjects per group. Three almond (50 to 100g per day), two peanut (35 to 68g per day), one pecan nut (72g per day) and four walnut (40 to 84g per day) studies showed ↓ in TC between 2% and 16% and LDL-C between 2% and 19%, compared with subjects consuming control diets. Consumption of macadamia nuts (50 to 100g per day) produced less convincing results.	Did not conduct a meta-analysis. Authors noted that studies had large differences in study designs of the dietary intervention trials. University.

Olmedilla-Alonso et al 2008 Study Design: Randomized Crossover Trial Class: A Rating: Neutral	Five weeks.	N=25 (15 men, 10 women). Mean age: 54.4±8.1 years.	Walnut-enriched Restructured Meat and Biomarkers of CHD Consumed a meat product, with or without walnuts, five times a week. Five weeks. One-month washout period between diets.	Compared to the meat products without walnuts, intake of the meat products with walnuts resulted in TC of 6.8mg per dL (95% CI: -12.8 to -0.85mg per dL); P=0.027. Compared to baseline, consumption of the meat products with walnuts resulted in a ↓ in TC of -10.7mg per dL (95% CI: -17.1 to -4.2mg per dL) P=0.002; LDL-C of -7.6mg per dL (95% CI: -2.2 to -13.0mg per dL), P=0.007; and body weight of -0.5kg (95% CI: -0.1 to -0.9kg), P=0.032; and an increase in g-tocopherol of 8.9mg per dL (95% CI: 1.0 to 16.8mg per dL), P=0.029.	Enrollment of subjects may have led to selection bias, and confounding factors were not controlled for in the analysis.
Phung OJ et al 2009 Study Design: Meta-analysis Class: M Rating: Positive Quality		N=142 participants. 40% hyperlipidemic; 21% T2D. Location: Five International RCTs.	Almonds Intake and Lipid Profiles	Almond consumption ranging from 25 to 168g per day significantly TC [weighted mean difference = -6.95mg per dL (95% CI: -13.12 to -0.772mg per dL)]. NS effects on HDL-C, TG or LDL:HDL ratio.	Authors note that the meta-analysis may be underpowered to demonstrate statistical significance for some endpoints or subgroups. Different background diets may have resulted in weight loss, potentially confounding the results. Four of five trials funded by Almond Board.

| Rajaram S et al 2009

Study Design: Randomized Crossover Trial

Class: A

Rating:

Neutral | Four weeks. | N=25 (14 males, 11 females).

Attrition: 7.4%.

Age: 23 to 65 years.

Location: United States. | Walnuts vs. Fatty Fish and Serum Lipid Markers

Three isoenergetic diets (30% total fat, less than 10% saturated fat):

1) Control diet with no nuts or fish

2) Walnut diet containing 42.5g (1.5oz) walnuts per 10.1mJ (2,400kcal)

3) Fish diet containing 113g (4oz raw) salmon twice per week.

Four weeks each, with a weekend break between diets. | Serum TC and LDL-C concentrations were lower on the walnut diet (4.87±0.18 and 2.77±0.15mmol per L, respectively, P<0.0001) than on the control diet (5.14±0.18 and 3.06±0.15mmol per L, respectively) and the fish diet (5.33±0.18 and 3.2±0.15mmol per L, respectively).

The fish diet resulted in lower serum TG (P<0.05), higher HDL-C (P<0.001), compared with the control and walnut diet.

Ratios: TC:HDL-C, LDL-C:HDL-C and apo B:apo A-I were lower (P<0.05) after intake of the walnut diet compared with the control and fish diets. | Authors noted the relatively small sample size.

Short washout period between treatments. |

319

Sabate J, Corder-Macintyre Z et al, 2005 Study Design: Randomized crossover trial Class: A Rating: Positive Quality	Six months.	N=90, relatively healthy subjects (less than 1kg weight Δ in the last six months; BMI less than 35kg/m^2. Attrition: 5.23%. Location: United States.	Walnuts, Body Weight and Body Composition Two diets for six months each: A walnut-supplemented diet (28 to 56g per day, 12% of energy) and a control diet.	Walnut diet resulted in greater daily energy intake of 133kcal. Walnut intake group gained weight (0.4±0.1kg), BMI (0.2±0.1kg/m^2), both P<0.01. Fat mass (0.2±0.1kg) and lean mass (0.2±0.1kg), both P<0.05. After adjusting for energy no differences were observed in body weight or body composition parameters, except for BMI (0.1±0.1kg/m^2) P<0.05.	No limitations were noted.

Salas-Salvado J, Fernandez-Ballart J et al, 2008 Study Design: Randomized Controlled Trial Class: A Rating: Positive Quality	Cross-sectional study of a cohort subjected to RCT (Estruch et al, 2006).	N=772 (339 men and 433 women), asymptomatic. Age: 55 and 80 years. Location: United States. Length of time not clear.	Mediterranean Diet (Nuts and Circulating Markers of Inflammation). Food intake by a semi-quantitative FFQ. Measured Serum concentrations of high-sensitive CRP, interleukin-6 (IL-6), intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). Adjusted for age, gender, BMI, diabetes, smoking, and use of statins, non-steroidal anti-inflammatory drugs and aspirin.	↑ consumption of nuts and virgin olive oil showed the lowest concentrations of VCAM-1, ICAM-1, IL-6 and CRP; only in ICAM-1 was this significantly different in the case of nuts (P for trend = 0.003) and for VCAM-1 in the case of virgin olive oil (P for trend = 0.02). ↑ consumption of fruits and cereals was associated with ↓ concentrations of IL-6 (P for trend = 0.005). ↑ adherence to the Mediterranean-type diet did not show significantly ↓ concentration of inflammatory markers (P<0.1 for VCAM-1 and ICAM-1).	Authors note the possibility of measurement error in FFQ. Some associations may be overlooked. Score used may not be discriminatory enough of adherence to the Mediterranean dietary pattern. Study design may not have been the right choice to achieve their objective.

321

Salas-Salvadó J, Garcia-Arellano A et al, 2008 Study Design: Prospective cohort study Class: B Rating: Positive Quality	Three-arm, randomized clinical trial.	N=1,224. Presence of T2D or three or more CVD risk factors: Current smoker BP 140/90mmHg or treatment with antihypertensive drugs LDL-C of 160mg per dL or higher or treatment with hypolipidemic drugs HDL-C level of 40mg per dL or lower BMI of 25kg/m^{2}or higher Family history of premature CVD. Recruited from the PREDIMED (Prevención con DietaMediterránea) Study. Attrition: 4%. Age: 55 and 80 years. Location: United States.	Mediterranean Diet + Mixed Nuts and Incidence of MetS Multicenter recruiting. Food intake by a semi-quantitative FFQ. 14-item questionnaire: Individual adherence to the MedDiet, dieticians gave personalized dietary advice to participants in both MedDiet groups during a 30-minute session. Dietitians delivered a separate 60-minute group session for each MedDiet group. Given written material with descriptions of typical Mediterranean foods, seasonal shopping lists, meal plans and recipes. Participants assigned to the MedDiet groups were given either free VOO (15L for three months) or packets of mixed nuts [1,350g of walnuts (15g per day), 675g of hazelnuts (7.5g per day) and 675g of almonds (7.5g per day) every three months].	One-year prevalence of high WC, elevated TG level and high BP significantly ↓ in the MedDiet + nuts group compared with the control group (P<0.05). One-year prevalence of MetS was ↓ by 6.7% (MedDiet + VOO), 13.7% (MedDiet + nuts) and 2.0% (control diet), respectively (MedDiet + nuts vs. control groups, P=0.01; MedDiet + VOO vs. control group, P=0.18). No differences among groups in the incidence or reversion of high fasting glucose or low HDL-C levels. MedDiet + nuts was associated with MetS reversion among individuals who had the syndrome at baseline.	Participants were older subjects at high risk for CVD. Nearly 45% had diabetes mellitus and 61.4% had MetS; results cannot be extrapolated to the general population. Nutritional education for the low-fat diet group was less intense than the behavioral intervention in the MedDiet groups. Study duration was too short to address clinical outcomes.

Sheridan MJ, Cooper JN et al, 2007 Study Design: Randomized crossover (time series) trial Class: A Rating: Neutral		N=15 (11 males, 4 females) free-living subjects, with primary, moderate hyper-cholesterolemia (serum cholesterol greater than 210mg per dL). Average (mean ± SEM) age: 60±3 years. Attrition: 25%. Location: United States.	Pistachio Nut Intake, Blood Lipids, BMI and BP Outpatient dietary counseling and blood analysis. Four weeks of dietary modification with 15% caloric intake from pistachio nuts. Measures of outcome: Serum lipid levels of TC, HDL-C, LDL-C, VLDL-C, TGs, apo A-1 and B-100. BMI, BP, and nutrient intake (total energy, fat, protein and fiber). All outcomes measured at baseline, during and after dietary intervention.	Total energy or percent of energy from protein, CHO or fat not different. On pistachios diet: Significant ↓ was seen for percent energy from saturated fat (mean difference, –2.7%; 95% CI: –5.4% to –0.08%; P=0.04). Significant rise for percent energy from PUFA fat (mean difference, 6.5%; 95% CI: 4.2% to 8.9%; P<0.0001). Rise in fiber intake (mean difference, 15g; 95% CI: 8.4g to 22g; P=0.0003). Significant ↓ in TC/HDL-C (mean difference, –0.38; 95% CI: –0.57 to –0.19; p = 0.001), LDL-C/HDL-C (mean difference, –0.40; 95% CI: –0.66 to –0.15; P=0.004), B-100/A-1 (mean difference, –0.11; 95% CI: –0.19 to –0.03; P=0.009). Significant ↑ in HDL-C (mean difference, 2.3; 95% CI: 0.48 to 4.0; P=0.02). No differences for TC, TG, LDL-C, VLDL-C, apo A-1 or apo B-100. No Δs observed in BMI or BP.	Small number of random sample, all above middle age. Short study duration does not allow for inferences on sustainability or outcomes. Design flaws and lack of proper controls, not described. Meets exclusion criteria. Not possible to assess whether the eating of pistachios as a snack food is sustainable over time as a healthy dietary behavior. Difficult to assess how the inclusion of this single food source might alter other aspects of the diet, perhaps unfavorably. Not possible to assess biases as clinical setting, environment, socioeconomic status and co-morbidity. Supported by California Pistachio Commission.

323

Wien, Sabate et al, 2004 Study Design: Randomized trial Class: A Rating: Positive Quality	Four weeks.	N=65 overweight or obese adults. Age: 27 to 79 years. BMI: 27 to 55kg/m^2. Almond diet: N=32; mean LDL-C, 99±5mg per dL. CHO diet: N=33; mean HDL-C, 108±5mg per dL. Attrition: 20%. Location: United States.	Formula-based LCD enriched with 84g per day of almonds or self-selected complex CHOs of equivalent calorie content.	HDL-C ↑ in the CHO group and ↓ in the almond groups (+15 vs. -6%, P=0.05). TC, TG, LDL-C and LDL-C to HDL-C ratio ↓ significantly to a similar extent in both dietary interventions.	

Research recommendations

Conduct randomized controlled trials comparing different types of nuts on intermediate markers, such as serum lipids, and classify each specific type of nut as more or less associated with CVD risk reduction.

Search plan and results

Inclusion criteria

- Health outcomes:
  - Cardiovascular disease (CVD)/coronary heart disease (CHD) risk
  - Blood lipids - LDL-C, HDL-C; non HDL-C
  - Markers of Inflammation
  - Insulin sensitivity; glucose tolerance
  - Type 2 diabetes risks.
- Subjects/Population
  - Age: Two years to adults.
- Setting:
  - Any, except ICU, burn unit inpatient or emergency care, US and International
  - Non-hospitalized.
- Health status:
  - Healthy
  - Dyslipidemia, Hyperlipidemia* or Hypercholesterolemia, CHD, CVD, Type 2 Diabetes
  - *According to ATP III (2004), hyperlipidemia is defined as a TC greater than 200 and/or LDL-Cgreater than 130 without CVD; LDL-C greater than 100 with CVD; and LDL-C greater than 70 for patients with a CHD

324

event, stroke, TIA, peripheral vascular disease AND ONE OF THE FOLLOWING:1) acute coronary syndrome, 2) type 2 diabetes mellitus, 3) metabolic syndrome, 4) a SINGLE POORLY CONTROLLED risk factor, 5) 3 risk factors irrespective of how well controlled.
  - o Note: in ATP III, diabetes is regarded as a CHD risk equivalent.
- Nutrition related problem/condition: *Cardiac Events:* MI, arythmia, angioplasty, stent, death, weight gain, incidence of type 2 diabetes, gall bladder disease
- Study design preferences:
  - o Randomized controlled trials
  - o Meta-analysis and systematic reviews
  - o Prospective cohort studies.
  - o Intervention: Feeding period must be greater than four weeks.
- Size of study groups:
  - o Sample size must equal 10 subjects for each study group. This would include 10 subjects in the intervention group and 10 subjects in the control or comparison group
  - o Study dropout rate: Less than 20%; preference for smaller dropout rates.
- Authorship:
  - o If an author is included on more than one review article or primary research article that is similar in content, the most recent review or article will be accepted and earlier versions will be rejected
  - o If an author is included on more than one review article or primary research article and the content is different, then both reviews may be accepted.
- Languages: Limited to articles in English.
- Other: Article must be published in peer-reviewed journal.
- Year range: 2004 to November 2009.

Exclusion criteria

- Subjects/Population
- Age: Less than two years of age.
- Setting: ICU, burn unit, emergency care, hospitalized.
- Health status: Diagnosed with disease.
- Nutrition Related Problem/Condition: Cardiac Events: Other than stroke.
- Size of study groups: Sample sizes <10.
- Study designs:
  - o Cross sectional studies
  - o Case-control studies
  - o Feeding periods < four weeks
- Experimental fat must be from natural sources.
- Study dropout rate**:** Dropout rate in a study is 20% or greater.
- Year range: Prior to Dec 2003.
- Authorship: Studies by same author similar in content.
- Languages: Articles not in English.
- Other**:** Animal studies; Abstracts or presentations.

Search terms and electronic databases used

PubMed:

> (nuts[mh] OR hazelnut* OR filbert* OR chestnut* OR Walnuts OR pecans OR almonds OR (brazilian nuts) OR pistachios OR (macadamia nuts) OR cashews) AND ("Coronary Disease"[Mesh] OR "Heart Diseases"[Mesh] OR "Cardiovascular Diseases"[Mesh:NoExp] OR Myocardial infarction[mh] OR "Diabetes Mellitus, Type 2"[Mesh] OR "Dyslipidemias"[Mesh] OR "Weight Gain"[Mesh] OR "Blood Pressure"[Mesh] OR "Hypertension"[Mesh]) Eng/humans 218

> "Dyslipidemias"[Mesh] (includes hypercholesterolemia OR hyperlipidemia)

Date searched: 11/24/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 218
- Total articles identified to review from electronic databases: 54
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 14
- Number of Review Articles Identified: 3
- Total Number of Articles Identified: 17
- Number of Articles Reviewed but Excluded: 20

Included articles (References)

Systematic reviews/Meta-analyses

1. Banel DK, Hu FB. Effects of walnut consumption on blood lipids and other cardiovascular risk factors: a meta-analysis and systematic review. *Am J Clin Nutr.* 2009 Jul; 90 (1): 56-63. Epub 2009 May 20. PMID: 19458020.
2. Mukuddem-Petersen J., Oosthuizen W, and Jerling JC. A systematic review of the effects of nuts on blood lipid profiles in humans. *J. Nutr.* 135: 2, 082-2, 089, September 2005. PMID: 16140880
3. Phung OJ, Makanji SS, White CM, Coleman CI. Almonds have a neutral effect on serum lipid profiles: a meta-analysis of randomized trials. *J Am Diet Assoc.* 2009 May; 109 (5): 865-873. Review. PMID: 19394473.

Randomized controlled trials

1. Gebauer SK, West SG, Kay CD, Alaupovic P, Bagshaw D, Kris-Etherton PM. Effects of pistachios on cardiovascular disease risk factors and potential mechanisms of action: a dose-response study. *Am J Clin Nutr.* 2008 Sep; 88 (3): 651-659. PMID: 18779280.
2. Griel AE, Cao Y, Bagshaw DD, Cifelli AM, Holub B, Kris-Etherton PM. A macadamia nut-rich diet reduces total and LDL-cholesterol in mildly hypercholesterolemic men and women. *J Nutr.* 2008 Apr; 138 (4): 761-767. PMID: 18356332.
3. Olmedilla-Alonso B, Granado-Lorencio F, Herrero-Barbudo C, Blanco-Navarro I, Blázquez-García S, Pérez-Sacristán B. Consumption of restructured meat

Archived from www.NEL.gov on March 21, 2017

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.

4. Rajaram S, Haddad EH, Mejia A, Sabaté J. Walnuts and fatty fish influence different serum lipid fractions in normal to mildly hyperlipidemic individuals: a randomized controlled study. *Am J Clin Nutr.* 2009 May; 89 (5): 1, 657S-1, 663S. Epub 2009 Apr 1. PMID: 19339404.

5. Sabaté J, Cordero-Macintyre Z, Siapco G, Torabian S, Haddad E. Does regular walnut consumption lead to weight gain? *Br J Nutr.* 2005 Nov; 94 (5): 859-864. PMID: 16277792.

6. Salas-Salvadó J, Fernández-Ballart J, Ros E, Martínez-González MA, Fitó M, Estruch R, Corella D, Fiol M, Gómez-Gracia E, Arós F, Flores G, Lapetra J, Lamuela-Raventós R, Ruiz-Gutiérrez V, Bulló M, Basora J, Covas MI; PREDIMED Study Investigators. Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: one-year results of the PREDIMED randomized trial. *Arch Intern Med.* 2008 Dec 8;168 (22): 2, 449-2, 458. PMID: 19064829. (Hand Search)

7. Sheridan MJ, Cooper JN, Erario M, Cheifetz CE. Pistachio nut consumption and serum lipid levels. *J Am Coll Nutr.* 2007 Apr; 26 (2):141-148. PMID: 17536125.

8. *Prospective cohort studies:*

9. 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: 1940363.

10. Bes-Rastrollo M, Sabaté J, Gómez-Gracia E, Alonso A, Martínez JA, Martínez-González MA. Nut consumption and weight gain in a Mediterranean cohort: The SUN study. *Obesity* (Silver Spring). 2007 Jan; 15 (1):107-116. PMID: 17228038.

11. Djoussé L, Rudich T, Gaziano JM. Nut consumption and risk of hypertension in US male physicians. *Clin Nutr.* 2009 Feb; 28 (1):10-14. Epub 2008 Oct 2. PMID: 18834651.

12. 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.

13. Salas-Salvadó J, Garcia-Arellano A, Estruch R, Marquez-Sandoval F, Corella D, Fiol M, Gómez-Gracia E, Viñoles E, Arós F, Herrera C, Lahoz C, Lapetra J, Perona JS, Muñoz-Aguado D, Martínez-González MA, Ros E; PREDIMED Investigators. Components of the Mediterranean-type food pattern and serum inflammatory markers among patients at high risk for cardiovascular disease. *Eur J Clin Nutr.* 2008 May; 62 (5): 651-659. Epub 2007 Apr 18. PMID: 17440519.

American Dietetic Association (ADA) Sort List for Almonds updated by USDA-NEL Searches

ADA Evidence Summaries and Worksheets were made available to the Subcommittee for review along with the NEL search. Last update August 2008.

1. What is the relationship between consuming almonds and cholesterol levels in subjects with hyperlipidemia?

Jenkins DJ, Kendall CW, Marchie A, Parker TL, Connelly PW, Qian W, Haight JS, Faulkner D, Vidgen E, Lapsley KG, Spiller GA. Dose response of almonds on coronary heart disease risk factors: blood lipids, oxidized low-density lipoproteins, lipoprotein (a), homocysteine, and pulmonary nitric oxide: a randomized, controlled, crossover trial. Circulation. 2002 Sep 10; 106 (11): 1, 327-1, 332. PMID: 12221048.

Sabate J, Haddad E, Tanzman JS, Jambazian P, Rajaram S. Serum lipid response to the graduated enrichment of a Step I diet with almonds: a randomized feeding trial. Am J Clin Nutr. 2003 Jun; 77 (6): 1, 379-1, 384. PMID: 12791613.

Spiller GA, Miller A, Olivera K, Reynolds J, Miller B, Morse SJ, Dewell A, Farquhar JW. Effects of plant-based diets high in raw or roasted almonds, or roasted almond butter on serum lipoproteins in humans. J Am Coll Nutr. 2003 Jun; 22 (3): 195-200. PMID: 12805245.

Spiller GA, Jenkins DJA, Bosello O, Gates JE, Cragen LN, Bruce B. Nuts and plasma lipids: an almond diet lowers LDL-C while preserving HDL-C. J Am Coll Nutr. 1998; 17 (3): 285-290.

Spiller GA, Jenkins DJA, Cragen LN, Gates JE, Bosella O, Berra K, Rudd C, Stevenson M, Superko R. Effect of a diet high in monounsaturated fat from almonds on plasma cholesterol and lipoproteins. J Am Coll Nutr. 1992; 11 (2): 126-130.

2. What is the relationship between consuming almonds and cholesterol levels in subjects with normal cholesterol levels?

Abbey M, Noakes M, Belling GB, Nestel PJ. Partial replacement of saturated fatty acids with almonds or walnuts lowers total plasma cholesterol and low-density-lipoprotein cholesterol. 1994. Am J Clin Nutr. 59 (5): 995-999.

Hyson DA, Schneeman BO, Davis PA. Almonds and almond oil have similar effects on plasma lipids and LDL oxidation in healthy men and women. J Nutr. 2002 Apr; 132 (4): 703-7. PMID: 11925464.

Kurlandsky SB, Stote KS. Cardioprotective effects of chocolate and almond consumption in healthy women. Nutr. Res. 2006; 26: 509-516.

Wien MA, Sabate JM, Ikle DN, Cole SE, Kandeel FR. Almonds vs complex carbohydrates in a weight reduction program. Int J Obes Relat Metab Disord. 2003 Nov; 27 (11): 1, 365-1, 372. Erratum in: *Int J Obes Relat Metab Disord*. 2004 Mar; 28 (3): 459. PMID: 14574348.

3. What is the relationship between consuming almonds and the risk of coronary heart disease?

No evidence exists to describe this relationship.

Note: ADA Sort List for "Nuts" dated 2004 provided to Subcommittee as ADA evidence summaries and conclusion statements.

Excluded articles

328

Articles	Reason for Exclusion
Allen LH. <u>Priority areas for research on the intake, composition, and health effects of tree nuts and peanuts</u>. *J Nutr.* 2008 Sep;138 (9):1, 763S-1, 765S. PMID: 18716183.	Conference summary on the health effects of nut consumption.
Barceló F, Perona JS, Prades J, Funari SS, Gomez-Gracia E, Conde M, Estruch R, Ruiz-Gutiérrez V. <u>Mediterranean-style diet effect on the structural properties of the erythrocyte cell membrane of hypertensive patients: the Prevencion con Dieta Mediterranea Study.</u> *Hypertension.* 2009 Nov; 54 (5): 1, 143-1, 150. Epub 2009 Oct 5. PMID: 19805640.	The variable study is erythrocyte membrane properties.
Berry SE, Tydeman EA, Lewis HB, Phalora R, Rosborough J, Picout DR, Ellis PR.<u>Manipulation of lipid bioaccessibility of almond seeds influences postprandial lipemia in healthy human subjects.</u> *Am J Clin Nutr.* 2008 Oct; 88 (4): 922-929. PMID: 18842777.	Postprandial study.
Blomhoff R, Carlsen MH, Andersen LF, Jacobs DR Jr. <u>Health benefits of nuts: potential role of antioxidants.</u> *Br J Nutr.*2006 Nov; 96 Suppl 2: S52-60. Erratum in: *Br J Nutr.* 2008 Feb; 99(2): 447-448. PMID: 17125534.	Narrative review; study of antioxidants in nuts.
Canales A, Benedí J, Nus M, Librelotto J, Sánchez-Montero JM, Sánchez-Muniz FJ. <u>Effect of walnut-enriched restructured meat in the antioxidant status of overweight/obese senior subjects with at least one extra CHD-risk factor.</u> *J Am Coll Nutr.*2007 Jun; 26 (3): 225-232. PMID: 17634167.	Captured in systematic reviewby Banel and Hu, 2009.
Chapman KM, Chan MW, Clark CD. <u>Factors influencing dairy calcium intake in women.</u> *J Am Coll Nutr.* 1995 Aug; 14 (4): 336-340. PMID: 8568109.	Study is about calcium rich foods.

Chung FM, Shieh TY, Yang YH, Chang DM, Shin SJ, Tsai JC, Chen TH, Tai TY, Lee YJ. <u>The role of angiotensin-converting enzyme gene insertion/deletion polymorphism for blood pressure regulation in areca nut chewers.</u> *Transl Res.* 2007 Jul; 150 (1): 58-65. Epub 2007 May 23. PMID: 17585864.	Study involves local nut chewed for the tannin content - areca tannin.
Djoussé L, Rudich T, Gaziano JM. <u>Nut consumption and risk of heart failure in the Physicians' Health Study I.</u> *Am J Clin Nutr.* 2008 Oct; 88 (4): 930-933. PMID:18842778.	Dependent variable not included in the question.
Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Ruiz-Gutiérrez V, Covas MI, Fiol M, Gómez-Gracia E, López-Sabater MC, Vinyoles E, Arós F, Conde M, Lahoz C, Lapetra J, Sáez G, Ros E; PREDIMED Study Investigators. <u>Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial.</u> *Ann Intern Med.* 2006 Jul 4; 145 (1): 1-11. PMID: 1681892.	High attrition rate >20%.
Garg ML, Blake RJ, Wills RB, Clayton EH. <u>Macadamia nut consumption modulates favourably risk factors for coronary artery disease in hypercholesterolemic subjects.</u> *Lipids.* 2007 Jun; 42 (6): 583-587. Epub 2007 Apr 17. PMID: 17437143.	High attrition rate >20%.
Gebauer SK, Psota TL, Harris WS, Kris-Etherton PM. <u>n-3 fatty acid dietary recommendations and food sources to achieve essentiality and cardiovascular benefits.</u> *Am J Clin Nutr.* 2006 Jun; 83 (6 Suppl): 1, 526S-1, 535S. Review. PMID: 16841863.	Narrative review n-3 oils (consider moving to n-3 marine and plants)
Gillen LJ, Tapsell LC, Patch CS, Owen A, Batterham M. <u>Structured dietary advice incorporating walnuts achieves optimal fat and energy balance in patients with type 2 diabetes mellitus.</u> *J Am Diet Assoc.* 2005 Jul;105 (7): 1, 087-1, 096. PMID: 15983525.	Variable studied is structural dietary advice to include walnut.

Jenkins DJ, Kendall CW, Marchie A, Josse AR, Nguyen TH, Faulkner DA, Lapsley KG, Blumberg J. Almonds reduce biomarkers of lipid peroxidation in older hyperlipidemic subjects. *J Nutr.* 2008 May; 138 (5): 908-913. PMID: 18424600.	Captured in systematic review by A meta-analysisby Phung et al, 2009.
Jenkins DJ, Kendall CW, Marchie A, Josse AR, Nguyen TH, Faulkner DA, Lapsley KG, Singer W. Effect of almonds on insulin secretion and insulin resistance in nondiabetic hyperlipidemic subjects: a randomized controlled crossover trial. *Metabolism.* 2008 Jul; 57 (7): 882-887. PMID: 18555827.	High attrition rate >20%.
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.	Narrative review.
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.	Non-RCT; Independent variable: portfolio diet; Outcomes not be attributable to almonds alone.
Jiménez-Gómez Y, López-Miranda J, Blanco-Colio LM, Marín C, Pérez-Martínez P, Ruano J, Paniagua JA, Rodríguez F, Egido J, Pérez-Jiménez F. Olive oil and walnut breakfasts reduce the postprandial inflammatory response in mononuclear cells compared with a butter breakfast in healthy men. *Atherosclerosis.* 2009 Jun; 204 (2): e70-6. Epub 2008 Sep 17. PMID: 18952211.	Postprandial study.
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.	Variable studied not included; plant sterols and red cell fragility.

Kranz S, Smiciklas-Wright H, Francis LA. Diet quality, added sugar, and dietary fiber intakes in American preschoolers. *Pediatr Dent.* 2006 Mar-Apr; 28 (2): 164-171; discussion 192-198. PMID: 16708792.	Study involves fiber, sugar and diet quality.
López-Uriarte P, Bulló M, Casas-Agustench P, Babio N, Salas-Salvadó J. Nuts and oxidation: a systematic review. *Nutr Rev.*2009 Sep; 67 (9): 497-508. Review. PMID: 19703258.	Review covers oxidation and oxidation enzymes.
Mercanligil SM, Arslan P, Alasalvar C, Okut E, Akgül E, Pinar A, Geyik PO, Tokgözo?lu L, Shahidi F. Effects of hazelnut-enriched diet on plasma cholesterol and lipoprotein profiles in hypercholesterolemic adult men. *Eur J Clin Nutr.* 2007 Feb; 61 (2): 212-220. Epub 2006 Sep 13. PMID: 16969381.	Small # N=15; Experimental diet (>250 kcal than baseline/control); methods issues.
Mozaffarian D. Does alpha-linolenic acid intake reduce the risk of coronary heart disease? A review of the evidence. *Altern Ther Health Med.*2005 May-Jun; 11 (3): 24-30; quiz 31, 79. Review. PMID: 15945135.	Study involves ALAintake. Move to n-3 plants.
Mukuddem-Petersen J, Stonehouse Oosthuizen W, Jerling JC, Hanekom SM, White Z. Effects of a high walnut and high cashew nut diet on selected markers of the metabolic syndrome: a controlled feeding trial. *Br J Nutr.* 2007 Jun; 97(6): 1, 144-1, 153. Epub 2007 Mar 7. PMID: 17381974	Captured in systematic review by Banel and Hu, 2009.
Muñoz KA, Krebs-Smith SM, Ballard-Barbash R, Cleveland LE. Food intakes of US children and adolescents compared with recommendations. *Pediatrics.*1997 Sep; 100 (3 Pt 1):323-329. Erratum in: Pediatrics. 1998 May;101(5):952-3. PMID: 9282700.	Study about food intake of children.
Nash SD, Westpfal M. Cardiovascular benefits of nuts. *Am J Cardiol.* 2005 Apr 15; 95 (8): 963-965. No abstract available. PMID: 15820163.	Narrative review.

332

Nies LK, Cymbala AA, Kasten SL, Lamprecht DG, Olson KL. Complementary and alternative therapies for the management of dyslipidemia. *Ann Pharmacother.*2006 Nov; 40 (11): 1, 984-1, 992. Epub 2006 Oct 17. Review. PMID: 17047144.	Review of therapeutic approaches.
Nitzan Kaluski D, Basch CE, Zybert P, Deckelbaum RJ, Shea S. Calcium intake in preschool children--a study of dietary patterns in a low socioeconomic community. *Public Health Rev.* 2001; 29 (1): 71-83. PMID: 11780718.	Study of dietary patterns.
Ritter-Gooder PK, Lewis NM, Heidal KB, Eskridge KM. Validity and reliability of a quantitative food frequency questionnaire measuring n-3 fatty acid intakes in cardiac patients in the Midwest: a validation pilot study. *J Am Diet Assoc.* 2006 Aug;106(8):1, 251-1, 255. PMID: 16863722.	Study involves validation of a FFQ.
Ros E. Nuts and novel biomarkers of cardiovascular disease. *Am J Clin Nutr.* 2009 May; 89 (5):1, 649S-1, 656S. Epub 2009 Mar 25. Review. PMID: 19321561.	Narrative review; used to identify references.
Ros E, Mataix J. Fatty acid composition of nuts--implications for cardiovascular health. *Br J Nutr.* 2006 Nov; 96 Suppl 2: S29-35. Erratum in: *Br J Nutr.* 2008 Feb;99 (2): 447-448. PMID: 17125530.	Narrative review.
Ros E, Núñez I, Pérez-Heras A, Serra M, Gilabert R, Casals E, Deulofeu R. A walnut diet improves endothelial function in hypercholesterolemic subjects: a randomized crossover trial. *Circulation.* 2004 Apr 6; 109 (13): 1, 609-1, 614. Epub 2004 Mar 22. PMID: 15037535.	Captured in systematic review by Banel and Hu, 2009.
Sabaté J, Ang Y. Nuts and health outcomes: new epidemiologic evidence. *Am J Clin Nutr.*2009 May; 89(5):1, 643S-1, 648S. Epub 2009 Mar 25. Review. PMID: 19321572.	Narrative review scoring evidence on nutrient intake.

333

Schutte AE, Van Rooyen JM, Huisman HW, Mukuddem-Petersen J, Oosthuizen W, Hanekom SM, Jerling JC. <u>Modulation of baroreflex sensitivity by walnuts versus cashew nuts in subjects with metabolic syndrome.</u> *Am J Hypertens.* 2006 Jun; 19 (6): 629-636. PMID: 16733237.	Dependent variable not included in the question.
Spaccarotella KJ, Kris-Etherton PM, Stone WL, Bagshaw DM, Fishell VK, West SG, Lawrence FR, Hartman TJ. <u>The effect of walnut intake on factors related to prostate and vascular health in older men.</u> *Nutr J.* 2008 May 2; 7: 13. PMID: 18454862.	Captured in systematic review Banel and Hu, 2009.
Tapsell LC, Gillen LJ, Patch CS, Batterham M, Owen A, Baré M, Kennedy M. <u>Including walnuts in a low-fat/modified-fat diet improves HDL cholesterol-to-total cholesterol ratios in patients with type 2 diabetes.</u> *Diabetes Care.* 2004 Dec; 27 (12): 2, 777-2, 783. PMID: 15562184.	Captured in systematic review Banel and Hu, 2009.
Tapsell LC, Batterham MJ, Teuss G, Tan SY, Dalton S, Quick CJ, Gillen LJ, Charlton KE. <u>Long-term effects of increased dietary polyunsaturated fat from walnuts on metabolic parameters in type II diabetes.</u> *Eur J Clin Nutr.* 2009 Aug; 63(8): 1, 008-1, 015. Epub 2009 Apr 8. PMID: 19352378.	High attrition rate, 30%.
Wolfe WS, Campbell CC. <u>Food pattern, diet quality, and related characteristics of schoolchildren in New York State.</u> J *Am Diet Assoc.*1993 Nov; 93 (11): 1, 280-1, 284. PMID: 8227878.	Out of date range; food patterns.
Zazpe I, Sanchez-Tainta A, Estruch R, Lamuela-Raventos RM, Schröder H, Salas-Salvado J, Corella D, Fiol M, Gomez-Gracia E, Aros F, Ros E, Ruíz-Gutierrez V, Iglesias P, Conde-Herrera M, Martinez-Gonzalez MA. <u>A large randomized individual and group intervention conducted by registered dietitians increased adherence to Mediterranean-type diets: the PREDIMED study.</u> *J Am Diet Assoc.* 2008 Jul; 108(7):1, 134-1, 144; discussion 1, 145. PMID: 18589019.	Study reports on behavioral intervention aspect of the same study captured earlier.

Zibaeenezhad MJ, Shamsnia SJ, Khorasani M. Walnut consumption in hyperlipidemic patients. *Angiology*. 2005 Sep-Oct; 56 (5): 581-583. PMID: 16193197.	Case-control study.