
2010 Dietary Guidelines Advisory Committee: Systematic Reviews of the Nutrient Adequacy 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 Nutrient Adequacy Subcommittee. The [*Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 2010*](#) summarizes these systematic review findings and provides interpretations and implications related to these reviews.

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ACKNOWLEDGEMENTS

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CHAPTER 1. OVERVIEW AND NEEDS FOR FUTURE RESEARCH

OVERVIEW

The Nutrient Adequacy Subcommittee (SC) addressed two major questions related to achieving the recommended intakes of nutrients:

- Folate intake and health outcomes in the US following mandatory folic acid fortification
- Selected dietary behaviors and nutrient intake.

A number of recently published, comprehensive, systematic reviews were available to inform the SC's review of several of its initial research questions.

Since January, 1998, the US Food and Drug Administration (FDA) has mandated the supplementation of all flour and uncooked cereal grains with folic acid, and the members of the SC have sought to evaluate the benefits and detrimental effects of the policy on the health of Americans. Because Canada has had a similar policy, the SC decided to include articles from Canada.

Meeting food and nutrient intake recommendations is challenging for many Americans. To gain an understanding of the depth and breadth of research in these areas, the SC conducted a series of exploratory literature searches. The exploratory searches helped the SC narrow the scope of its Nutrition Evidence Library (NEL) systematic reviews to the following three individual behaviors:

- Breakfast consumption
- Snacking
- Eating frequency.

The *Energy Balance and Weight Management Subcommittee* examined complementary questions relating to the effects of breakfast intake, snacking and eating frequency on energy balance and weight maintenance.

NEEDS FOR FUTURE RESEARCH

Nutrients and Dietary Components Over-Consumed

1. Develop and test behavior-based interventions designed to lower dietary intakes of nutrients and dietary components that are over-consumed, focusing on solid fats and added sugars (SoFAS).

- **Rationale:** SoFAS contribute a substantial number of calories to the typical American diet without adding important micronutrients. Interventions that are proven successful in lowering dietary components that are over-consumed are needed to assist consumers and health care providers.

Food Groups and Selected Dietary Components Under-Consumed

2. Conduct clinical trials in children and adults to critically examine the impact of adherence to the 2010 Dietary Guidelines for Americans as a total dietary approach to a healthy lifestyle on body weight change, cardiovascular disease (CVD), type 2 diabetes, cancer and osteoporosis and related clinical endpoints.

- **Rationale:** Theoretically, food-based dietary guidance supports achievement of nutrient adequacy across age-sex groups. Total diets, including variation in eating and dietary patterns, compared to individual nutrients, have been insufficiently tested for their health outcome.

3. Quantitatively and qualitatively investigate how the food environment facilitates or hinders achievement of food groups and dietary components recommendations, notably in individuals enrolled in food assistance programs, particularly children participating in school breakfast and lunch programs and across various ethnic and cultural groups.

- **Rationale:** Compliance with dietary guidance is poor. Understanding the food environment at all levels will assist individuals and shape public policy toward intakes that meet recommendations for food groups and dietary components.

Vitamin D

4. Conduct high-quality, long-term dose-response studies with relevant health outcomes including bone, as well as functional outcomes related to the immune system, autoimmune disorders and chronic diseases such as coronary heart disease (CHD), hypertension (HTN), cancer and diabetes.

- **Rationale:** There is a need for additional research on the relation between threshold values of 25(OH)D and relevant functional outcomes at each life stage and in understudied populations.

5. Investigate the metabolic partitioning, fate and mobilization of key vitamin D metabolites at recommended and greater than recommended levels.

- **Rationale:** Studies that assess the availability of stored vitamin D, and relative contributions of endogenously produced and dietary vitamin D, and impact of important confounders, such as body weight and body fat on vitamin status are warranted (Brannon, 2008b).

Folate

6. Conduct studies on the long-term health impact of fortification on neural tube defects (NTDs), colorectal cancer (CRC), stroke, cognitive function and other health outcomes, such as emerging evidence suggesting that high folic acid intakes in some pregnant women may lead to asthma in their offspring (Whitrow, 2009), to fully understand the impact of this ecological experiment.

- **Rationale:** A substantial amount of time has elapsed since the US and Canada mandated folic acid fortification. Since 1998, many research studies have evaluated the benefits and risks of fortification. Much of the research demonstrated benefit, while some of the research has shown increased health risk. Further research is warranted.

Vitamin, Mineral, and Nutrient Supplements

7. Conduct studies on the precision in self-reported intakes of multivitamin/mineral supplements.

- **Rationale:** More than one-half of the population reports the use of nutrient supplements; however, the frequency and consistency of this use is sporadic for many. Greater accuracy in self-reported use of nutrient supplements is important to understanding short- and long-term health effects.

8. Develop accurate composition and bioavailability data across the multitude of vitamin, mineral and nutrient supplements. Evaluate outcomes based on nutrient composition and bioavailability within the multivitamin/mineral matrix.

- **Rationale:** Precise composition of supplements is critical to determining interactions of nutrients within each supplement preparation and potential benefits and risks of the matrix of nutrients from supplements consumed with foods.

9. Conduct randomized controlled trials that rigorously test health outcomes, including safety and risk assessments, of nutrient supplements in a diverse range of healthy population groups.

- **Rationale:** Research on the efficacy and safety of nutrient supplements is vital to the guidance of public policy recommendations, given that the majority of Americans use nutrient supplements at any point in time.

Nutrient Adequacy and Eating Behaviors

10. Convene a consensus panel to define breakfast, breakfast consumers and breakfast skipping; snacking; and eating frequency that can be consistently applied to studies.

- **Rationale:** Identifying healthful eating behaviors is important to primary prevention of chronic disease in Americans. Common definitions of specific eating behaviors are vital to testing and understanding the role of these behaviors in health and wellness.

11. Conduct longitudinal studies on the cumulative nutritional risks of breakfast skipping and health benefits of breakfast consumption. Identify critical components of breakfast and snacks, such as vegetables, fruits, whole grains and fluid milk and milk products, and their related health benefits.

- **Rationale:** Breakfast intake is associated with positive outcomes such as improved school performance among children. Further understanding of other nutrition-related health benefits is needed.

CHAPTER 2. DIETARY BEHAVIORS AND NUTRIENT INTAKE – BREAKFAST INTAKE

IS BREAKFAST INTAKE ASSOCIATED WITH ACHIEVING RECOMMENDED NUTRIENT INTAKES?

Conclusion statement

Moderate evidence supports a positive relationship between the behavior of breakfast consumption and intakes of certain nutrients in children, adolescents, and adults.

Grade

Moderate

Evidence summary overview

This conclusion is based on the review of 15 studies published since 2004. Of these 15 studies, one is a systematic review that includes studies with children and adolescents (Rampersaud et al, 2005), while four original studies include only adults (Kerver et al, 2006; Song et al, 2005; van der Heijden et al, 2007; Williams, 2005), nine evaluate children or adolescents (Affenito et al, 2005; Dubois et al, 2008; Matthys et al, 2007; Nelson et al, 2007; Stockman et al, 2004; Timlin et al, 2009; Williams et al, 2007; Williams et al, 2009; Woodruff et al, 2008) and one includes adolescents and adults (Song et al, 2006). Not all nutrients are evaluated in all studies. However, in those studies in which selected micronutrients are examined, individuals who consume breakfast on a daily basis consistently have higher intakes of thiamin, niacin, riboflavin, vitamins B₆ and B₁₂, dietary folate, vitamins A and C, calcium, iron, magnesium, phosphorus, potassium and zinc. In studies that include dietary fiber, breakfast intake is associated with higher intakes. An equal number of studies show that breakfast consumers have higher, lower, or no difference in total fat, saturated fat, cholesterol and sodium intakes compared to non-consumers of breakfast.

Evidence summary paragraphs

Affenito et al, 2005 (positive quality), conducted a longitudinal cohort study to examine the association of breakfast intake with dietary calcium, fiber and body mass index (BMI). The study used data (1,166 white and 1,213 African-Americans aged nine or 10 years at baseline) from the National Heart, Lung and Blood Institute (NHLBI) Growth and Health Study, a nine-year, longitudinal cohort with annual three-day food records. Generalized estimation equations methodology (adjusting for effects of site, age, race, parental education, physical activity and total energy intake) was used to examine differences in frequency of breakfast eating by age and race. The number of days breakfast was eaten tended to decrease with increasing age. Approximately 77% of white girls and 57% of African-American girls eat breakfast on all three days, compared with 32% and 22%, respectively, by age 19. White girls reported greater frequency of breakfast consumption than African-American girls did ($X^2[1]=203.42$, $P<0.0001$) on all three days and the racial difference decreased with increasing age. Frequency of breakfast eating was found to be significantly associated with calcium intake ($X^2[3]=81.29$, $P<0.0001$). Number of days eating breakfast was significantly

associated with an increase in fiber intake ($X^2[3]=86.53$, $P<0.001$), with the greatest difference (adjusted estimate of 1.13g.) between girls who ate breakfast all three days and those who reported no breakfast eating. In conclusion, days eating breakfast were associated with higher calcium and fiber intake, regardless if adjustment variables.

Dubois et al, 2008 (positive quality), used cross-sectional data from the Longitudinal Study of Child Development in Quebec (1998-2012) (LSCDQ) to examine the association between skipping breakfast, daily energy, macronutrients and food intakes and BMI in 1,549 Canadian pre-school children, aged 49 (SD 3.12) months old. Food consumption and anthropometric measurements were derived from parent or day-care attendant's responses to 24-hour recall interviews and eating behavior questionnaires. Ten percent of children ate breakfast on fewer than seven days per week. Total daily energy and nutrients intakes were not significantly different from those of pre-school children who ate breakfast every day, except for protein intake (55.8g for breakfast skippers and 58.7g for breakfast eaters; $P\leq 0.05$). Overall it was observed that eating breakfast every day was associated with having a more even distribution of energy intake across meals throughout the day.

Kerver et al, 2006 (positive quality), used cross-sectional data from the Third National Health and Nutrition Examination (NHANES) survey to test the hypothesis that specific meal and snack patterns are associated with selected nutrient intakes. Subjects in this study were 15,978 US adults 20 years and older who self-reported meals or snacks. For this analysis, meals reported as breakfast and brunch were collapsed into the breakfast group. Subjects were divided into categories of daily eating frequency (one to two, three, four, five and at least six), based on the sample distribution and 17.7% of the population reported skipping breakfast. After adjusting for sex, ethnicity, alcohol intake, vitamins, minerals, BMI, physical activity and income, the breakfast skippers group (which consumed only lunch, dinner and two snacks), when compared with the breakfast, lunch and dinner group, had lower intakes of all micronutrients analyzed (vitamin B₆ 1.83±0.04mg; folic acid 252±97.29µg; vitamin C 97.6±4.19mg; calcium 818±26.8mg; magnesium 310±5.79mg; iron 14.5±0.25mg; potassium 2,995±67.4mg; and dietary fiber 16.8±0.37g.) except sodium (3,810±66.5mg) ($P<0.0001$).

Matthys et al, 2007 (positive quality), analyzed data from a cross-sectional survey to describe breakfast consumption patterns. A total of 341 adolescents (13-18 years old), selected from all educational levels in the Belgian secondary school system, completed a seven-day food record. Qualitative and quantitative aspects of breakfast were combined into a so-called "individual breakfast score" on the basis of food groups present in the breakfast and the amount of energy. Overall, the individual breakfast score was less than three (i.e., never eat or usually do not eat breakfast). In both boys and girls, the energy intake and the proportional contribution of proteins were significantly higher in subjects having a good-quality breakfast, score of 5 ($P=0.022$ and <0.001 respectively). Girls who consumed a good-quality breakfast had a significantly higher proportional intake of polysaccharides than the low-quality breakfast consumers ($P=0.002$). In both boys and girls, the intake at breakfast of the selected micronutrients (calcium, phosphorous, iron, magnesium, thiamin, riboflavin, vitamin C) was significantly higher in subjects consuming a good-quality breakfast ($P<0.001$ for all micronutrients). Both male and female adolescents who consumed a good-quality breakfast had significantly higher intakes of bread, fruit, vegetables, milk

and milk products, and fruit juice, while their intake of soft drinks was significantly lower than those who consumed a low-quality breakfast. Female good-quality breakfast consumers also had significantly higher intakes of cereal products, cheese and water. In conclusion, the consumer of a good-quality breakfast has a better overall dietary pattern on a nutrient and food-group level, than the consumer of a low-quality breakfast. Note: No adjustments for confounders were mentioned.

Nelson et al, 2007 (positive quality), in a cross-sectional study undertook secondary analysis of the 1997 National Diet and Nutrition Survey of Young People aged four to 18 years in order to describe the contribution of school meals to daily food and nutrient intakes and to compare the findings with data collected in English primary and secondary schools in 2004-2005. Seven-day food consumption data according to age, sex, household income, free school meals and breakfast consumption for 1,456 school children (743 primary- and 713 secondary-school pupils) were evaluated. Sixty-two percent of pupils reported having breakfast with cereal, 29% had breakfast without cereal and overall 9% had no breakfast. The percentage not reporting breakfast was lowest in primary-school boys (4%) and girls (5%), and the highest was in secondary-school boys (9%) and girls (25%). Nutrient intakes of pupils who did not have breakfast were significantly lower than of those who did have breakfast, whether or not cereal was included (data were not available). However, the contribution to daily nutrient intakes from school meals was highest in those who had not had breakfast, intermediate in those who had breakfast without cereal and lowest in those who had breakfast with cereal.

Rampersaud et al, 2005 (neutral quality), in a systematic review evaluated 47 studies examining the association of breakfast consumption with nutritional adequacy (nine studies), body weight (16 studies) and academic performance (22 studies) in children and in adolescents. Although the quality of breakfast was variable within and between studies, children who reported eating breakfast on a consistent basis tended to have superior nutritional profiles than their breakfast-skipping peers. Breakfast eaters generally consumed more daily calories yet were less likely to be overweight, but not all studies associated breakfast skipping with overweight. Two studies reported that children and adolescents skipped breakfast more than any other meal. The breakfast-skipping prevalence reported in three other studies ranged from 12% to 34%. Six studies showed that breakfast eaters tended to have a higher total daily intake of energy compared with breakfast skippers, suggesting that skippers did not consume more calories at other meals to compensate for the deficit. Correspondingly, breakfast eaters tended to have higher daily intakes of total carbohydrate (CHO) (from two studies), total protein (from six studies), total fat (from two studies) and saturated fat (from one study). Four studies showed that fiber intake was significantly higher in breakfast eaters vs. skippers and the inclusion of a ready-to-eat cereal seemed to contribute to daily fiber intake. Associations of breakfast habits on serum lipids have been inconsistent. Breakfast eaters have higher daily intakes of micronutrients and are more likely to meet nutrient intake recommendations compared with breakfast skippers. Nutrients that seemed to be particularly affected across a variety of studies and population groups include vitamins A and C, riboflavin, calcium, zinc and iron. Data related to the effects of breakfast on micronutrient status (i.e., blood or tissue concentrations) are not widely reported except with regard to ready-to-eat cereal

(RTEC) consumption. Seven studies showed that children and adolescents who skipped breakfast did not, on average, make up the nutrient deficits at other meals during the day, which has also been observed in adults (from two studies). The data from one population-based survey indicate that children and adolescents tend to have similar nutrient intakes from daily meals other than breakfast, regardless of whether they skip or consume breakfast. The same study mentioned that female adolescents who skipped breakfast had lower intakes of nutrients at other meals compared with female adolescent breakfast consumers. Several studies showed that the inclusion of RTEC and milk enhance calcium and iron intake.

Song WO et al, 2005 (positive quality), used cross-sectional data to test the hypothesis that breakfast consumption is associated with weight status measure by BMI, using data from the NHANES 1999-2000. Survey participants are breakfast consumers who reported consuming a meal they identified as breakfast. Also, dietary recalls were used to estimate daily intake of total energy, fiber, fat, CHO and protein with reference of the US Department of Agriculture (USDA) Survey Database. Data from men and women ≥ 19 years ($N=4,218$) were evaluated using multiple logistic and linear regression models, with controls for covariates (age, sex, ethnicity, smoking habits and energy intake). Breakfast consumers were more likely than breakfast non-consumers to be older, female, white, non-smokers, regular exercisers (9.7% vs. 6.1%; $P<0.001$) and trying to control their weight (10.8% vs. 6.3%; $P<0.01$). Seventy-seven percent of adults consumed breakfast in one given day with significant difference between the sexes (74.7 % men vs. 79.4% women [$P<0.05$]). Rate of breakfast consumption increased with age from 62.8% among 19- to 29-years-olds to 92.5% among participants aged 70 years old and older. The percent of breakfast consumption was highest among whites (80.4%), compared with 68.7% for African-Americans and 71.7% for Hispanics. Energy intake from fat was not significantly different between breakfast consumers and non-consumers (33% vs. 32%). Among men and women, breakfast consumers had significantly higher daily dietary fiber intake than breakfast non-consumers ($17\pm 0.3g$ vs. $12\pm 0.4g$) and RTEC breakfast consumers also had significantly higher daily dietary fiber intake than non-RTEC breakfast consumers ($P<0.001$ for both comparisons). In conclusion, when evaluating the association of breakfast consumption with the lower prevalence of overweight and obesity, types of meals should be considered as an important determinant.

Song et al, 2006 (positive quality), used cross-sectional data to test the association between the intake of RTEC, milk, and calcium using data from the NHANES 1999-2000. Data were stratified according to sex, age and by consumption of breakfast, RTEC and milk. Breakfast consumers tend to be older and white ($P<0.01$). The highest prevalence of breakfast consumption was found among four- to eight-year-old children (93.5%), adults older than age 71 years (92.1%) and whites (79.3%). Multiple regression analysis was performed to determine the predictability of total calcium intake from breakfast and milk or RTEC consumption. In this analysis, children aged four to eight years were excluded because they were found to have a distinctive amount and pattern of RTEC and milk consumption, leaving a sample of 6,631 subjects. Breakfast consumption, milk with RTEC and milk without RTEC were all significant predictors for daily calcium intake ($P<0.05$) after controlling for age and

ethnicity.

Stockman et al, 2005 (positive quality), conducted a prospective cohort study to determine and compare the distribution of energy and nutrient intakes among meals and snacks, and related eating occasion frequency to the BMI of 180 healthy adolescents males (14 to 18 years old) recruited from local school and community groups in Canada. Anthropometric information and 24-hour diet recall on three consecutive days, including two weekdays and one weekend day, were evaluated. Also, subjects were instructed to self-report the type of every eating occasion, such as breakfast, lunch, dinner and snacks. The relation of breakfast consumption to energy and nutrient intakes was evaluated by categorizing subjects into consistent (consumed breakfast all three days) or inconsistent (skipped breakfast at least one of the three days.) Both dinner and breakfast were the largest contributors of calcium (328.8 ± 19.4 and 299.0 ± 16.0 mg, respectively) and iron (4.50 ± 0.20 and 5.39 ± 0.35 mg, respectively.) Conversely, breakfast was the smallest contributor of energy, CHOs, total fat and saturated fat. Breakfast was the most frequently skipped meal (26%) on at least once of the three days of food records. Consistent breakfast consumers had significantly higher iron intakes relative to inconsistent breakfast consumers (16.4 ± 0.49 and 13.5 ± 0.91 , $P=0.0041$). However, there were no significant differences in energy, macronutrient, cholesterol, dietary fiber, calcium or sodium intakes.

Timlin et al, 2009 (positive quality), examined the association of breakfast frequency in both cross-sectional and prospective data from the Eating Among Teens (EAT) project, which was a five-year longitudinal study of eating patterns and weight concerns among adolescents from the Minneapolis/St. Paul, Minnesota, metropolitan area. Surveys were completed in 1998-1999 (time 1) and 2003-2004 (time 2), with a final sample size of 2,216 (1,007 boys and 1,215 girls). The mean age at time 1 was 14.9 ± 1.6 and at time 2 was 19.4 ± 1.7 years. The ethnic background of the participants was: 63.1% white, 9.9% black, 17.7% Asian, 3.8% Hispanic, 2.7% Native American and 2.85% mixed or other. Breakfast frequency was assessed with the question "During the past week, how many days did you eat breakfast?" Respondents were classified as never, intermittent and daily breakfast eaters. Also, dietary intake was assessed with the 149-item Youth and Adolescent Food Frequency Questionnaire (YAQ). Results showed that individuals who never ate breakfast were more likely to be girls (16.4%) than boys (13.0%; $P=0.03$) at baseline. The greatest change over time was observed in boys, with 16.8% decrease of breakfast intake from time 1 to time 2, but no significant (NS) difference by sex. Overall, those who ate breakfast daily were more likely to be white, to come from a higher socio-economic status, and to engage in higher levels of physical activity. In girls, the overall diet of daily breakfast eaters compared with those who intermittently or never ate breakfast was higher in total energy ($P<0.01$ for both), fiber ($P<0.05$ and $P<0.01$, respectively) and cholesterol ($P<0.01$ for both). In boys, statistically significant differences by daily breakfast eaters and intermittent eater were observed for dietary CHO ($P<0.05$) and fiber ($P<0.05$) (higher for daily breakfast) and for the percentage of calories from saturated fat (lower for daily breakfast) ($P<0.05$). However, values were not significantly different for respondents who had breakfast daily or never.

Van der Heijden et al, 2007 (positive quality), conducted a prospective study aimed to investigate the association between breakfast consumption and long-term weight gain

in an adult male population over a 10-year period. Data on body weight, dietary factors, and lifestyle variables were obtained from the Health Professionals Follow-up Study. Dietary data were assessed every four years, using a semi-quantitative food frequency questionnaire (FFQ). This analysis used 1992 as a baseline, which included data from 20,064 healthy men. Of all men, 16.9% reported not usually consuming breakfast. At baseline, breakfast consumers had a greater estimated daily percentage of energy from carbohydrates (50.1 vs. 46.1%) and estimated total fiber (7.3 vs. 5.0g per day) intake and whole grain intake (29.4 vs. 17.5g per day). Breakfast consumers had lower estimated daily percentage of energy from fat (30.6 vs. 32.6%), polyunsaturated fat (PUFA) (5.9 vs. 6.0%), monounsaturated fat (MUFA) (12.0 vs. 12.8%), saturated fat (10.1 vs. 11.0%) and trans-fat (1.5 vs. 1.7%).

Williams, 2005 (positive neutral quality), conducted a cross-sectional study, the Australian Bureau of Statistics (ABS) was commissioned by Kellogg's (Australia), to analyze data collected in the 1995-1996 Australian National Nutrition Survey. The study aimed to describe the nutrients provided to Australian adults by the breakfast meal and to compare the food and nutrient intakes and health of regular breakfast eaters and breakfast skippers. The survey included 24-hour recalls, physical measurements, and a food habits questionnaire of 10,851 Australians, aged 19 years and older. The findings showed that the typical Australian breakfast was low in fat, high in CHO, and a good source of thiamin, riboflavin, niacin, calcium and magnesium. People who did not eat breakfast cereal were much more likely to have inadequate nutrient intakes, especially of thiamin, riboflavin, calcium, magnesium and iron. Those who regularly ate breakfast had significantly better diets overall, higher in CHOs and dietary fiber, and richer in almost all vitamins and minerals, especially thiamin, riboflavin, folate, calcium, iron and magnesium. For every nutrient, a significantly higher proportion of eaters than skippers met the Reference Daily Intake (RDI) or dietary target on the day of the survey. These differences were significant for thiamin, riboflavin, folate, calcium, and magnesium and also (for women only) iron. The proportion of skippers in the oldest age groups consuming less than 70% of the RDI was more than twice that of breakfast eaters for almost every nutrient, including protein. Adult breakfast eaters also consumed significantly more servings of cereal foods in the day than the breakfast skippers (males, 6.3 vs. 3.4, $P<0.001$; females (4.4 vs. 2.8, $P<0.001$) and were more than twice as likely to meet the target for servings of cereal foods (28% vs. 14%, $P<0.001$). Adult male breakfast eaters were also more likely than skippers to meet the target of >55% energy from CHO (18% vs. 10%, $P<0.001$). More eaters met the dietary targets for fiber than breakfast skippers, especially in the oldest age groups (males aged 65+, 26.4% vs. 5.4%, $P<0.001$; females aged 55+, 16.1% vs. 2.1%, $P<0.001$).

Williams et al, 2009 (positive quality), conducted a cross-sectional study to assess whether weight status, nutrient intake and dietary adequacy were associated with breakfast consumption patterns. The study sample, African-American (AA) children aged one to 12 years ($N=1,389$), was from the 1999-2002 NHANES. There were 7.4% of one- to five-year-old children and 16.9% of six- to 12-year old children who skipped breakfast. Breakfast skippers had lower mean energy intakes than children who consumed RTEC or other breakfast. Compared with those who either skipped breakfast or consumed other breakfast foods, children in the RTEC breakfast category

had the highest mean daily intakes of vitamins A and B₁₂, thiamin, riboflavin, folate, and iron ($P \leq 0.05$ for all). No differences were found in mean daily intakes of vitamin B₆, niacin, calcium and zinc between breakfast skippers and other breakfast consumers. Those eating RTEC had lower intakes of vitamin E than breakfast skippers ($P \leq 0.05$), and children who consumed RTEC for breakfast had the highest intakes from CHOs and total sugars and the lowest intake from total fat when compared with the breakfast skippers and other breakfast consumers groups ($P \leq 0.05$). Breakfast skippers and other breakfast consumers had higher intakes of MUFA and PUFA than RTEC breakfast consumers ($P \leq 0.05$).

Woodruff et al, 2008 (positive quality), used cross-sectional data to describe weight concerns, dieting and meal skipping of adolescents, and determine associations with Healthy Eating Index-C (HEI-C). Participants were recruited from Ontario and Alberta schools using a two-stage stratified, randomized, sampling procedure. The final sample included 1,826 students from grades nine and 10. Diet quality was assessed using a modified version of the US-based HEI, possible scores range from zero to 100, with 100 points referring to perfect diet quality and lower status indicating larger deviations from the recommended intakes: Poor (≤ 50 HEI-C score), needs improvement (50-80 HEI-C score) or good (> 80 HEI-C score). More females than males skipped breakfast (30% vs. 24%; $P = 0.008$). No differences in meal skipping were observed by grade, body weight, body weight status. The mean HEI-C score across all participants was 69.0% (± 13.2), falling into the "Needs Improvement" category. Furthermore, mean diet quality scores were higher for those consuming breakfast (71 ± 12.4 vs. 64 ± 14.0 ; $P < 0.001$). Participants who skipped breakfast were more likely to have a worse diet quality (OR=0.42 95% CI: 0.33, 0.54) ($P < 0.001$) than those who consumed the meal.

Williams et al, 2007 (positive quality), conducted a cross-sectional study, Kellogg's (Australia) commissioned the Australian Bureau of Statistics (ABS), to analyze data collected in the 1995-1996 Australian National Nutrition Survey. The study aimed to describe the nutrients provided to Australian children by the breakfast meal and to compare the food and nutrient intakes and health of regular breakfast eaters and breakfast skippers. The survey included 24-hour recalls, physical measurements and food habits questionnaire of 3,007 Australian children, aged two to 18 years. Those having breakfast five days or more a week are classified as regular breakfast eaters, while those who said they ate it rarely or never are classified as breakfast skippers. The breakfast meal was self-defined by the participants (data from those two- to 14-years old were obtained through the parent or guardian). The breakfast meal provided between 12% and 19% of the daily energy intake. Those who regularly ate breakfast had better nutrient intakes overall, higher in dietary fiber and in almost all vitamins and minerals, especially thiamin, riboflavin, folate, calcium, iron and magnesium. These differences, however, were not significantly different in the older age groups. There were no significant (NS) differences in daily intakes of sugar or fat between breakfast eaters and skippers, except for boys aged eight to 11 years.

Overview table

Author, Year, Study Design, Class, Rating	Population/ Subjects	Data Collection and Methods	Definitions of Skipping Breakfast	Prevalence of Skipping Breakfast	Significant Outcomes
<p>Affenito SG et al 2005</p> <p>Study Design: Longitudinal Cohort Study</p> <p>Class: B</p> <p>Rating: Positive Quality</p>	<p>Data from the NHLBI Growth and Health study.</p> <p>Nine-year longitudinal cohort study.</p> <p>Baseline N=1,015 (100% female; 57% white, 43% African-American).</p> <p>End of Study N=964.</p> <p>Age at baseline: Nine- to 10-year-old children.</p> <p>Age at end of study: 18-19-year-old adults.</p>	<p>Three-day diet record, annually for nine years.</p> <p>Retention rates were: 82% at visit 7th, 89% at visit 10th.</p>	<p>B=intake between 5 am-10 am weekdays or 5 am-11 am weekend days.</p> <p>B Skipper=no B reported on any day of three-day record.</p> <p>B Skipper compared to:</p> <p>One day of B</p> <p>Two days of B</p> <p>Three days of B.</p>	<p>0.9% of white, nine-year-old girls.</p> <p>2.5% of African-American, nine-year-old girls.</p> <p>19.1% of white, 19-year-old girls.</p> <p>24.2% of African-American, 19-year-old girls.</p>	<p>One, two or three-day B Consumers vs. B Skippers had greater estimated daily intakes of calcium and fiber when adjusted for total energy intake.</p> <p>Three-day B Consumers vs. B Skippers had greater estimated total daily calcium (75.6mg per day) and fiber (1.13g per day) intakes when adjusted for race, age, study site, total energy intake, physical activity and parental education.</p>

<p>Dubois L et al 2009</p> <p>Study Design: Cross-sectional Study</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Data from the Longitudinal Study of Child Development, Quebec.</p> <p>N=2,103.</p> <p>N (final)=1,520</p>	<p>24-hour diet recall.</p> <p>Eating behavior survey for B pattern.</p>	<p>1,549 pre-school children in the Longitudinal Study of Child Development in Quebec (1998-2012, LSCDQ).</p> <p>Quebec, Canada.</p>	<p>B=food intake between 6-9 am.</p> <p>B Skipper=not consuming B every day of the week vs. B Consumer=consuming B every day of the week.</p>	<p>B Consumers vs. B Skippers Total daily energy and nutrient intakes were ND different, except for the protein intake (55.8g for B skippers and 58.7g for B eaters (P≤0.05) consumed more energy, CHO and fat at B and total daily protein.</p> <p>B Consumers vs. B Skippers consumed more vegetables, grains and milk products</p>
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<p>Kerver JM, Yang EJ et al, 2006</p> <p>Study Design: Cross-sectional design</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Data from the NHANES III, 1988-1994.</p> <p>N=15,978 (52.6% female).</p> <p>Age: 20+ year-old adults.</p> <p>82.7% non-Hispanic White</p> <p>11.8% non-Hispanic Black</p> <p>5.5% Mexican-American.</p>	<p>24-hour diet recall.</p>	<p>B=self-identified first eating occasion in 24-hour recall.</p> <p>Eating frequency per day:</p> <p>One to two times per day</p> <p>Three times per day</p> <p>Four times per day</p> <p>Five times per day</p> <p>At least six times per day</p> <p>Eating intake patterns of Breakfast (B), Lunch (L), Dinner (D), Snacks (S):</p> <p>B, L, D, at least two S</p> <p>B, L, D, one S</p> <p>B, L, at least two S</p> <p>B, L, D</p> <p>L, D, at least two S</p> <p>Other.</p> <p>B Skipper=L, D, at least two S eating pattern.</p>	<p>17.7% of 20+ year-old adults.</p>	<p>B skippers group consuming lunch, dinner and two snacks, compared with the consumers of B, L and D group, had the lowest intakes of all micronutrients analyzed (Vitamin B₆ 1.83±0.04g, folic acid 252±97.29ug, vitamin C 97.6±4.19mg, calcium 818±26.8mg, magnesium 310±5.79mg, iron 14.5±0.25mg, potassium 2,995±67.4mg and dietary fiber 16.8±0.37g) examined except sodium (3,810±66.5mg) (P<0.0001), after adjusting for sex, ethnicity, alcohol intake, vitamins, minerals, BMI, physical activity and income.</p>
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<p>Matthys C, De Henauw S et al, 2007</p> <p>Study Design: Cross-sectional survey</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Data from a cross-sectional survey in the Belgian secondary school system.</p> <p>N=341 (62% female).</p> <p>13- to 18-year-old adolescents.</p>	<p>Seven-day diet record.</p>	<p>B=self-identified first eating occasion after waking that included a solid food or beverage.</p> <p>B Skipper=no B or limited B (<100kcal)=B Label.</p> <p>No B, usually no B, usually low quality B, or infrequently good quality B=B Score.</p> <p>Label 1+Score 1-3=B Skipper (or Low Quality) vs. Label 5+Score 5=B Consumer (B nearly every day or Good Quality).</p> <p>Quantitative aspects of B included:</p> <p>Frequency of having B</p> <p>Relative contribution of target food groups (cereal, dairy products and fruit/vegetable).</p> <p>Qualitative and quantitative aspects of B were combined into a so-called "individual breakfast score."</p>	<p>13.2% of 13- to 18-year-old boys.</p> <p>16.9% of 13- to 18-year-old girls.</p>	<p>B Consumers (Good Quality) vs. B Skippers (Low Quality) Overall, the individual B score was less than three (never eat or usually do not eat B). For boys and girls, the energy intake and the proportional contribution of proteins were significantly ↑ in subjects having a good-quality B, score of 5 (P=0.022, and <0.001, respectively).</p> <p>Girls who consumed a good-quality B had a significantly ↑ proportional intake of polysaccharides, than the low-quality B consumers (P=0.002).</p> <p>For boys and girls, the intake at B of the selected micronutrients (Calcium, phosphorous, iron, magnesium, thiamin, riboflavin, vitamin C) was significantly ↑ in subjects consuming a good-quality B (P<0.001 for all micronutrients.).</p> <p>B Consumers (Good Quality) vs. B Skippers (Low Quality) had ↑ estimated intakes of bread, fruit, cereal (girls only), vegetables, milk and milk products, cheese (girls only), fruit juice, water and ↓ estimated intakes of soft drinks.</p>
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<p>Nelson M, Lowes K et al, 2007</p> <p>Study Design: Cross-sectional study</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Data from the National Diet and Nutrition Survey of Young People, 1997 (England). N=1,456.</p> <p>Age: Four-to 18-year-old children and adolescents.</p>	<p>Seven-day diet record, weighed foods.</p>	<p>B Skipper=not reported (assume missed B on all days of seven-day record).</p>	<p>9% of four- to 18-year-old children and adolescents.</p>	<p>62% consumed Cereal B. 29% consumed non-Cereal B.</p> <p>B Consumers vs. B Skippers had greater daily intakes of energy, total protein, CHO and fat, non-starch polysaccharides, folate, vitamins A and C, calcium, iron, zinc and sodium.</p>
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<p>Rampersaud GC, Pereira MA et al, 2005</p> <p>Study Design: Narrative Review</p> <p>Class: R</p> <p>Rating: Neutral Quality</p>	<p>Summary report.</p> <p>Medline search from 1970 through February 2004.</p> <p>Terms: Breakfast, children and adolescents.</p> <p>47 articles were reviewed:</p> <p>Nine related to nutrient adequacy</p> <p>16 related to body weight</p> <p>22 related to cognitive or academic performance.</p>	<p>Not applicable.</p>	<p>Not applicable.</p>	<p>Not applicable.</p>	<p>Breakfast eaters generally consumed more daily calories, yet were less likely to be overweight, and not all studies associated B skipping with overweight.</p> <p>Two studies report that children and adolescents skipped B more than any other meal. The B-skipping prevalence (day of survey) reported in other three studies ranged from 12% to 34%.</p> <p>Six studies showed that B eaters tended to have a ↑ total daily intake of energy compared with B skippers, suggesting that skippers did not consume more calories at other meals to compensate for the deficit. Correspondingly, B eaters tended to have ↑ daily intakes of total CHO (from two studies), total protein (from six studies), total fat (from two studies) and saturated fat (one study).</p> <p>Four studies showed that fiber intake was significantly ↑ in B eaters vs. skippers and the inclusion of a RTEC seemed to contribute to daily fiber intake. Associations of B habits on serum lipids have been inconsistent. Breakfast eaters have ↑ daily intakes of micronutrients and are more likely to meet nutrient intake recommendations compared with B skippers.</p> <p>Nutrients that seem to be particularly affected across a variety of studies and population groups include vitamins A and C, riboflavin, calcium, zinc, and iron. Data related to the effects of B on micronutrient status (i.e., blood or tissue concentrations) are not widely reported except with regard to RTEC consumption.</p> <p>Seven studies showed that children and adolescents who skipped B did not, on average, make up the nutrient deficits at other meals during the day, which has also been observed in adults (from two studies). One population-based survey data indicate that children and adolescents tend to have similar nutrient intakes from daily meals other than B, regardless of whether they skip or consume breakfast. The same study mentioned that female adolescents who skipped B had ↓ intakes of nutrients at other meals, compared with female adolescent B consumers. Several studies showed that the inclusion of RTEC and milk enhance calcium and iron intake.</p>
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<p>Song et al 2005</p> <p>Study Design: cross-sectional</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Data from the NHANES 1999-2000.</p> <p>N=4,218.</p> <p>Age: 19+ year-old adults.</p>	<p>24-hour diet recall.</p>	<p>B Skipper=no B self-identified on day of 24-hour recall.</p>	<p>25.3% of men</p> <p>20.6% of women</p> <p>19.6% White</p> <p>31.1% African-American</p> <p>28.4% Hispanic</p> <p>32.3% others.</p>	<p>B Consumers vs. B Skippers: B consumers had significantly ↑ daily dietary fiber intake than B non-consumers (17± 0.3g vs. 12±0.4g), and RTEC B consumers also had significantly ↑ daily dietary fiber intake than non-RTEC B consumers (P<0.001 for both comparisons).</p> <p>Further nutrient analysis not conducted.</p>
<p>Song WO, Chun OK et al, 2006</p> <p>Study Design: Cross-sectional study</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Data from the NHANES 1999-2000.</p> <p>N=6,631.</p> <p>35.5% White</p> <p>23.2% African-American</p> <p>33.1% Hispanic</p> <p>8.2% Others.</p> <p>Age: At least nine years old.</p> <p>Note: Four- to eight-years old 6.5% excluded from analysis.</p>	<p>24-hour diet recall.</p>	<p>B Skipper=missed B on day of 24-hour recall.</p> <p>Actual estimated milk consumed.</p> <p>RTEC consumption:</p> <p>RTEC B</p> <p>RTEC + milk B</p> <p>Other B.</p>	<p>At least nine: 23.8%</p> <p>Data for at least nine:</p> <p>25.5% of men</p> <p>22.2% of women</p> <p>20.7% white</p> <p>31.9% African-American</p> <p>28% Hispanic</p> <p>31.7% others.</p>	<p>Breakfast consumption, milk with RTEC and milk without RTEC were all significant predictors for daily calcium intake (P<0.05) after controlling for age and ethnicity.</p>

<p>Stockman NK, Schenkel TC et al, 2005</p> <p>Study Design: Prospective cohort study</p> <p>Class: B</p> <p>Rating: Positive Quality</p>	<p>Data from the local high school community in Canada.</p> <p>N=180 (0% female).</p> <p>14- to 18-year-old adolescents.</p> <p>Race and ethnicity not reported.</p>	<p>Three-day 24-hour recall.</p>	<p>B Skipper=missed B on at least one of three days of diet record (Inconsistent B) vs. B Consumer=consumed B on all three days of diet record (Consistent B).</p>	<p>26% of 14- to 18-year-old adolescents.</p>	<p>B Consumers vs. B Skippers had ↑ estimated daily intake of iron (16.4 ± 0.49 and 13.5 ± 0.91, $P=0.0041$), but not intakes of energy, total protein, CHO, fat, cholesterol, calcium, sodium or fiber.</p>
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<p>Timlin et al 2008</p> <p>Study Design: longitudinal prospective cohort</p> <p>Class: B</p> <p>Rating: Positive Quality</p>	<p>Data from the Eating Among Teens (EAT)-I, 1998-1999 and EAT-II, 2003-2004 Minneapolis/St Paul, Minnesota, metropolitan area.</p> <p>N=2,216 (54.8% female).</p> <p>Age: 14.9±1.6 year-old adolescents (baseline, 1998-1999)</p> <p>Age: 19.4±1.7 year-old adolescents (Time 2, 2003-2004).</p> <p>63.1% White 9.9% Black 3.8% Hispanic 17.7% Asian 2.7% Native American 2.9% Others.</p>	<p>Youth and Adolescent FFQ.</p>	<p>B Skipper=self-reported “never” had intake of B during the past week.</p> <p>B Consumer=self-reported “daily” intake of B during the past week.</p>	<p>16.4% of 13-17 year-old girls (baseline).</p> <p>13.0% of 13-17 year-old boys (baseline).</p> <p>13.8% of 18-22 year-old girls (Time 2).</p> <p>18.9% of 18-22 year-old boys (Time 2).</p>	<p>For girls (baseline), B Consumers vs. B Skippers: In girls, the overall diet of daily B eaters, compared with those who were intermittent or never eaters was higher in total energy (P<0.01 for both), fiber (P<0.05 and P<0.01 respectively) and cholesterol (P<0.01 for both).</p> <p>In boys, statistically significant differences by daily B eaters and intermittent eater were observed for dietary CHO (P<0.05) and fiber (P<0.05) (higher for daily B) and for the percentage of calories from saturated fat (lower for daily B) (P<0.05).</p>
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<p>van der Heijden AA, Hu FB et al, 2007</p> <p>Study Design: Sub-analysis of the Health Professional Follow-up Study, which was a prospective cohort study</p> <p>Class: B</p> <p>Rating: Positive Quality</p>	<p>Data from the Health Professionals Follow-up Study, 1992 (introduction of B question). N=20,064.</p> <p>Age at baseline: 40- to 75-year-old adults.</p> <p>Age in 1992: 46- to 81-year-old adults.</p>	<p>Semi-quantitative FFQ for past 12 months, 1990.</p>	<p>B Skipper=self-report of "no," did not consume B.</p>	<p>16.9% of 46-81 year old adult men.</p>	<p>B Consumers vs B Skippers had greater estimated daily percentage of energy from CHO (50.1 vs. 46.1%) and estimated total fiber (7.3 vs. 5.0g per day) intake.</p> <p>B Consumers vs. B Skippers had lower estimated daily percentages of energy from fat (30.6 vs. 32.6%), PUFA (5.9 vs. 6.0%), MUFA (12.0 vs. 12.8%), saturated fat (10.1 vs. 11.0%) and trans-fat (1.5 vs. 1.7%) and lower estimated daily alcohol intake (9.7 vs. 13.1g per day)</p> <p>B Consumers vs. B Skippers had greater estimated intake of whole grain (29.4 vs. 17.5g per day).</p>
<p>Williams BM et al 2009</p> <p>Study Design: Cross-sectional Analysis</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Data from the NHANES, 1999-2002. N=1,389 (100% African-American). Age: One- to 12-year-old children and adolescents.</p>	<p>24-hour diet recall.</p>	<p>B Skipper=self-reported missed B on day of 24-hour recall.</p> <p>B Skipper vs. RTEC.</p> <p>B vs. non-RTEC B.</p> <p>Mean Adequacy Ratio (MAR)=average of the percentage of the Estimated Average Requirement for 13 nutrients (truncated to 100%, if needed).</p>	<p>7.4% of one- to five- year-old children.</p> <p>16.9% of six- to 12-year-old children.</p>	<p>Compare with those who either skipped B or consumed other B, children in the RTEC breakfast category had the highest mean daily intakes of vitamins A and B₁₂, thiamin, riboflavin, folate and iron (P≤0.05 for all). No differences were found in mean daily intakes of vitamin B₆, niacin, calcium and zinc between B skippers and other breakfast consumers.</p> <p>RTEC had lower intake of vitamin E than B skippers (P≤0.05); and children who consumed RTEC for B had the highest intakes from CHO and total sugars and the lowest intake from total fat when compared with the B skippers and other B consumers groups (P≤0.05). B skippers and other B consumers had higher intakes of MUFA and PUFA than RTEC B consumers (P≤0.05).</p> <p>The MAR was highest in RTEC B Consumers (95.7±0.2%) vs. non-RTEC B Consumers (93.2±0.4%) vs. B Skippers (84.3±1.2%).</p>

<p>Williams P, 2005</p> <p>Study Design: Cross-sectional study</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Data from the Australian National Nutrition Survey, 1995-1996.</p> <p>N=10,851.</p> <p>Age: 19+ year-old-adults.</p>	<p>24-hour diet recall.</p>	<p>B Skipper=self-identified as consuming B "rarely" or "never."</p>	<p>Not reported.</p>	<p>B Consumers vs. B Skippers had ↑ estimated daily median intakes of energy, protein, CHO, thiamin, riboflavin, niacin, folate, vitamins A and C, calcium, iron, magnesium, phosphorus, zinc (women only), potassium and fiber and lesser estimated daily median intakes of fat and total sugar. B was a good source (≥25% of RDI) of protein, thiamin, riboflavin, niacin, folate (men only), vitamins A (men only) and C, calcium, iron, magnesium and phosphorus, but not zinc or fiber.</p> <p>B made substantial contribution to overall nutrient intake in 65+ year-old men and 55+ year-old women B was low in fat (24-28% of total B energy intake) and high in CHO (56-59% of total B energy intake).</p> <p>B Consumers vs. B Skippers consumed more servings of cereal per day and met dietary targets for daily fiber intake, particularly in 65+ year-old B Consumers.</p>
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<p>Williams P, 2007</p> <p>Study Design: Cross-sectional study</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Data from the Australian National Nutrition Survey, 1995-1996.</p> <p>N=3,007.</p> <p>Age: Two to 18 year old children and adolescents.</p>	<p>24-hour diet recall.</p>	<p>B Skipper=self-identified as consuming B “rarely” or “never.”</p>	<p>Not reported.</p>	<p>B Consumers vs. B Skippers had higher estimated daily median intakes of thiamin, riboflavin, niacin, calcium, magnesium and fiber, but these values were NS different in adults.</p> <p>More B Consumers vs. B Skippers met RDI goals for nutrient intakes.</p> <p>B was a good source ($\geq 25\%$ of RDI) of thiamin, riboflavin, niacin, vitamin C, calcium and iron.</p> <p>B Consumers vs. B Skippers did not differ in total sugar or fat intake, except in eight- to 11-year-old boys where B.</p> <p>Consumers had higher estimated intakes.</p> <p>B was low in fat (26-30% of total B energy intake) and high in CHO (55% of total B energy intake).</p> <p>B Consumers vs. B Skippers consumed more servings of cereal per day.</p>
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<p>Woodruff SJ et al 2008</p> <p>Study Design: Cross-sectional Study</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Participants were recruited from Ontario and Alberta schools using a two-stage stratified, randomized sampling procedure</p> <p>N=1,826 (55.6% female).</p> <p>Age: 13- to 17-year-old adolescents.</p>	<p>24-hour diet recall, web-based.</p> <p>Healthy Eating Index-C (Canada) for diet quality, range from zero=lowest to 100=highest quality.</p>	<p>B Skipper=missed B on day of 24-hour recall.</p>	<p>27.3% of 13- to 17-year-old adolescents.</p> <p>More female (30%) vs. male (24%) B Skippers.</p>	<p>B Consumers had mean±SD HEI-C score higher (71±12.4) than B Skippers (64±14.0), although both groups' scores suggested "needs improvement."</p> <p>Compared to B Consumers, B Skippers had worse diet quality [OR=0.42 (95% CI=0.33, 0.54)].</p>
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Search plan and results

Inclusion criteria

- *Subjects/Population:* Human subjects
- *Age:* Children, men and women of all ages
- *Setting:* International
- *Health status:* Healthy and those with elevated chronic disease risk (CHD/CVD, type 2 diabetes, metabolic syndrome and obesity)
- *Nutrition-related problem/condition:* None.

Search Criteria

- *Study design preferences:* RCT or clinical controlled studies, large non-randomized observational studies, cohort, case-control studies, systematic reviews and meta-analysis
- *Size of study groups:* The sample size must equal 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:* June 2004 to present
- *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-reviewed journal.

Exclusion criteria

- *Subjects/Population:*
 - Animal and in vitro studies
 - Malnourished or developing populations or disease incidence not relative to US population (e.g., malaria)
- *Setting:* Hospitalized patients
- *Health status:* Medical treatment or therapy and diseased subjects
- *Nutrition-related problem/condition:* All conditions.

Search Criteria

- *Size of study groups:* Sample sizes less than 10
- *Study dropout rate:* Dropout rate of 20% or greater
- *Year range:* Prior to June 2004
- *Authorship:* Studies by same author similar in content
- *Languages:* Articles not in English
- *Other:* Abstracts or presentations and articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed:

breakfast* AND (food group* OR bread[mh] OR "dairy products"[mh] OR "dietary fiber"[mh] OR eggs[mh] OR yogurt OR fruit[mh] OR meat[mh] OR vegetables[mh] OR nuts[mh] OR cereals[mh] OR bread[mh] OR whole grain* OR food[majr] AND (eating[mh] OR "Nutritional Status"[Mesh] OR "nutritional requirements"[mesh] OR "Nutritive Value"[Mesh] OR "nutrient adequacy")

"breakfast consumption" OR breakfast* AND consumption*?

breakfast* AND skip*

Breakfast AND ("diet quality" OR (nutriti* AND adequacy*))

OR "Micronutrients"[Mesh] OR (meal frequency) OR (consumption AND patterns) OR (dietary AND pattern*) OR "Deficiency Diseases"[Mesh] NOT (skip* OR Editorial[ptyp] OR Letter[ptyp] OR review[ptyp] OR "Feeding Behavior"[mesh])

Breakfast AND "Feeding Behavior"[mesh]

Date searched: 10/07/2009 and 10/08/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 871
- Total articles identified to review from electronic databases: 78
- Articles identified via handsearch or other means: 2
- Number of Primary Articles Identified: 14
- Number of Review Articles Identified: 1
- Total Number of Articles Identified: 15
- Number of Articles Reviewed but Excluded: 63

Included articles (References)

1. Affenito SG, Thompson DR, Barton BA, Franko DL, Daniels SR, Obarzanek E, Schreiber GB, Striegel-Moore RH. Breakfast consumption by African-American and white adolescent girls correlates positively with calcium and fiber intake and negatively with body mass index. *J Am Diet Assoc.* 2005 Jun; 105(6): 938-945. PMID: 15942545.
2. Dubois L, Girard M, Potvin Kent M, Farmer A, Tatone-Tokuda F. Breakfast skipping is associated with differences in meal patterns, macronutrient intakes and overweight among pre-school children. *Public Health Nutr.* 2009 Jan; 12(1): 19-28. Epub 2008 Mar 18. PMID: 18346309.
3. Kerver JM, Yang EJ, Obayashi S, Bianchi L, Song WO. Meal and snack patterns are associated with dietary intake of energy and nutrients in US adults. *J Am Diet Assoc.* 2006 Jan; 106(1): 46-53. PMID: 16390666.
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11. van der Heijden AA, Hu FB, Rimm EB, van Dam RM. A prospective study of breakfast consumption and weight gain among U.S. men. *Obesity (Silver Spring).* 2007 Oct; 15(10): 2, 463-2, 469. PMID: 17925472.
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13. Williams P. Breakfast and the diets of Australian adults: An analysis of data from the 1995 National Nutrition Survey. *Int J Food Sci Nutr.* 2005 Feb; 56(1): 65-79. PMID: 16019316.
14. Williams P. Breakfast and the diets of Australian children and adolescents: An analysis of data from the 1995 National Nutrition Survey. *Int J Food Sci Nutr.* 2007 May; 58(3): 201-216. PMID: 17514538.
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Excluded articles

Excluded Articles	Reason for Exclusion
Albertson AM, Franko DL, Thompson D, Eldridge AL, Holschuh N, Affenito SG, Bauserman R, Striegel-Moore RH. <u>Longitudinal patterns of breakfast eating in black and white adolescent girls.</u> <i>Obesity (Silver Spring)</i> . 2007 Sep; 15(9): 2, 282-2, 292.	Does not answer the question; about breakfast and body weight.
Alexander KE, Ventura EE, Spruijt-Metz D, Weigensberg MJ, Goran MI, Davis JN. <u>Association of breakfast skipping with visceral fat and insulin indices in overweight Latino youth.</u> <i>Obesity (Silver Spring)</i> . 2009 Aug; 17(8): 1, 528-1, 533. Epub 2009 May 7. PMID: 19424166.	Does not answer the question; about breakfast and body weight.
Ask AS, Hernes S, Aarek I, Johannessen G, Haugen M. <u>Changes in dietary pattern in 15-year-old adolescents following a four-month dietary intervention with school breakfast: A pilot study.</u> <i>Nutr J</i> . 2006 Dec 7; 5: 33. PMID: 17150115.	Does not answer the question; about breakfast and body weight.
Barton BA, Eldridge AL, Thompson D, Affenito SG, Striegel-Moore RH, Franko DL, Albertson AM, Crockett SJ. <u>The relationship of breakfast and cereal consumption to nutrient intake and body mass index: The National Heart, Lung, and Blood Institute Growth and Health Study.</u> <i>J Am Diet Assoc</i> . 2005 Sep; 105(9): 1, 383-1, 389. PMID: 16129079.	Does not answer the question; about cereal consumption.
Berg C, Lappas G, Wolk A, Strandhagen E, Torén K, Rosengren A, Thelle D, Lissner L. <u>Eating patterns and portion size associated with obesity in a Swedish population.</u> <i>Appetite</i> . 2009 Feb; 52(1): 21-26. Epub 2008 Jul 25. PMID: 18694791.	Does not answer the question; about breakfast and body weight.
Bertéus Forslund H, Torgerson JS, Sjöström L, Lindroos AK. <u>Snacking frequency in relation to energy intake and food choices in obese men and women compared to a reference population.</u> <i>Int J Obes (Lond)</i> . 2005 Jun; 29(6): 711-719. PMID: 15809664.	Does not answer the question; meals, snacks and body weight.
Burgess-Champoux TL, Larson N, Neumark-Sztainer D, Hannan PJ, Story M. <u>Are family meal patterns associated with overall diet quality during the transition from early to middle adolescence?</u> <i>J Nutr Educ Behav</i> . 2009 Mar-Apr; 41(2): 79-86. PMID: 19304252.	Does not answer the question; family meals and nutrient adequacy.

<p>Carels RA, Young KM, Coit C, Clayton AM, Spencer A, Wagner M. <u>Skipping meals and alcohol consumption. The regulation of energy intake and expenditure among weight loss participants.</u> <i>Appetite</i>. 2008 Nov; 51(3): 538-545. Epub 2008 Apr 15. PMID: 18511146.</p>	<p>Does not answer the question; about breakfast and body weight.</p>
<p>Chitra U, Reddy CR. <u>The role of breakfast in nutrient intake of urban schoolchildren.</u> <i>Public Health Nutr</i>. 2007 Jan; 10(1): 55-58. PMID: 17212843.</p>	<p>Does not answer the question; quality of meals and consumption pattern.</p>
<p>Clark CA, Gardiner J, McBurney MI, Anderson S, Weatherspoon LJ, Henry DN, Hord NG. <u>Effects of breakfast meal composition on second meal metabolic responses in adults with Type 2 diabetes mellitus.</u> <i>Eur J Clin Nutr</i>. 2006 Sep; 60(9): 1, 122-1, 129. Epub 2006 May 3. PMID: 16670695.</p>	<p>Does not answer the question; about glycemic response.</p>
<p>Cluskey M, Edlefsen M, Olson B, Reicks M, Auld G, Bock MA, Boushey CJ, Bruhn C, Goldberg D, Misner S, Wang C, Zaghloul S. <u>At-home and away-from-home eating patterns influencing preadolescents' intake of calcium-rich food as perceived by Asian, Hispanic and Non-Hispanic white parents.</u> <i>J Nutr Educ Behav</i>. 2008 Mar-Apr; 40(2): 72-79. PMID: 18314082.</p>	<p>Does not answer the question; about eating patterns, parental perspective.</p>
<p>Condon EM, Crepinsek MK, Fox MK. <u>School meals: Types of foods offered to and consumed by children at lunch and breakfast.</u> <i>J Am Diet Assoc</i>. 2009 Feb; 109(2 Suppl): S67-S78. PMID: 19166674.</p>	<p>Does not answer the question; comparison of meals.</p>
<p>Croezen S, Visscher TL, Ter Bogt NC, Veling ML, Haveman-Nies. <u>Skipping breakfast, alcohol consumption and physical inactivity as risk factors for overweight and obesity in adolescents: Results of the E-MOVO project. A.</u> <i>Eur J Clin Nutr</i>. 2009 Mar; 63(3): 405-412. Epub 2007 Nov 28. PMID: 18043703.</p>	<p>Does not answer the question; about breakfast and body weight.</p>
<p>Crossman A, Anne Sullivan D, Benin M. <u>The family environment and American adolescents' risk of obesity as young adults.</u> <i>Soc Sci Med</i>. 2006 Nov; 63(9): 2, 255-2, 267. Epub 2006 Jul 7. PMID: 16828216.</p>	<p>Does not answer the question; about breakfast and obesity.</p>
<p>Dialektakou KD, Vranas PB. <u>Breakfast skipping and body mass index among adolescents in Greece: Whether an association exists depends on how breakfast skipping is defined.</u> <i>J Am Diet Assoc</i>. 2008 Sep; 108(9): 1, 517-1, 525. PMID: 18755326.</p>	<p>Does not answer the question; about breakfast and body weight.</p>

<p>Dubois L, Girard M, Potvin Kent M. <u>Breakfast eating and overweight in a pre-school population: Is there a link?</u> <i>Public Health Nutr.</i> 2006 Jun; 9(4): 436-442. PMID: 16870015.</p>	<p>Does not answer the question; about breakfast and body weight.</p>
<p>Duncan JS, Schofield G, Duncan EK, Rush EC. <u>Risk factors for excess body fatness in New Zealand children.</u> <i>Asia Pac J Clin Nutr.</i> 2008; 17(1): 138-147. PMID: 18364339.</p>	<p>Does not answer the question; about breakfast and body weight.</p>
<p>Ells LJ, Hillier FC, Shucksmith J, Crawley H, Harbige L, Shield J, Wiggins A, Summerbell CD. <u>A systematic review of the effect of dietary exposure that could be achieved through normal dietary intake on learning and performance of school-aged children of relevance to UK schools.</u> <i>Br J Nutr.</i> 2008 Nov; 100(5): 927-936. Epub 2008 Apr 1. Review. PMID: 18377677.</p>	<p>Does not answer the question; effects of nutrition on learning.</p>
<p>Farshchi HR, Taylor MA, Macdonald IA. <u>Deleterious effects of omitting breakfast on insulin sensitivity and fasting lipid profiles in healthy lean women.</u> <i>Am J Clin Nutr.</i> 2005 Feb; 81(2): 388-396. PMID: 15699226.</p>	<p>Does not answer the question; breakfast intake and glucose and lipids intake.</p>
<p>Fernández San Juan PM. <u>Dietary habits and nutritional status of school aged children in Spain.</u> <i>Nutr Hosp.</i> 2006 May-Jun; 21(3): 374-378. PMID: 16771121.</p>	<p>Commentary.</p>
<p>Garrido G, Webster AL, Chamorro M. <u>Nutritional adequacy of different menu settings in elite Spanish adolescent soccer players.</u> <i>Int J Sport Nutr Exerc Metab.</i> 2007 Oct; 17(5): 421-432. PMID: 18046052.</p>	<p>Does not answer the question; evaluation of two different meals for adolescent soccer players in Spain.</p>
<p>Gleason PM, Dodd AH. <u>School breakfast program but not school lunch program participation is associated with lower body mass index.</u> <i>J Am Diet Assoc.</i> 2009 Feb; 109(2 Suppl): S118-S128. PMID: 19166666.</p>	<p>Does not answer the question; about breakfast and body weight.</p>
<p>Gross SM, Bronner Y, Welch C, Dewberry-Moore N, Paige DM. <u>Breakfast and lunch meal skipping patterns among fourth-grade children from selected public schools in urban, suburban, and rural maryland.</u> <i>J Am Diet Assoc.</i> 2004 Mar; 104(3): 420-423. PMID: 14993865.</p>	<p>Does not answer the question; consumption patterns at breakfast and lunch.</p>
<p>Hirschler V, Buzzano K, Erviti A, Ismael N, Silva S, Dalamon R. <u>Overweight and lifestyle behaviors of low socioeconomic elementary school children in Buenos Aires.</u> <i>BMC Pediatr.</i> 2009 Feb 24; 9: 17. PMID: 19239682.</p>	<p>It doesn't answer the question; breakfast skipping, snacking and body weight.</p>

<p>Klunklin S, Channoonthuan K. <u>Snack consumption in normal and undernourished preschool children in Northeastern Thailand.</u> <i>J Med Assoc Thai.</i> 2006 May ;89(5): 706-713. PMID: 16756059.</p>	<p>Does not answer the question; snacks and sodium intake.</p>
<p>Kosti RI, Panagiotakos DB, Mihos CC, Alevizos A, Zampelas A, Mariolis A, Tountas Y. <u>Dietary habits, physical activity and prevalence of overweight/obesity among adolescents in Greece: The Vyronas study.</u> <i>Med Sci Monit.</i> 2007 Oct; 13(10): CR437-CR444. PMID: 17901850.</p>	<p>Does not answer the question; about breakfast and body weight.</p>
<p>Larson NI, Neumark-Sztainer D, Hannan PJ, Story M. <u>Family meals during adolescence are associated with higher diet quality and healthful meal patterns during young adulthood.</u> <i>J Am Diet Assoc.</i> 2007 Sep; 107(9): 1, 502-1, 510. PMID: 17761227.</p>	<p>Does not answer the question; family meals and nutrient adequacy.</p>
<p>Lazzeri G, Giallombardo D, Guidoni C, Zani A, Casorelli A, Grasso A, Pozzi T, Rossi S, Giacchi M. <u>Nutritional surveillance in Tuscany: Eating habits at breakfast, mid-morning and afternoon snacks among 8- to 9-year-old children.</u> <i>J Prev Med Hyg.</i> 2006 Sep; 47(3): 91-99. PMID: 17217185.</p>	<p>Does not answer the question; about breakfast and body weight.</p>
<p>Lin W, Yang HC, Hang CM, Pan WH. <u>Nutrition knowledge, attitude, and behavior of Taiwanese elementary school children.</u> <i>Asia Pac J Clin Nutr.</i> 2007; 16 Suppl 2: 534-546. PMID: 17723993.</p>	<p>Does not answer the question; nutrition knowledge in Taiwanese children.</p>
<p>Lioret S, Touvier M, Lafay L, Volatier JL, Maire B. <u>Are eating occasions and their energy content related to child overweight and socioeconomic status?</u> <i>Obesity (Silver Spring)</i> 2008 Nov; 16(11): 2, 518-2, 523. Epub 2008 Sep 4. PMID: 18772863.</p>	<p>Does not answer the question; eating frequency, breakfast, snacks, weight.</p>
<p>Maddah M, Rashidi A, Mohammadpour B, Vafa R, Karandish M. <u>In-school snacking, breakfast consumption, and sleeping patterns of normal and overweight Iranian high school girls: A study in urban and rural areas in Guilan, Iran.</u> <i>J Nutr Educ Behav.</i> 2009 Jan-Feb; 41(1): 27-31. PMID: 19161917.</p>	<p>Does not answer the question; about TV, skipping breakfast and BMI.</p>
<p>Maddah M, Nikooyeh B. <u>Factors associated with overweight in children in Rasht, Iran: Gender, maternal education, skipping breakfast and parental obesity.</u> <i>Public Health Nutr.</i> 2009 Jun 23: 1-5. [Epub ahead of print] PMID: 19545473.</p>	<p>Does not answer the question; determinant of obesity in Iranian children.</p>
<p>Magnusson MB, Hulthén L, Kjellgren KI. <u>Obesity, dietary pattern and physical activity among children in a suburb with a high proportion of immigrants.</u> <i>J Hum Nutr Diet.</i> 2005 Jun; 18(3): 187-194. PMID: 15882381.</p>	<p>Does not answer the question; TV, skipping breakfast and BMI.</p>

<p>Malinauskas BM, Raedeke TD, Aeby VG, Smith JL, Dallas MB. <u>DiETING practices, weight perceptions, and body composition: A comparison of normal weight, overweight, and obese college females.</u> <i>Nutr J.</i> 2006 Mar 31; 5: 11. PMID: 16579846.</p>	<p>Does not answer the question; about self-monitoring.</p>
<p>Marín-Guerrero AC, Gutiérrez-Fisac JL, Guallar-Castillón P, Banegas JR, Rodríguez-Artalejo F. <u>Eating behaviours and obesity in the adult population of Spain.</u> <i>Br J Nutr.</i> 2008 Nov; 100(5): 1, 142-1, 148. Epub 2008 Apr 1. PMID: 18377684.</p>	<p>Does not answer the question; about breakfast and body weight.</p>
<p>Mariscal-Arcas M, Romaguera D, Rivas A, Feriche B, Pons A, Tur JA, Olea-Serrano F. <u>Diet quality of young people in southern Spain evaluated by a Mediterranean adaptation of the Diet Quality Index-International (DQI-I).</u> <i>Br J Nutr.</i> 2007 Dec; 98(6): 1, 267-1, 273. Epub 2007 Jul 19. PMID: 17640424.</p>	<p>Does not answer the question; evaluation of a diet quality of a young Mediterranean population.</p>
<p>Merten MJ, Williams AL, Shriver LH. <u>Breakfast consumption in adolescence and young adulthood: Parental presence, community context, and obesity.</u> <i>J Am Diet Assoc.</i> 2009 Aug; 109(8): 1, 384-1, 391. PMID: 19631044.</p>	<p>Does not answer the question; about breakfast and body weight.</p>
<p>Mota J, Fidalgo F, Silva R, Ribeiro JC, Santos R, Carvalho J, Santos MP. <u>Relationships between physical activity, obesity and meal frequency in adolescents.</u> <i>Ann Hum Biol.</i> 2008 Jan-Feb; 35(1): 1-10. PMID: 18274921.</p>	<p>Does not answer the question; about breakfast and body weight.</p>
<p>Nagel G, Wabitsch M, Galm C, Berg S, Brandstetter S, Fritz M, Klenk J, Peter R, Prokopchuk D, Steiner R, Stroth S, Wartha O, Weiland SK, Steinacker J. <u>Determinants of obesity in the Ulm Research on Metabolism, Exercise and Lifestyle in Children (URMEL-ICE).</u> <i>Eur J Pediatr.</i> 2009 ct; 168(10): 1, 259-1, 267. Epub 2009 Jun 28. PMID: 19562371.</p>	<p>Does not answer the question; about breakfast and body weight.</p>
<p>Niemeier HM, Raynor HA, Lloyd-Richardson EE, Rogers ML, Wing RR. <u>Fast food consumption and breakfast skipping: Predictors of weight gain from adolescence to adulthood in a nationally representative sample.</u> <i>J Adolesc Health.</i> 2006 Dec; 39(6): 842-849. Epub 2006 Sep 27. PMID: 17116514.</p>	<p>Does not answer the question; about breakfast and body weight.</p>
<p>O'Dea JA, Wilson R. <u>Socio-cognitive and nutritional factors associated with body mass index in children and adolescents: Possibilities for childhood obesity prevention.</u> <i>Health Educ Res.</i> 2006 Dec; 21(6): 796-805. Epub 2006 Nov 9. PMID: 17095571.</p>	<p>Does not answer the question; nutritional and socio-cognitive factors associated with BMI.</p>

<p>Øverby NC, Margeirsdottir HD, Brunborg C, Dahl-Jørgensen K, Andersen LF; Norwegian Study Group for Childhood Diabetes. <u>Sweets, snacking habits, and skipping meals in children and adolescents on intensive insulin treatment.</u> <i>Pediatr Diabetes</i>. 2008 Aug; 9(4 Pt 2): 393-400. PMID: 18774998.</p>	<p>Does not answer the question; population with diabetes.</p>
<p>Panagiotakos DB, Antonogeorgos G, Papadimitriou A, Anthracopoulos MB, Papadopoulos M, Konstantinidou M, Fretzayas A, Priftis KN. <u>Breakfast cereal is associated with a lower prevalence of obesity among 10- to 12-year-old children: the PANACEA study.</u> <i>Nutr Metab Cardiovasc Dis</i>. 2008 Nov; 18(9): 606-612. Epub 2008 May 23. PMID: 18502106.</p>	<p>Does not answer the question; about breakfast and body weight.</p>
<p>Prochnik Estima Cde C, da Costa RS, Sichieri R, Pereira RA, da Veiga GV. <u>Meal consumption patterns and anthropometric measurements in adolescents from a low socioeconomic neighborhood in the metropolitan area of Rio de Janeiro, Brazil.</u> <i>Appetite</i>. 2009 Jun; 52(3): 735-739. Epub 2009 Apr 5. PMID: 19501773.</p>	<p>Does not answer the question; meal consumption and anthropometrics.</p>
<p>Roseman MG, Yeung WK, Nickelsen J. <u>Examination of weight status and dietary behaviors of middle school students in Kentucky.</u> <i>J Am Diet Assoc</i>. 2007 Jul; 107(7): 1, 139-1, 145. PMID: 17604742.</p>	<p>Does not answer the question; weight status and dietary practices.</p>
<p>Shemilt I, Harvey I, Shepstone L, Swift L, Reading R, Mugford M, Belderson P, Norris N, Thoburn J, Robinson J. <u>A national evaluation of school breakfast clubs: Evidence from a cluster randomized controlled trial and an observational analysis.</u> <i>Child Care Health Dev</i>. 2004 Sep; 30(5): 413-427. PMID: 15320919.</p>	<p>Does not answer the question; study from England that compares two groups: school-based breakfast club vs. control.</p>
<p>Skemiene L, Ustinaviciene R, Radisauskas R, Kirvaitiene J, Lazauskas R, Sabonaityte S. <u>Nutritional habits of middle-aged schoolchildren from Kaunas town and Raseiniai district.</u> <i>Medicina (Kaunas)</i>. 2009; 45(4): 302-311. English, Lithuanian. PMID: 19423961.</p>	<p>Does not answer the question; nutritional habits of middle-aged school children in Lithuania.</p>
<p>Song Y, Joung H, Engelhardt K, Yoo SY, Paik HY. <u>Traditional v. modified dietary patterns and their influence on adolescents' nutritional profile.</u> <i>Br J Nutr</i>. 2005 Jun; 93(6): 943-949. PMID: 16022765.</p>	<p>Does not answer the question; about dietary patterns in Korea.</p>

<p>Storey KE, Forbes LE, Fraser SN, Spence JC, Plotnikoff RC, Raine KD, Hanning RM, McCargar LJ. <u>Diet quality, nutrition and physical activity among adolescents: The Web-SPAN (Web-Survey of Physical Activity and Nutrition) project.</u> <i>Public Health Nutr.</i> 2009 Jun 23: 1-9. [Epub ahead of print] PMID: 19545471.</p>	<p>Does not answer the question; diet quality and meal behaviors.</p>
<p>Storey KE, Hanning RM, Lambraki IA, Driezen P, Fraser SN, McCargar LJ. <u>Determinants of diet quality among Canadian adolescents.</u> <i>Can J Diet Pract Res.</i> 2009 Summer; 70(2): 58-65. PMID: 19515268.</p>	<p>Does not answer the question; determinants of diet quality.</p>
<p>Sun Y, Sekine M, Kagamimori S. <u>Lifestyle and Overweight Among Japanese Adolescents: The Toyama Birth Cohort Study.</u> <i>J Epidemiol.</i> 2009 Sep 19. PMID: 19776497.</p>	<p>Does not answer the question; TV viewing, snacking and obesity.</p>
<p>Sweeney NM, Horishita N. <u>The breakfast-eating habits of inner city high school students.</u> <i>J Sch Nurs.</i> 2005 Apr; 21(2): 100-105. PMID: 15801876.</p>	<p>Does not answer the question; breakfast eating habits.</p>
<p>Tapper K, Murphy S, Lynch R, Clark R, Moore GF, Moore L. <u>Development of a scale to measure 9- to 11-year-olds' attitudes towards breakfast.</u> <i>Eur J Clin Nutr.</i> 2008 Apr; 62(4): 511-518. Epub 2007 Mar 21. PMID: 17375113.</p>	<p>Does not answer the question; development and validation of a questionnaire to measure attitudes towards breakfast.</p>
<p>Vågstrand K, Barkeling B, Forslund HB, Elfhag K, Linné Y, Rössner S, Lindroos AK. <u>Eating habits in relation to body fatness and gender in adolescents: Results from the 'SWEDES' study.</u> <i>Eur J Clin Nutr.</i> 2007 Apr; 61(4): 517-525. Epub 2006 Sep 27. PMID: 17006444.</p>	<p>Does not answer the question; eating frequency, breakfast and snacks and weight.</p>
<p>Vanelli M, Iovane B, Bernardini A, Chiari G, Errico MK, Gelmetti C, Corchia M, Ruggerini A, Volta E, Rossetti S; Students of the Post-Graduate School of Paediatrics, University of Parma. <u>Breakfast habits of 1, 202 northern Italian children admitted to a summer sport school. Breakfast skipping is associated with overweight and obesity.</u> <i>Acta Biomed.</i> 2005 Sep; 76(2): 79-85. PMID: 16350552.</p>	<p>Does not answer the question; about breakfast and body weight.</p>
<p>Vereecken C, Dupuy M, Rasmussen M, Kelly C, Nansel TR, Al Sabbah H, Baldassari D, Jordan MD, Maes L, Niclasen BV, Ahluwalia N; HBSC Eating & Dieting Focus Group. <u>Breakfast consumption and its socio-demographic and lifestyle correlates in schoolchildren in 41 countries participating in the HBSC study.</u> <i>Int J Public Health.</i> 2009 Sep; 54 Suppl 2: 180-190. PMID: 19639257.</p>	<p>It doesn't answer the question; breakfast consumption and lifestyle factors.</p>

<p>Waqa G, Mavoia H. <u>Sociocultural factors influencing the food choices of 16- to 18-year-old indigenous Fijian females at school.</u> <i>Pac Health Dialog.</i> 2006 Sep; 13(2): 57-64. PMID: 18181391.</p>	<p>Does not answer the question; socio-cultural factors of obesity.</p>
<p>Woodruff SJ, Hanning RM. <u>Associations between family dinner frequency and specific food behaviors among grade six, seven, and eight students from Ontario and Nova Scotia.</u> <i>J Adolesc Health.</i> 2009 May; 44(5): 431-436. Epub 2009 Jan 9. PMID: 19380089.</p>	<p>It doesn't answer the question. Family meals and nutrient adequacy</p>
<p>Woodruff SJ, Hanning RM. <u>Effect of meal environment on diet quality rating.</u> <i>Can J Diet Pract Res.</i> 2009 Autumn; 70(3): 118-124. PMID: 19709467.</p>	<p>Does not answer the question; family meals.</p>
<p>Yahia N, Achkar A, Abdallah A, Rizk S. <u>Eating habits and obesity among Lebanese university students..</u> <i>Nutr J.</i> 2008 Oct 30; 7: 32. PMID: 18973661.</p>	<p>Does not answer the question; about breakfast and body weight.</p>
<p>Yang RJ, Wang EK, Hsieh YS, Chen MY. <u>Irregular breakfast eating and health status among adolescents in Taiwan.</u> <i>BMC Public Health.</i> 2006 Dec 7; 6: 295. PMID: 17150112.</p>	<p>Does not answer the question; about breakfast and body weight.</p>
<p>Zullig K, Ubbes VA, Pyle J, Valois RF. <u>Self-reported weight perceptions, dieting behavior, and breakfast eating among high school adolescents.</u> <i>J Sch Health.</i> 2006 Mar; 76(3): 87-92. PMID: 16475983.</p>	<p>Does not answer the question; about reasons for skipping breakfast.</p>

CHAPTER 3. DIETARY BEHAVIORS AND NUTRIENT INTAKE – SNACKING

WHAT IS THE RELATIONSHIP BETWEEN SNACKING AND NUTRIENT INTAKE?

Conclusion statement

A limited body of evidence supports a positive relationship between snacking and nutrient intakes in children, adolescents, adults, and older adults.

Grade

Limited

Evidence summary overview

This conclusion is based on the review of seven studies, three of which include children or adolescents (Macdiarmid et al, 2009; Maffeis et al, 2008; Sebastian et al, 2007) and four of which examine adults or older adults (Kerver et al, 2006; Ovaskainen et al, 2006; Stockman et al, 2005; Zizza et al, 2007). Not all nutrients are evaluated in all studies. In general, snacking is associated with higher intakes of macronutrients and dietary folate, vitamin C, calcium, magnesium, iron, potassium, and dietary fiber as well as total sugars and saturated fatty acids. Snacking by some adolescents and adults is associated with lower intakes of protein, fat, cholesterol, and iron, however data were inconsistent.

Evidence summary paragraphs

Kerver et al, 2006 (positive quality), conducted a cross-sectional study to test the hypothesis that specific meal and snack patterns are associated with selected nutrient intakes in 15,978 US adults (≥ 20 years old). Using the 24-hour dietary recall from the Third National Health and Nutrition Examination Survey (NHANES), meal and snack patterns were described in relation to nutrient intakes. Meal patterns were further categorized into five most commonly reported meal and snack combinations by population percentages of breakfast (B), lunch (L), dinner (D) and snacks (S). The majority of subjects reported consuming two or more snacks (62.3%), while 25.2% of the population reported consuming one snack, and 12.5% reported consuming no snacks. Those reporting no snacks consumed the least amount of protein and total fat. Those consuming B, L, D, and ≥ 2 S had the highest energy and carbohydrate (CHO) and lowest fat intakes. The groups reporting B, L, D, and 1 S and B, L, D, and ≥ 2 S had the highest intakes of all micronutrients [folic acid ($322 \pm 4.69 \mu\text{g}$), vitamin C ($116 \pm 3.12 \text{mg}$), calcium ($942 \pm 13.5 \text{mg}$), magnesium ($339 \pm 3.01 \text{mg}$), iron ($17.5 \pm 0.29 \text{mg}$), potassium ($3,177 \pm 23.4 \text{mg}$), and fiber ($18.6 \pm 0.2 \text{g}$)], except cholesterol, vitamin B₆, and sodium, which were consumed in the highest amounts by the B, L, D, group (cholesterol= $323 \pm 10.2 \text{mg}$; vitamin B₆= $2.10 \pm 0.05 \text{mg}$; and sodium= $3,946 \pm 48.4 \text{mg}$). These findings suggest that meal and snack patterns may be markers for nutrient intakes and therefore diet quality.

Macdiarmid et al, 2009 (positive quality), used cross-sectional data (N=156) from the National Survey of Sugar Intake among children in Scotland to investigate the meal and snacking patterns of school-aged children (five-17 years old). Meals and snacks were defined by a food-based classification system based on “core” (foods normally eating as part of a traditional meal) and “non core” (foods and drinks easily consumed

without a meal). A meal was defined as an event containing one or more “core” foods with or without “non-core” foods or drinks, while a snack was defined as an event containing only “non-core” foods or drinks. Seventy-eight percent of children had an average of between 2.5 and 3.5 meals per day and 98% of children ate one or more snacks. Boys ate similar number of snacks than girls, and children in the lowest socio-economic group ate fewer snacks than those in the highest socio-economic group. The number of meals and snacks eaten did not differ by age or body mass index (BMI) group. The median (inter-quartile range) number of items eaten within a snacking event was two (one to two) and in a meal was four (three to five) items two (one to two) “core” and two (one to three) “non-core” items. The average daily intake of saturated fatty acid (SFA) and non-milk extrinsic sugars (NMES) (% food energy) was higher from snacks than meals, but there was no difference in total fat. Snacks accounted for approximately a fifth of the total daily energy intake and total fat intake, a quarter of SFA intake and almost 40% of NMES intake. The only difference by sex, age, BMI, and SIMD group was that girls derived a higher proportion of their daily intake of total fat from snacks than boys: 19.8(17.0-22.5) for boys, and 23.7 (21.0-26.3) for girls. To investigate whether the number of snacks eaten was related to nutrient intake, children were grouped as infrequent (average of less than two snacks per day) or frequent snackers (average of more than two snacks per day). Frequent snackers had a higher daily intake of NMES (% food energy), but there was no statistical difference (SD) in percentage food energy from SFA or total fat, or total daily energy intake. Frequent snackers had more total eating events per day and fewer meals than infrequent snackers. The proportion of subjects eating breakfast did not differ between snacker groups. The number of meals, snacks and total eating events per day and daily energy and nutrient intake (total fat, SFA and NMES) on weekdays did not differ between term-time and school holidays. The number of snacks eaten on weekdays and weekend days did not differ significantly. In conclusion, children tended to follow a traditional pattern of three meals a day, which was consistent between age and BMI subgroups and between term-time and holidays.

Maffeis et al, 2008 (positive quality), conducted a prospective study to assess the type and number of snacks consumed weekly by a sample (N=1,837) of 8- to 10-year-old children from Italy. A questionnaire on the frequency of a child’s snacking (food and drink) weekly was filled out by a pediatrician. Energy and nutrient intakes were calculated by multiplying the frequency of weekly consumption by the nutrient composition of the portion size for each specific snack listed. Children consumed on average four snacks per day [mean values (SE) were: boys: 3.9 (0.07); girls: 3.8 (0.07), $P=0.27$]. The favorite snacks were: Fruit juice, fruit, bread with cold cuts, milk, tea, soft drinks, brioche, crackers, yogurt, bread, and cookies. Children preferred salty snacks to sweet snacks; they consumed 8.4 (0.16) servings per week of savory snacks vs. 7.2 (0.13) servings per week of sweet snacks ($P<0.001$). Energy intake and macronutrient composition was not statistically different between boys and girls. Macronutrient composition of snack serving was: 8.3 (0.1)% of protein, 64 (0.28)% of CHO, and 27.7 (0.25)% of fat from total energy.

Ovaskainen et al, 2006 (positive quality), used a random sample from a cross-sectional population survey (FINRISK 2002) in Finland, to assess prominence of snacks in energy intake. Dietary data were collected for 2,007 adults by using a computer-assisted 48-hour dietary recall in the national FINDIET. The interviewer selected the meal name from the following alternatives: breakfast, lunch, dinner, drink, evening snack, other snack and other eating event. To simplify the variety of meal,

meal type was divided into two categories: main meals and snacks. Daily energy was mostly derived from main meals comprising traditional mixed dishes, milk and bread. However, a snack-dominating meal pattern was observed in 19% of men and 24% of women. This meal pattern was associated with urbanization in both genders and with physical work in men. Higher sucrose intake and lower intake of micronutrients (not statistically different) were typical of the snack-dominating meal pattern compared to the others. In this population sodium content of the diet was lower for those with a snack-dominating meal pattern than the main-meal dominating diet group.

Sebastian et al, 2007 (positive quality), conducted a cross-sectional study to determine how snacking level impacts intake of nutrients and food groups. Dietary data based on 24-hour recall from 4,357 adolescents, 12 to 19 years of age participating in the NHANES 2001-2004 were analyzed. Food energy, CHO, total sugars, and vitamin C intake were positively associated, whereas protein and fat intake were negatively associated, with snacking frequency. Fruit intake increased, whereas solid fat intake decreased, as snacking incidence rose. Increasing snacking frequency was also associated with a greater likelihood of meeting milk and oil recommendations for boys and meeting fruit recommendations for both genders. Non-Hispanic black adolescents were less likely to meet their milk recommendations at low and high snacking levels and more likely to meet their fruit recommendations at high levels only. Foods consumed as snacks provided 12-39% of the day's total number of portions of the five MyPyramid food groups, 35% of total discretionary calorie intake, and 43% of total added sugar intake.

Stockman et al, 2005 (positive quality), conducted a retrospective cohort study to determine and compare the distribution of energy and nutrient intakes among meals and snacks, and related eating occasion frequency to the BMI of 180 healthy adolescents males (14 to 18 years old) recruited from local school and community groups in Canada. Anthropometric information and 24-hour dietary recall on three consecutive days, including two weekdays and one weekend day, were evaluated. Also, subjects were instructed to self-report the type of every eating occasion, such as breakfast, lunch, dinner, and snacks. Snacks tended to contribute fewer nutrients than meals; however, only cholesterol and iron intakes were statistically lower at snacks relative to all meals. Overall, the average daily number of snacks consumed was 1.63, with 77% of subjects consuming an average of at least one snack per day.

Zizza et al, 2007 (positive quality), used cross-sectional data from the NHANES 1999-2002 to compare the diets of snackers and nonsnackers, and to evaluate the influence of snacking on energy intakes and energy density in older adults. This study included 2,002 adults aged 65 years and older, and one day 24-hour dietary data was analyzed to classify eating occasions. The prevalence of snacking was high (84%) among this age group, and snackers had significantly higher daily intakes of energy, protein, CHO, and total fat. Alcohol intakes were not significantly different. In this population, snacks contributed almost a quarter of the energy and CHO intakes and a fifth of the daily fat intake. Also, snacking contributed 14% of daily protein intakes. Snackers had, on average, two and a half snacking occasions per day, with each snacking occasion contributing 150kcal. The average energy contribution of meals was not different between snackers and nonsnackers. The energy density of meals is significantly

greater for snackers than for non-snackers. In conclusion, results from this study demonstrate that snacking is an important dietary behavior among older adults.

Overview table

Author, Year, Study Design, Class, Rating	Study Subjects	Data Collection, Instruments and Methods	Prevalence of Snacking	Key Outcomes
<p>Kerver JM, Yang EJ et al, 2006</p> <p>Study Design: Cross-sectional design</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Data from the NHANES Study III, 1988-1994. N=15,978.</p> <p>Age: ≥ 20 years old adults.</p> <p>52.6% female.</p> <p>82.7% non-Hispanic White; 11.8% non-Hispanic Black; 5.5% Mexican-American.</p>	<p>24-hour diet recall</p> <p>Self-reported eating intake patterns of Breakfast (B), Lunch (L), Dinner (D), Snacks (S). Most common meal and snack combinations:</p> <ul style="list-style-type: none"> * B, L, D, ≥2 S * B, L, D, 1 S * B, L, ≥2 S * B, L, D * L, D, ≥2 S * Other. 	<p>From the population:</p> <p>62.3% reported consuming two or more snacks.</p> <p>25.2% reported consuming one snack.</p> <p>12.5% reported consuming no snacks.</p>	<p>Those reporting no snacks consumed the least amount of protein and total fat.</p> <p>Those consuming B, L, D, and ≥2 S had the highest energy and CHO and lowest fat intakes.</p> <p>The group reporting B, L, D, and 1 S and B, L, D, and ≥ 2 S had the highest intakes of all micronutrients: folic acid (322±4.69ug), vitamin C (116±3.12mg), calcium (942±13.5mg), magnesium (339±3.01mg), iron (17.5±0.29mg), potassium (3,177±23.4mg), and fiber (18.6±0.2g).</p> <p>The group reporting B, L, D had the highest intake of cholesterol, vitamin B₆, and sodium (cholesterol = 323±10.2mg; vitamin B₆ = 2.10±0.05mg; and sodium = 3,946±48.4mg).</p>

<p>Macdiarmid J, Loe J et al, 2009</p> <p>Study Design: Cross-sectional study</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Data from a cross-sectional data from the national Survey of Sugar Intake among children in Scotland.</p> <p>N=156.</p> <p>5-17 years old adolescents.</p>	<p>Four-day non-weighted diet diary (three weekdays and one weekend).</p> <p>Snack-eating event containing only 'non core' foods or drinks.</p> <p>'Non core' was defined as foods and drinks easily consumed without a meal.</p>	<p>98% of children ate one or more snacks per day.</p> <p>N=86</p> <p>Infrequent snackers or having \leqtwo snacks per day.</p> <p>N=70</p> <p>Frequent snackers or having >two snacks per day.</p>	<p>Children in the lower socio-economic group ate fewer snacks than those in the high socio-economic group.</p> <p>The number of meals and snacks eaten did not differ by age or BMI group.</p> <p>The median (inter-quartile range) number of items eaten within a snacking event was two.</p> <p>The average daily intake of saturated fatty acids (SFA) and non-milk extrinsic sugars (NMES) (% food energy) was higher from snacks than meals, but there was no difference in total fat.</p> <p>Snacks accounted for approximately a fifth of the total daily energy intake and total fat intake, a quarter of SFA intake and almost 40% of NMES intake.</p> <p>Total fat from snacks: 19.8(17.0-22.5) for boys, and 23.7 (21.0-26.3) for girls.</p> <p>Frequent snackers had a higher daily intake of NMES (% food energy).</p>
<p>Maffeis et al 2008</p> <p>Study Design: Prospective cohort study</p> <p>Class: B</p> <p>Rating: Positive Quality</p>	<p>Children were recruited from three different cities in Italy (Verona, Pisa and Naples); 2003.</p> <p>N=1,837 (924 males; 913 females).</p> <p>Age: 8-10 years old.</p>	<p>Questionnaire on the frequency of a child's snacking.</p> <p>Energy and nutrient intakes were calculated by multiplying the frequency of weekly consumption by the nutrient composition of the portion size for each specific snack listed.</p> <p>List of 22 snacks (foods and drinks) classified by sweet and savory.</p>	<p>Average of four snacks per day.</p>	<p>In both sexes, the favorite snacks were: fruit juice, fruit, bread with cold cuts, milk, tea, soft drinks, brioche, crackers, yogurt, bread, and cookies.</p> <p>Children preferred salty snacks to sweet snacks; they consumed 8.4 (0.16) servings per week of savory snacks vs 7.2 (0.13) servings per week of sweet snacks (P<0.001).</p> <p>Energy intake and macronutrient composition was not statistically different between boys and girls [(8.3 (0.1)% of protein, 64(0.28)% of CHO, and 27.7 (0.25)% of fat from total energy].</p>

<p>Ovaskainen ML, Reinivuo H et al, 2006</p> <p>Study Design: Cross-sectional design</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Data from a cross-sectional population survey (FINRISK 2002) in Finland.</p> <p>N=2,007 adults (912 males; N=1,095 females).</p> <p>Age: 25-64 years.</p>	<p>Dietary data collected by a computerized multiphased 48-hour recall by trained nutritionists.</p> <p>Self-reported type of meal from the following alternatives: Breakfast, lunch, dinner, snack, drink, evening snack, and other eating event.</p>	<p>Snack-dominating meal pattern was observed in 19% of men and 24% of women.</p>	<p>Snack dominating pattern was associated with urbanization in both genders and with physical work in men.</p> <p>Higher sucrose intake and lower intake of micronutrients (not statistically different) were typical of the snack-dominating meal pattern compared to the others.</p> <p>Sodium content of the diet was lower for those with a snack-dominating meal pattern [3,636 (92)mg for men, and 2,544 (53)mg for women] than the main-meal dominating diet group [3,992 (52) for men and 2,764(32)mg for women].</p>
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<p>Sebastian RS, Cleveland LE et al, 2008</p> <p>Study Design: Cross-Sectional Study</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Data from the NHANES 2001-2004.</p> <p>N=4,357.</p> <p>Age: 12-19 year old adolescents.</p>	<p>One 24-hour diet recall, collected in person by a trainer interviewer.</p> <p>P≤1 for all analysis was used.</p> <p>Eating occasion was self-reported from a defined list.</p> <p>Snacks occasions were described as: “snack,” “beverage,” “extended consumption” and the Spanish terms “merienda,” “entre comida,” “bebida,” “botana,” and “bocadillo.”</p>	<p>Mean nutrient intake by snacking category:</p> <p>0 Snacks N=502</p> <p>1 Snack N=1,111</p> <p>2 Snacks N=1,126</p> <p>3 Snacks N=834</p> <p>4+ Snacks N=784.</p>	<p>As snacking ↑:</p> <p>Energy-adjusted intakes for both genders reflected an ↑ in CHO, and this was paralleled by an ↑ in total sugar intake.</p> <p>Adjusted protein and fat were significantly lower in the diets of boys and girls.</p> <p>Intakes of vitamin A, vitamin E, and magnesium intake significantly ↑ for boys, and vitamin C intake significantly ↑ for both boys and girls.</p> <p>Intakes of vitamin B₆, folate, calcium, iron, and phosphorus were not significantly affected.</p> <p>Fruit intake ↑ and solid fat intake ↓ for both adolescent boys and girls.</p> <p>Intake of added sugars ↑ for girls only.</p> <p>Significantly improved the likelihood of meeting fruit recommendations for both genders and of meeting milk and oils recommendations for boys.</p> <p>More than one-third of all fruit portions and oils, about one-quarter of all grain and milk portions, and lesser proportions of vegetables and meat/beans portions were consumed at snacking occasions.</p> <p>Snacks contributed more than one-third of discretionary calories and added sugars, and approximately one-fourth of solid fats.</p>
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<p>Stockman NK, Schenkel TC et al, 2005</p> <p>Study Design: Prospective cohort study</p> <p>Class: B</p> <p>Rating: Positive Quality</p>	<p>Data from the local high school community in Canada.</p> <p>N=180.</p> <p>Age: 14-18 year old adolescents</p>	<p>Three-day 24-hour recall.</p> <p>Eating occasion was self-reported.</p>	<p>Daily number of snacks consumed was 1.63 with 77% of subjects consuming an average of at least one snack per day.</p>	<p>Snacks tended to contribute fewer nutrients than meals.</p> <p>Cholesterol and iron intakes were statistically lower at snacks relative to all meals.</p> <p>Protein = 13.4±0.97g from a total daily intake of 96.8±2.29g</p> <p>CHO = 85.7±5.04g from a total of 343.3±7.57g.</p> <p>Total fat = 22.4±1.37g from a total of 96.0±2.32g.</p> <p>Saturated fat = 7.55±0.50 from a total of 31.0±0.84g.</p> <p>Cholesterol = 34.3±3.24 from a total of 273.5±10.7mg.</p> <p>Dietary fiber = 2.89±0.21g from a total of 14.0±0.44g.</p> <p>Calcium = 177.1±15.8mg from a total of 1,022 ±37.9mg.</p> <p>Iron = 2.24 ±0.23mg from a total of 15.5±0.44mg.</p> <p>Sodium = 684.8±46.6 mg from a total of 4,334±98.9 mg).</p>
<p>Zizza CA, Tayie FA et al, 2007</p> <p>Study Design: Cross-Sectional Study</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Data from the NHANE S 1999-2002.</p> <p>N=2,002.</p> <p>Age: ≥65 year old adults (categorized as: 65-74 years; 75-84 years; ≥85 years).</p>	<p>One 24-hour diet recall, collected in person by a trainer interviewer.</p> <p>Eating occasion was self-reported from a defined list.</p> <p>Snacks occasions were describe as: “snack,” “beverage,” “extended consumption” and the Spanish terms “merienda,” “entre comida,” “bebida,” “botana,” and “bocadillo.”</p>	<p>Prevalence of snacking 84%.</p>	<p>Snackers had, on average, two and a half snacking occasions per day, with each snacking occasion contributing 150kcal.</p> <p>Snackers had significantly higher daily intakes of energy, protein, CHO, and total fat.</p> <p>Alcohol intakes were not SD.</p> <p>Snacking contributed almost a quarter of their energy and CHO intakes and a fifth of their daily fat intakes.</p> <p>Snacking contributed 14% of their daily protein intakes.</p> <p>The average energy contribution of meals was not different between snackers and non-snackers.</p> <p>The energy density of meals is significantly greater for snackers than for non-snackers.</p>

Search plan and results

Inclusion criteria

- *Subjects/Population:* Human subjects
- *Age:* Children, men and women of all ages
- *Setting:* International
- *Health status:* Healthy and those with elevated chronic disease risk (CHD/CVD, type 2 diabetes, metabolic syndrome and obesity)
- *Nutrition related problem/Condition:* None.

Search Criteria

- *Study design preferences:* RCT or clinical controlled studies, large non-randomized observational studies, cohort, case-control studies, systematic reviews and meta-analysis
- *Size of study groups:* The sample size must equal 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:* June 2004 to November 2009
- *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-reviewed journal.

Exclusion criteria

- *Subjects/Population:*
 - Animal and in vitro studies.
 - Malnourished/developing populations or disease incidence not relative to US population (e.g., malaria).
- *Setting:* Hospitalized patients.
- *Health status:* Medical treatment/therapy and diseased subjects.
- *Nutrition related problem/Condition:* All conditions.

Search Criteria

- *Size of study groups:* Sample sizes less than 10
- *Study dropout rate:* 20% or greater
- *Year range:* Prior to June 2004
- *Authorship:* Studies by same author similar in content
- *Languages:* Articles not in English
- *Other:* Abstracts or presentations and articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed:

(snack*) AND ("Nutritional Status"[majr] OR "nutritional requirements"[majr] OR "Nutritive Value"[majr] OR "nutrient adequacy" OR nutrient intake* OR "nutrient density" OR "diet quality")

(snack* OR fries OR cookies OR candies OR cakes OR desserts) AND ("Nutritional Status"[Mesh] OR "nutritional requirements"[mesh] OR "Nutritive Value"[Mesh] OR "nutrient adequacy" OR nutrient intake*)

Date searched: 11/17/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 300
- Total articles identified to review from electronic databases: 49
- Articles identified via handsearch or other means: 3
- Number of Primary Articles Identified: 5
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 7
- Number of Articles Reviewed but Excluded: 44

Included articles (References)

1. Kerver JM, Yang EJ, Obayashi S, Bianchi L, Song WO. Meal and snack patterns are associated with dietary intake of energy and nutrients in US adults. *J Am Diet Assoc.* 2006 Jan; 106(1): 46-53. PMID: 16390666.
2. Macdiarmid J, Loe J, Craig LC, Masson LF, Holmes B, McNeill G. Meal and snacking patterns of school-aged children in Scotland. *Eur J Clin Nutr.* 2009 Nov; 63(11): 1, 297-1, 304. Epub 2009 Aug 26. PMID: 19707230. Hand search (12-17-2009).
3. Maffeis C, Grezzani A, Perrone L, Del Giudice EM, Saggese G, Tatò L. Could the savory taste of snacks be a further risk factor for overweight in children? *J Pediatr Gastroenterol Nutr.* 2008 Apr; 46(4): 429-437. PMID: 18367957.
4. Ovaskainen ML, Reinivuo H, Tapanainen H, Hannila ML, Korhonen T, Pakkala H. Snacks as an element of energy intake and food consumption. *Eur J Clin Nutr.* 2006 Apr; 60(4): 494-501. PMID: 16319836. Hand search (12-17-2009).
5. Sebastian RS, Cleveland LE, Goldman JD. Effect of snacking frequency on adolescents' dietary intakes and meeting national recommendations. *J Adolesc Health.* 2008 May; 42(5): 503-511. Epub 2008 Feb 7. PMID: 18407046.
6. Stockman NK, Schenkel TC, Brown JN, Duncan AM. Comparison of energy and nutrient intakes among meals and snacks of adolescent males. *Prev Med.* 2005 Jul; 41(1): 203-210. Epub 2004 Dec 10. PMID: 15917012.
7. Zizza CA, Tayie FA, Lino M. Benefits of snacking in older Americans. *J Am Diet Assoc.* 2007 May; 107(5): 800-806. PMID: 17467375.

Excluded articles

Excluded Articles	Reason for Exclusion
Anderson JW, Patterson K. <u>Snack foods: comparing nutrition values of excellent choices and "junk foods"</u> . <i>J Am Coll Nutr</i> . 2005 Jun; 24(3): 155-1556; discussion 156-157. PMID: 15930478.	Compared high nutrient, low energy snacks to low nutrient, high energy snacks in a very loose manner; not objective.
Anderson VP, Cornwall J, Jack S, Gibson RS. <u>Intakes from non-breastmilk foods for stunted toddlers living in poor urban villages of Phnom Penh, Cambodia, are inadequate</u> . <i>Matern Child Nutr</i> . 2008 Apr; 4(2): 146-159. PMID: 18336647.	Does not answer the question; about eating practices of Cambodian infants.
Areekul W, Viravathana N, Aimpun P, Watthanakijthavongkul K, Khruacharoen J, Awaiwanont A, Khumtuikhrua C, Silsrikul P, Nilrat P, Saksoong S, Watthanatham J, Suwannahitatorn P, Sirimaneethum P, Meeprom N, Somboonruangsri W, Pongmanee K, Rangsin R. <u>Dietary behaviors and nutritional status of adolescents in a remote rural area of Thailand</u> . <i>J Med Assoc Thai</i> . 2005 Nov; 88 Suppl 3: S240-S246. PMID: 16858963.	Does not answer the question; nutrition status in Thailand.
Arsenault JE, Mora-Plazas M, Forero Y, López-Arana S, Marín C, Baylin A, Villamor E. <u>Provision of a school snack is associated with vitamin B-12 status, linear growth, and morbidity in children from Bogota, Colombia</u> . <i>J Nutr</i> . 2009 Sep; 139(9): 1, 744-1, 750. Epub 2009 Jul 8. PMID: 19587125.	Potentially malnourished before snack intervention in school; not conducted in a high human development country.
Benton D, Jarvis M. <u>The role of breakfast and a mid-morning snack on the ability of children to concentrate at school</u> . <i>Physiol Behav</i> . 2007 Feb 28; 90(2-3): 382-385. Epub 2006 Oct 31. PMID: 17078979.	Does not answer the question; about breakfast and snacking.
Briefel RR, Wilson A, Gleason PM. <u>Consumption of low-nutrient, energy-dense foods and beverages at school, home, and other locations among school lunch participants and nonparticipants</u> . <i>J Am Diet Assoc</i> . 2009 Feb; 109(2 Suppl): S79-S90. PMID: 19166676.	Does not include analyses for nutrients.
Burke LM, Slater G, Broad EM, Haukka J, Modulon S, Hopkins WG. <u>Eating patterns and meal frequency of elite Australian athletes</u> . <i>Int J Sport Nutr Exerc Metab</i> . 2003 Dec; 13(4): 521-538. PMID: 14967874.	Does not answer the question; about eating patterns and food frequency.

<p>Colapinto CK, Fitzgerald A, Taper LJ, Veugelers PJ. <u>Children's preference for large portions: Prevalence, determinants, and consequences.</u> <i>J Am Diet Assoc.</i> 2007 Jul; 107(7): 1, 183-1, 190. PMID: 17604749.</p>	<p>Does not answer the question; about fast food intake and snacking related to BMI.</p>
<p>Croll JK, Neumark-Sztainer D, Story M, Wall M, Perry C, Harnack L. <u>Adolescents involved in weight-related and power team sports have better eating patterns and nutrient intakes than non-sport-involved adolescents.</u> <i>J Am Diet Assoc.</i> 2006 May; 106(5): 709-717. PMID: 16647329.</p>	<p>Not evaluated by snacking; nutrients were not specific to snacking patterns but to team sport participation.</p>
<p>Davee AM, Blum JE, Devore RL, Beaudoin CM, Kaley LA, Leiter JL, Wigand DA. <u>The vending and à la carte policy intervention in Maine public high schools.</u> <i>Prev Chronic Dis.</i> 2005 Nov; 2 Spec no: A14. Epub 2005 Nov 1. PMID: 16263047.</p>	<p>Does not answer the question; snacking and overweight.</p>
<p>Delva J, O'Malley PM, Johnston LD. <u>Availability of more-healthy and less-healthy food choices in American schools: A national study of grade, racial/ethnic, and socioeconomic differences.</u> <i>Am J Prev Med.</i> 2007 Oct; 33(4 Suppl): S226-S239. PMID: 17884570.</p>	<p>Does not answer the question; about healthy advice available in schools.</p>
<p>Downs SM, Arnold A, Marshall D, McCargar LJ, Raine KD, Willows ND. <u>Associations among the food environment, diet quality and weight status in Cree children in Québec.</u> <i>Public Health Nutr.</i> 2009 Sep; 12(9): 1, 504-1, 511. Epub 2009 Jan 15. PMID: 19144239.</p>	<p>Does not answer the question; about food frequency and BMI.</p>
<p>Fox MK, Dodd AH, Wilson A, Gleason PM. <u>Association between school food environment and practices and body mass index of US public school children.</u> <i>J Am Diet Assoc.</i> 2009 Feb; 109(2 Suppl): S108-S117. PMID: 19166665.</p>	<p>Does not answer the question; about school food environment and BMI.</p>
<p>Garrido G, Webster AL, Chamorro M. <u>Nutritional adequacy of different menu settings in elite Spanish adolescent soccer players.</u> <i>Int J Sport Nutr Exerc Metab.</i> 2007 Oct; 17(5): 421-32. PMID: 18046052.</p>	<p>Does not answer the question; evaluation of two different menu settings.</p>
<p>Gonzalez W, Jones SJ, Frongillo EA. <u>Restricting snacks in U.S. elementary schools is associated with higher frequency of fruit and vegetable consumption.</u> <i>J Nutr.</i> 2009 Jan; 139(1): 142-144. Epub 2008 Dec 3. PMID: 19056643.</p>	<p>Does not answer the question; about restricting snacks.</p>

<p>Hallund J, Hatløy A, Benesi I, Thilsted SH. <u>Snacks are important for fat and vitamin intakes among rural African women: A cross-sectional study from Malawi.</u> <i>Eur J Clin Nutr.</i> 2008 Jul; 62(7): 866-871. Epub 2007 May 30. PMID: 17538535.</p>	<p>Not high human development country; half of women were lactating.</p>
<p>Hang CM, Lin W, Yang HC, Pan WH. <u>The relationship between snack intake and its availability of 4th to 6th graders in Taiwan.</u> <i>Asia Pac J Clin Nutr.</i> 2007; 16 Suppl 2: 547-553. PMID: 17723994.</p>	<p>Does not answer the question; evaluation of snacks in Taiwan.</p>
<p>Harris JL, Bargh JA, Brownell KD. <u>Priming effects of television food advertising on eating behavior.</u> <i>Health Psychol.</i> 2009 Jul; 28(4): 404-413. PMID: 19594263.</p>	<p>Does not answer the question; about TV advertisement and food intake.</p>
<p>Harrison K, Marske AL. <u>Nutritional content of foods advertised during the television programs children watch most.</u> <i>Am J Public Health.</i> 2005 Sep; 95(9): 1, 568-1, 574. PMID: 16118368.</p>	<p>Does not answer the question; about TV advertisement and food intake.</p>
<p>Husby I, Heitmann BL, O'Doherty Jensen K. <u>Meals and snacks from the child's perspective: The contribution of qualitative methods to the development of dietary interventions.</u> <i>Public Health Nutr.</i> 2009 Jun; 12(6): 739-747. Epub 2008 Aug 1. PMID: 18671890.</p>	<p>Sample size of less than 10 per group (N=9 in group one and N=8 in group two).</p>
<p>Huus K, Brekke HK, Ludvigsson JF, Ludvigsson J. <u>Relationship of food frequencies as reported by parents to overweight and obesity at five years.</u> <i>Acta Paediatr.</i> 2009 Jan; 98(1): 139-143. Epub 2008 Sep 24. PMID: 18823298.</p>	<p>It doesn't answer the question; about food frequency and obesity.</p>
<p>Karupaiah T, Chinna K, Mee LH, Mei LS, Noor MI. <u>What's on Malaysian television? A survey on food advertising targeting children.</u> <i>Asia Pac J Clin Nutr.</i> 2008; 17(3): 483-491. PMID: 18818170.</p>	<p>It doesn't answer the question; about TV viewing and food influence in Malaysia.</p>
<p>Klunklin S, Channoonmuang K. <u>Snack consumption in normal and undernourished preschool children in Northeastern Thailand.</u> <i>J Med Assoc Thai.</i> 2006 May; 89(5): 706-713. PMID: 16756059.</p>	<p>It doesn't answer the question; related to undernourished population.</p>

<p>Kresic G, Simundic B, Mandic ML, Kendel G, Zezelj SP. <u>Daily menus can result in suboptimal nutrient intakes, especially calcium, of adolescents living in dormitories.</u> <i>Nutr Res.</i> 2008 Mar; 28(3): 156-165. PMID: 19083403.</p>	<p>It doesn't answer the question; about daily menus in Croatia.</p>
<p>Larson NI, Neumark-Sztainer DR, Story MT, Wall MM, Harnack LJ, Eisenberg ME. <u>Fast food intake: Longitudinal trends during the transition to young adulthood and correlates of intake.</u> <i>J Adolesc Health.</i> 2008 Jul; 43(1): 79-86. Epub 2008 Mar 10. PMID: 18565441.</p>	<p>It doesn't answer the question; about fast food intake.</p>
<p>Lengyel CO, Whiting SJ, Zello GA. <u>Nutrient inadequacies among elderly residents of long-term care facilities.</u> <i>Can J Diet Pract Res.</i> 2008 Summer; 69(2): 82-88. PMID: 18538061.</p>	<p>It doesn't answer the question; about therapeutic diets.</p>
<p>Maddah M, Rashidi A, Mohammadpour B, Vafa R, Karandish M. <u>In-school snacking, breakfast consumption, and sleeping patterns of normal and overweight Iranian high school girls: A study in urban and rural areas in Guilan, Iran.</u> <i>J Nutr Educ Behav.</i> 2009 Jan-Feb; 41(1): 27-31. PMID: 19161917.</p>	<p>Does not answer the question; snacking and BMI in Iran.</p>
<p>Maillot M, Darmon N, Darmon M, Lafay L, Drewnowski A. <u>Nutrient-dense food groups have high energy costs: An econometric approach to nutrient profiling.</u> <i>J Nutr.</i> 2007 Jul; 137(7): 1, 815-1, 820. PMID: 17585036.</p>	<p>Does not answer the question; about nutrient profile.</p>
<p>Mariscal-Arcas M, Rivas A, Velasco J, Ortega M, Caballero AM, Olea-Serrano F. <u>Evaluation of the Mediterranean Diet Quality Index (KIDMED) in children and adolescents in Southern Spain.</u> <i>Public Health Nutr.</i> 2009 Sep; 12(9): 1, 408-1, 412. Epub 2008 Dec 17. PMID: 19087384.</p>	<p>Does not answer the question; about diet quality.</p>
<p>Miller CK, Gabbay RA, Dillon J, Apgar J, Miller D. <u>The effect of three snack bars on glycemic response in healthy adults.</u> <i>J Am Diet Assoc.</i> 2006 May; 106(5): 745-748. PMID: 16647336.</p>	<p>Does not answer the question; about snack and glycemic response.</p>
<p>Moore GF, Tapper K, Murphy S, Clark R, Lynch R, Moore L. <u>Validation of a self-completion measure of breakfast foods, snacks and fruits and vegetables consumed by 9- to 11-year-old schoolchildren.</u> <i>Eur J Clin Nutr.</i> 2007 Mar; 61(3): 420-430. Epub 2006 Sep 20. PMID: 16988648.</p>	<p>Does not answer the question; validity and reliability of dietary recall questionnaires.</p>

<p>Muthayya S, Thomas T, Srinivasan K, Rao K, Kurpad AV, van Klinken JW, Owen G, de Bruin EA. <u>Consumption of a mid-morning snack improves memory but not attention in school children.</u> <i>Physiol Behav.</i> 2007 Jan 30; 90(1): 142-150. Epub 2006 Nov 1. PMID: 17081574.</p>	<p>Does not answer the question; mid-morning snack and attention in schools.</p>
<p>Nakaya Y, Okita K, Suzuki K, Moriwaki H, Kato A, Miwa Y, Shiraishi K, Okuda H, Onji M, Kanazawa H, Tsubouchi H, Kato S, Kaito M, Watanabe A, Habu D, Ito S, Ishikawa T, Kawamura N, Arakawa Y; Hepatic Nutritional Therapy (HNT) Study Group. <u>BCAA-enriched snack improves nutritional state of cirrhosis.</u> <i>Nutrition.</i> 2007 Feb; 23(2): 113-120. PMID: 17234504.</p>	<p>Does not answer the question; study of a late evening snack in a population with cirrhosis.</p>
<p>Novaes JF, Franceschini Sdo C, Priore SE. <u>Mother's overweight, parents' constant limitation on the foods and frequent snack as risk factors for obesity among children in Brazil.</u> <i>Arch Latinoam Nutr.</i> 2008 Sep; 58(3) :256-264. PMID: 19137988.</p>	<p>Does not answer the question of snacks and nutrient intake.</p>
<p>Øverby NC, Margeirsdottir HD, Brunborg C, Dahl-Jørgensen K, Andersen LF; Norwegian Study Group for Childhood Diabetes. <u>Sweets, snacking habits, and skipping meals in children and adolescents on intensive insulin treatment.</u> <i>Pediatr Diabetes.</i> 2008 Aug; 9(4 Pt 2): 393-400. PMID: 18774998.</p>	<p>Population under study is on intensive insulin treatment.</p>
<p>Park SY, Paik HY, Skinner JD, Spindler AA, Park HR. <u>Nutrient intake of Korean-American, Korean, and American adolescents.</u> <i>J Am Diet Assoc.</i> 2004 Feb; 104(2): 242-245. PMID: 14760574.</p>	<p>Does not answer the question. Description of nutrient intake in Korea.</p>
<p>Phillips S, Jacobs Starkey L, Gray-Donald K. <u>Food habits of Canadians: Food sources of nutrients for the adolescent sample.</u> <i>Can J Diet Pract Res.</i> 2004 Summer; 65(2): 81-84. PMID: 15217526.</p>	<p>Does not answer the question; about nutrient intake.</p>
<p>Powell LM, Szczypka G, Chaloupka FJ, Braunschweig CL. <u>Nutritional content of television food advertisements seen by children and adolescents in the United States.</u> <i>Pediatrics.</i> 2007 Sep; 120(3): 576-583. PMID: 17766531.</p>	<p>Does not answer the question; about nutritional content of food advertisements.</p>
<p>Skinner JD, Ziegler P, Pac S, Devaney B. <u>Meal and snack patterns of infants and toddlers.</u> <i>J Am Diet Assoc.</i> 2004 Jan; 104(1 Suppl 1): s65-S70. PMID: 14702020.</p>	<p>Does not answer the question; description of infant meal patterns.</p>

<p>Sweitzer SJ, Briley ME, Robert-Gray C. <u>Do sack lunches provided by parents meet the nutritional needs of young children who attend child care?</u> <i>J Am Diet Assoc.</i> 2009 Jan; 109(1): 141-144. PMID: 19103336.</p>	<p>Does not answer the question of snacks and nutrients.</p>
<p>Van der Horst K, Timperio A, Crawford D, Roberts R, Brug J, Oenema A. <u>The school food environment associations with adolescent soft drink and snack consumption.</u> <i>Am J Prev Med.</i> 2008 Sep; 35(3): 217-223. Epub 2008 Jul 10. PMID: 18617354.</p>	<p>It doesn't answer the question; about snack and related cognitions.</p>
<p>Wu SJ, Chang YH, Wei IL, Kao MD, Lin YC, Pan WH. <u>Intake levels and major food sources of energy and nutrients in the Taiwanese elderly.</u> <i>Asia Pac J Clin Nutr.</i> 2005; 14(3): 211-220. PMID: 16169831.</p>	<p>Does not answer the question; about dietary intake.</p>
<p>Ziegler P, Briefel R, Ponza M, Novak T, Hendricks K. <u>Nutrient intakes and food patterns of toddlers' lunches and snacks: Influence of location.</u> <i>J Am Diet Assoc.</i> 2006 Jan; 106(1 Suppl 1): S124-S134. PMID: 16376636.</p>	<p>Does not answer the question; about infants and toddlers.</p>
<p>Ziegler P, Hanson C, Ponza M, Novak T, Hendricks K. <u>Feeding Infants and Toddlers Study: Meal and snack intakes of Hispanic and non-Hispanic infants and toddlers.</u> <i>J Am Diet Assoc.</i> 2006 Jan; 106(1 Suppl 1): S107-S123. PMID: 16376635.</p>	<p>Does not answer the question; about infants and toddlers.</p>

CHAPTER 4. DIETARY BEHAVIORS AND NUTRIENT INTAKE – EATING FREQUENCY

WHAT IS THE RELATIONSHIP BETWEEN EATING FREQUENCY AND NUTRIENT INTAKE?

Conclusion statement

Inadequate evidence is available to evaluate the relationship between eating frequency and nutrient intakes.

Grade

Limited

Evidence summary overview

Only three cross-sectional studies published since 2004 (Kerver JM et al, 2006; Macdiarmid J et al, 2009; and Storey KE et al, 2000), met the criteria for review to evaluate the relationship between eating frequency and nutrient intakes. Given this lack of robust evidence, a conclusion is not drawn regarding nutrient intakes and eating frequency.

Evidence summary paragraphs

Kerver et al, 2006 (positive quality), conducted a cross-sectional study to test the hypothesis that specific meal and snack patterns are associated with selected nutrient intakes in US adults. Using the 24-hour dietary recall from the Third National Health and Nutrition Examination Survey (NHANES), meal and snack patterns were described in relation to nutrient intakes. The study included US adults aged 20 years or older (N=15,978). On average, subjects reported a daily eating frequency of 4.90 (SE=0.04) with a range of one to 18 (median=4.18; mode=4). Daily eating frequency was categorized into five groups (one to two, three, four, five and six or more) based on distribution of the data. More frequent eaters (six or more times a day) were more likely to be middle aged (40 to 59 years), white, smokers, heavier drinkers, vitamin and mineral supplement users, with higher income and education levels than less-frequent eaters (one to two times a day). The most common meal pattern (31.6%) consisted of breakfast (B), lunch (L), dinner (D), and two or more snacks (S). Subjects who reported consuming this meal pattern were more likely to be female, middle-aged (40 to 59 years), white, nonsmokers, moderate drinkers, vitamin and mineral supplement users with higher education and income levels and moderate activity levels (33rd to 66th percentile). After controlling for the effects of age, sex, ethnicity, smoking status, alcohol intake, vitamin and mineral supplement use, body mass index (BMI), physical activity, income and energy intakes, daily eating frequency was positively related to carbohydrate (CHO) ($51.1 \pm 0.4\%$ of energy), folic acid (302 ± 4 mcg), vitamin C (11.3 ± 3.3 mg), calcium 887 ± 12 mg), magnesium (330 ± 3 mg), iron (16.4 ± 0.3 mg), potassium ($3,088 \pm 28$ mg) and fiber (17.6 ± 0.2 g), and inversely related to protein ($14.9 \pm 0.1\%$ of energy), total fat (32.7 ± 0.3 of energy), cholesterol (261 ± 5 mg) and sodium ($3,500 \pm 34$ mg) intakes. The groups reporting B, L, D and one S and B, L, D, and two or more S had the highest intakes of all micronutrients examined except cholesterol, vitamin B₆ and sodium, which were consumed in the highest amounts by the B, L, D, group (cholesterol= 323 ± 10.2 mg; vitamin B₆= 2.10 ± 0.05 mg; and

sodium=3,946±48.4mg). These findings suggest that meal and snack patterns may be markers for nutrient intakes and therefore diet quality.

Storey et al, 2009 (positive quality), conducted a cross-sectional study to identify whether students with poor diet quality had different macronutrient intakes, increased consumption of “other foods” and increased frequency of suboptimal meal behaviors (skipping meals and consuming meals away from home) in comparison with those with average or superior diet quality. Data included 2,850 Alberta and Ontario adolescents aged 14 to 17 years and diet quality was assessed using a food-based diet quality index modified to reflect the Canada’s Food Guide to Healthy Eating (CFGHE) (Poor, zero to one; Average, two to three; Superior, all four food groups). Univariate analysis revealed that those with poor diet quality had a lower frequency of breakfast (three or fewer days a week) consumption than did those with average and superior diet quality (every day); $P=0.002$. Frequency of consuming meals away from home yielded significant main effects for diet quality (Wilks’ lambda=0.97, $F(12, 4,810)=5.63$, $P<0.001$). Those with poor diet quality consumed significantly more meals or snacks (once a week) away from home at all locations than did those with superior diet quality (once a month).

Macdiarmid et al, 2009 (neutral quality), used cross-sectional data ($N=56$) from the National Survey of Sugar Intake among children in Scotland to investigate the meal and snacking patterns of school-aged children (five to 17 years old). Meals and snacks were defined by a food-based classification system based on ‘core’ (foods normally eaten as part of a traditional meal) and ‘non-core’ (foods and drinks easily consumed outside of a meal) foods. A meal was defined as an event containing one or more ‘core’ foods with or without ‘non-core’ foods or drinks, and a snack was defined as an event containing only ‘non-core’ foods or drinks. Seventy-eight percent of children had an average of between 2.5 and 3.5 meals per day and 98% of children ate one or more snacks. Boys ate significantly more meals than girls but a similar number of snacks, and children in the high-deprivation group ate more meals and fewer snacks than those in the lower-deprivation group. The number of meals and snacks eaten did not differ by age or BMI group. The median (inter-quartile range) number of items eaten within a snacking event was two (one to two) and in a meal was four (three to five) items [two (one to two) ‘core’ and two (one to three) ‘non-core’ items]. The average daily intake of saturated fatty acids (SFA) and non-milk extrinsic sugars (NMES) (% food energy) was higher from snacks than meals, but there was no difference in total fat. The number of meals, snacks, and total eating events per day and daily energy and nutrient intake (total fat, SFA and NMES) on weekdays did not differ between term-time and school holidays. The significant difference in the number of meals eaten on weekdays compared with weekend days was due to the wider variation in frequency of meals on weekdays rather than a difference in the median frequency. Despite the differences in meal frequency, the average daily energy, total fat, SFA and NMES intake (% food energy) did not differ significantly between weekdays and weekend days. In conclusion, children tended to follow a traditional pattern of three meals a day, which was consistent between age and BMI subgroups and between term-time and holidays.

Overview table

Author, Year, Study Design, Class, Rating	Study Subjects	Data Collection Instruments and Methods	Definitions of Meals	Prevalence of Meal Frequency	Key Outcomes
<p>Kerver JM, Yang EJ et al, 2006</p> <p>Study Design: Cross-sectional design</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Data from the NHANES III 1988 to 1994.</p> <p>N=15,978.</p> <p>Age: Adults 20 years or older.</p> <p>52.6% female; 82.7% non-Hispanic white; 11.8% non-Hispanic black; 5.5% Mexican-American.</p>	<p>24-hour diet recall.</p>	<p>B=self-identified first eating occasion in 24-hour recall.</p> <p>Eating frequency per day * one to two times a day; * three times a day; * four times a day; * five times a day; * six or more time a day.</p> <p>Eating intake patterns of B, Lunch (L), Dinner (D), Snacks (S):</p> <p>* B, L, D, ≥ two S</p> <p>* B, L, D, one S</p> <p>* B, L, ≥ two S</p> <p>* B, L, D</p> <p>* L, D, ≥ two S</p> <p>* Other.</p> <p>B Skipper = L, D, ≥ two S eating pattern.</p>	<p>Daily eating frequency = 4.90 (SE=0.04); range = one to 18; median = 4.18; mode = four.</p> <p>Most common meal pattern = B, L, D and ≥ two S (31.6%).</p>	<p>Daily eating frequency was positively related to CHO (51.1±0.4% of energy), folic acid (302±4ug), vitamin C (11.3±3.3mg), calcium (887±12mg), magnesium (330±3mg), iron (16.4±0.3mg), potassium (3,088±28mg) and fiber (17.6±0.2g) and inversely related to protein (14.9±0.1% of energy), total fat (32.7±0.3 of energy), cholesterol (261±5mg) and sodium (3,500±34mg) intakes.</p> <p>Groups reporting B, L, D, and one S and B, L, D, and ≥ two S had the highest intakes of all micronutrients examined, except cholesterol, vitamin B₆ and sodium, which were consumed in the highest amounts by the B, L, D, group (cholesterol=323±10.2mg; vitamin B₆=2.10±0.05mg and sodium=3,946±48.4mg).</p>

<p>Storey KE, Hanning RM et al, 2009</p> <p>Study Design: Cross-sectional study</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Data from Alberta and Ontario Adolescents Study.</p> <p>N=2,850.</p> <p>Age: 14- to 17-year-old male adolescents.</p>	<p>24-hour recall (one weekday).</p> <p>Self administered web-based survey (nutrient intakes and meal behaviors).</p> <p>Diet quality was assessed using a food-based diet quality index modified to reflect the Canada's Food Guide to Healthy Eating (CFGHE) numbers:</p> <p>Poor: Zero to one</p> <p>Average: Two to three</p> <p>Superior: All four food groups.</p>	<p>Frequency of meal consumption: How often do you usually eat breakfast, lunch, dinner, morning snacks, afternoon snacks, evening snacks?</p> <p>Frequency of meals away from home: How often do you eat meals or snacks prepared away from home?</p> <p>Mean of morning, afternoon, evening snacks = overall frequency of snack consumption.</p>	<p>Meal frequency for superior diet quality:</p> <p>B=4.38±0.17</p> <p>L=4.68±0.12</p> <p>D=4.87±0.08.</p> <p>Meal frequency for poor diet quality:</p> <p>B=3.89±0.06</p> <p>L=4.46±0.05</p> <p>D=4.83±0.03</p> <p>S=3.41±0.05</p>	<p>Those with poor diet quality had a ↓ frequency of breakfast (three or fewer days a week) consumption than did those with average and superior diet quality (every day); P=0.002.</p> <p>Frequency of consuming meals away from home yielded significant main effects for diet quality [Wilks' lambda=0.97, F (12, 4,810) = 5.63, P<0.001].</p> <p>Those with poor diet quality consumed significantly more meals or snacks (once a week) away from home at all locations, than did those with superior diet quality (once a month).</p>
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<p>Macdiarmid J, Loe J et al, 2009</p> <p>Study Design: Cross-sectional study</p> <p>Class: D</p> <p>Rating: Positive Quality</p>	<p>Data from a cross-sectional data from the National Survey of Sugar Intake among children in Scotland.</p> <p>N=156</p> <p>Age: Five- to 17-year-old adolescents.</p>	<p>Four-day non-weighed diet diary (three weekdays and one weekend day).</p>	<p>Meals and snacks were defined by a food-based classification system based on 'core' (foods normally eating as part of a traditional meal) and 'non-core' (foods and drinks easily consumed out with a meal) foods.</p> <p>Meal: Eating event containing one or more 'core' foods with or without 'non-core' foods or drinks.</p> <p>Snack: Eating event containing only 'non-core' foods or drinks.</p>	<p>Total eating events per day (median inter-quartile range):</p> <p>Term-time (N=114)=5.3 (5.0 to 6.3)</p> <p>School holidays (N=34)=5.3(4.6 to 6.0)</p> <p>Weekdays (N=106)=5.3 (5.0 to 6.1)</p> <p>Weekend day (N=106)=5.0 (4.0 to 6.0).</p>	<p>78% of children had an average of between 2.5 and 3.5 meals per day.</p> <p>Boys ate significantly more meals than girls but a similar number of snacks.</p> <p>Children from lower socio-economic groups ate more meals and fewer snacks than those in the high socio-economic group.</p> <p>Number of meals and snacks eaten did not differ by age or BMI median (inter-quartile range).</p> <p>The number of items eaten within in a meal was four (three to five) items [two (one to two) 'core' and two (one to three 'non-core' items].</p> <p>Average daily intake of SFA and non-milk extrinsic sugars (NMES) (% food energy) was ↑ from snacks than meals, but there was no difference in total fat.</p> <p>Number of meals, snacks and total eating events per day and daily energy and nutrient intake (total fat, SFA and NMES) on weekdays did not differ between term-time and school holidays.</p> <p>Total fat, SFA and NMES intake (% food energy) did not differ significantly between weekdays and weekend days.</p>
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Search plan and results

Inclusion criteria

- *Subjects/Population*: Human subjects.
- *Age*: Children, men and women of all ages.
- *Setting*: International.
- *Health Status*: Healthy and those with elevated chronic disease risk (CHD/CVD, type 2 diabetes, metabolic syndrome and obesity).
- *Nutrition Related Problem/Condition*: None.

Search Criteria

- *Study Design Preferences*: Randomized controlled trial (RCT) or clinical controlled studies, large non-randomized observational studies, cohort, case-control studies, systematic reviews and meta-analysis.
- *Size of Study Groups*: The sample size must equal 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*: June 2004 to November 2009.
- *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-reviewed journal.

Exclusion criteria

- *Subjects/Population*:
 - Animal and in vitro studies
 - Malnourished/developing populations or disease incidence not relative to US population (e.g., malaria).
- *Setting*: Hospitalized patients.
- *Health Status*: Medical treatment/therapy and diseased subjects.
- *Nutrition Related Problem/Condition*: All conditions.

Search Criteria

- *Study Design Preferences*: Not applicable.
- *Size of study groups*: Sample sizes <10.
- *Study Dropout rate*: If the dropout rate in a study is 20% or greater, the study will be rejected.
- *Year Range*: Prior to June 2004.
- *Authorship*: Studies by same author similar in content.
- *Languages*: Articles not in English.
- *Other*: Abstracts or presentations and articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed:

("meal frequency" OR "eating frequency" OR "meal times" OR "meal timing" OR "lunch frequency" OR "dinner frequency" OR (eating occasion*)) AND ("Nutritional Status"[mh] OR "nutritional requirements"[mh] OR "Nutritive Value"[mh] OR "nutrient adequacy" OR (nutrient intake*) OR "nutrient density" OR "diet quality" OR "nutrition assessment"[mh]) Limits: Humans, English

Date searched: 11/18/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 169
- Total articles identified to review from electronic databases: 24
- Articles identified via handsearch or other means: 1
- Number of Primary Articles Identified: 2
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 3
- Number of Articles Reviewed but Excluded: 22

Included articles (References)

1. Kerver JM, Yang EJ, Obayashi S, Bianchi L, Song WO. Meal and snack patterns are associated with dietary intake of energy and nutrients in US adults. *J Am Diet Assoc.* 2006 Jan; 106 (1): 46-53. PMID: 16390666.
2. Macdiarmid J, Loe J, Craig LC, Masson LF, Holmes B, McNeill G. Meal and snacking patterns of school-aged children in Scotland. *Eur J Clin Nutr.* 2009 Nov; 63 (11): 1, 297-1, 304. Epub 2009 Aug 26. PMID: 19707230.
3. Storey KE, Hanning RM, Lambraki IA, Driezen P, Fraser SN, McCargar LJ. Determinants of diet quality among Canadian adolescents. *Can J Diet Pract Res.* 2009 Summer; 70 (2): 58-65. PMID: 19515268.

Excluded articles

Excluded Articles	Reason for Exclusion
<p>Bridge A, Kipp W, Raine K, Konde-Lule J. <u>Nutritional status and food consumption patterns of young children living in Western Uganda.</u> <i>East Afr Med J.</i> 2006 Nov; 83 (11): 619-625.PMID: 17455451.</p>	<p>Does not answer the question. Study done in Uganda.</p>
<p>Buijzen M, Schuurman J, Bomhof E. <u>Associations between children's television advertising exposure and their food consumption patterns: A household diary-survey study.</u> <i>Appetite.</i> 2008 Mar-May; 50 (2-3): 231-239. Epub 2007 Jul 25.PMID: 17804119.</p>	<p>Does not answer the question. Exposure to food advertising an food consumption.</p>

<p>Burgess-Champoux TL, Larson N, Neumark-Sztainer D, Hannan PJ, Story M. <u>Are family meal patterns associated with overall diet quality during the transition from early to middle adolescence?</u> <i>J Nutr Educ Behav.</i> 2009 Mar-Apr; 41 (2): 79-86. PMID: 19304252.</p>	<p>Does not answer the question. Family meal patterns.</p>
<p>Cluskey M, Edlefsen M, Olson B, Reicks M, Auld G, Bock MA, Boushey CJ, Bruhn C, Goldberg D, Misner S, Wang C, Zaghoul S. <u>At-home and away-from-home eating patterns influencing preadolescents' intake of calcium-rich food as perceived by Asian, Hispanic and Non-Hispanic white parents.</u> <i>J Nutr Educ Behav.</i> 2008 Mar-Apr; 40 (2): 72-79. PMID: 18314082.</p>	<p>Does not answer the question. Eating patterns at home and away-from-home.</p>
<p>Demory-Luce D, Morales M, Nicklas T, Baranowski T, Zakeri I, Berenson G. <u>Changes in food group consumption patterns from childhood to young adulthood: The Bogalusa Heart Study.</u> <i>J Am Diet Assoc.</i> 2004 Nov; 104 (11): 1, 684-1, 691. PMID: 15499355.</p>	<p>Does not answer the question. About changes in consumption patterns.</p>
<p>Feldman S, Eisenberg ME, Neumark-Sztainer D, Story M. <u>Associations between watching TV during family meals and dietary intake among adolescents.</u> <i>J Nutr Educ Behav.</i> 2007 Sep-Oct; 39 (5): 257-263. PMID: 17826345.</p>	<p>Does not answer the question. Association of food intake and TV watching during family times.</p>
<p>Fox MK, Devaney B, Reidy K, Razafindrakoto C, Ziegler P. <u>Relationship between portion size and energy intake among infants and toddlers: Evidence of self-regulation.</u> <i>J Am Diet Assoc.</i> 2006 Jan; 106 (1 Suppl 1): S77-S83. PMID: 16376632.</p>	<p>Does not answer the question. Assess dietary intake of infants and toddlers.</p>
<p>Fox MK, Gordon A, Nogales R, Wilson A. <u>Availability and consumption of competitive foods in US public schools.</u> <i>J Am Diet Assoc.</i> 2009 Feb; 109 (2 Suppl): S57-S66. PMID: 19166673.</p>	<p>Does not answer the question. Availability of competitive foods.</p>
<p>Hanning RM, Woodruff SJ, Lambraki I, Jessup L, Driezen P, Murphy CC. <u>Nutrient intakes and food consumption patterns among Ontario students in grades six, seven and eight.</u> <i>Can J Public Health.</i> 2007 Jan-Feb; 98 (1): 12-16. PMID: 17278670.</p>	<p>Does not answer the question. About frequency of meals and weight.</p>

<p>Kant AK, Graubard BI. <u>Eating out in America, 1987-2000: Trends and nutritional correlates.</u> <i>Prev Med.</i> 2004 Feb; 38 (2): 243-249. PMID: 14715218.</p>	<p>Does not answer the question. Eating Out in America.</p>
<p>Kant AK, Graubard BI. <u>Secular trends in patterns of self-reported food consumption of adult Americans: NHANES 1971-1975 to NHANES 1999-2002.</u> <i>Am J Clin Nutr.</i> 2006 Nov; 84 (5): 1, 215-1, 223. PMID: 17093177.</p>	<p>Does not answer the question. Meals and snack consumption and food density.</p>
<p>Larson NI, Neumark-Sztainer D, Hannan PJ, Story M. <u>Family meals during adolescence are associated with higher diet quality and healthful meal patterns during young adulthood.</u> <i>J Am Diet Assoc.</i> 2007 Sep; 107 (9): 1, 502-1, 510. PMID: 17761227.</p>	<p>Does not answer the question. About family meals.</p>
<p>Maddah M, Rashidi A, Mohammadpour B, Vafa R, Karandish M. <u>In-school snacking, breakfast consumption, and sleeping patterns of normal and overweight Iranian high school girls: A study in urban and rural areas in Guilan, Iran.</u> <i>J Nutr Educ Behav.</i> 2009 Jan-Feb; 41 (1): 27-31. PMID: 19161917.</p>	<p>Does not answer the question. Skipping breakfast and obesity in Iran.</p>
<p>Moffat T, Galloway T. <u>Food consumption patterns in elementary school children.</u> <i>Can J Diet Pract Res.</i> 2008 Fall; 69 (3): 152-154. PMID: 18783641.</p>	<p>Does not answer the question. Description of food patterns.</p>
<p>Mota J, Fidalgo F, Silva R, Ribeiro JC, Santos R, Carvalho J, Santos MP. <u>Relationships between physical activity, obesity and meal frequency in adolescents.</u> <i>Ann Hum Biol.</i> 2008 Jan-Feb; 35 (1): 1-10. PMID: 18274921.</p>	<p>Does not answer the question. About obesity.</p>
<p>Piammongkol S, Marks GC, Williams G, Chongsuvivatwong V. <u>Food and nutrient consumption patterns in third trimester Thai-Muslim pregnant women in rural southern Thailand.</u> <i>Asia Pac J Clin Nutr.</i> 2004; 13 (3): 236-241. PMID: 15331334.</p>	<p>Does not answer the question. About food intake and socio-economic factors.</p>
<p>Pobocik RS, Trager A, Monson LM. <u>Dietary patterns and food choices of a population sample of adults on Guam.</u> <i>Asia Pac J Clin Nutr.</i> 2008; 17 (1): 94-100. PMID: 18364333.</p>	<p>Does not answer the question. Describe dietary patterns of adults in Guam.</p>

<p>Prochnik Estima Cde C, da Costa RS, Sichieri R, Pereira RA, da Veiga GV. <u>Meal consumption patterns and anthropometric measurements in adolescents from a low socioeconomic neighborhood in the metropolitan area of Rio de Janeiro, Brazil.</u> <i>Appetite</i>. 2009 Jun; 52 (3): 735-739. Epub 2009 Apr 5. PMID: 19501773.</p>	<p>Does not answer the question. About obesity.</p>
<p>Schunk JM, McArthur LH, Maahs-Fladung CA. <u>Correlates for healthful snacking among middle-income midwestern women.</u> <i>J Nutr Educ Behav</i>. 2009 Jul-Aug; 41 (4): 274-280. PMID: 19508933.</p>	<p>Does not answer the question. Measure snack quality.</p>
<p>Thang NM, Popkin BM. <u>Patterns of food consumption in Vietnam: Effects on socioeconomic groups during an era of economic growth.</u> <i>Eur J Clin Nutr</i>. 2004 Jan; 58 (1): 145-153. PMID: 14679380.</p>	<p>Does not answer the question. Inequalities on diets in Vietnam.</p>
<p>Vågstrand K, Barkeling B, Forslund HB, Elfhag K, Linné Y, Rössner S, Lindroos AK. <u>Eating habits in relation to body fatness and gender in adolescents—results from the 'SWEDES' study.</u> <i>Eur J Clin Nutr</i>. 2007 Apr; 61 (4): 517-525. Epub 2006 Sep 27. PMID: 17006444.</p>	<p>Does not answer the question. Eating habits and body fat (Included breakfast).</p>
<p>Woodruff SJ, Hanning RM. <u>Associations between family dinner frequency and specific food behaviors among grade six, seven, and eight students from Ontario and Nova Scotia.</u> <i>J Adolesc Health</i>. 2009 May; 44 (5): 431-436. Epub 2009 Jan 9. PMID: 19380089.</p>	<p>Does not answer the question. Family meals frequency.</p>

CHAPTER 5. DIETARY BEHAVIORS AND NUTRIENT INTAKE – MANDATORY FOLIC ACID FORTIFICATION AND NEURAL TUBE DEFECTS

WHAT IMPACT HAS MANDATORY FOLIC ACID FORTIFICATION HAD ON THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE US AND CANADA?

Conclusion statement

Strong and consistent evidence demonstrates a large reduction in the incidence of neural tube defects (NTDs) in the US and Canada following mandatory folic acid fortification.

Grade

Strong

Evidence summary overview

Of the 13 studies, nine of the studies were conducted in the United States and four were conducted in Canada. All studies were of neutral quality. Given the ecologic nature of mandatory fortification, it was impossible to conduct a controlled trial during this time.

Three of the US studies (Besser et al, 2007; Chen et al, 2008; Forrester et al, 2005) were conducted in single states: Arkansas, California, and Hawaii, respectively. All other US studies were conducted in multiple states or nationally represented using several different population-based birth registries. Only two of the studies did not demonstrate a decline in neural tube defects (NTD) post-fortification (Besser et al, 2007; Chen et al, 2008). Both of these trials were conducted in a single state: Arkansas and California, respectively. The study of Mosely et al, 2007 conducted in Arkansas had investigated a statewide folic acid supplementation trial during the transition to mandatory folic acid grain fortification; therefore, there is serious confounding, and it is not possible to fully ascertain the effects of the grain fortification vs. folic acid supplementation.

Of the four Canadian studies, one was conducted in Nova Scotia (Persad et al, 2002), one in Alberta (Godwing et al, 2008) and the other two were in seven of ten Canadian provinces (De Wals et al, 2007 and 2008). It appears that the two studies of De Wals et al (2007 and 2008) are the same cohort. All of the Canadian studies demonstrated a decline in NTDs. Similarly, it appears that the studies of Williams et al (2002 and 2009) used data from the same 24 population-based birth defect surveillance programs.

Only De Wals et al (2007 and 2008) and Williams et al (2002 and 2009) examined the NTD trends before fortification, during optional fortification and post-fortification in Canada and the United States, respectively. Only the studies of De Wals et al (2007 and 2008) demonstrated a continued reduction in NTD going from optional to mandatory fortification. The studies of Williams et al (2002 and 2009) demonstrated the reduction in NTD from pre- to mandatory fortification. They did not show a difference between optional fortification and mandatory fortification. The study of Williams et al, 2009, also examined the NTD reductions by race and ethnicity. The prevalence of spina bifida (SB) decreased 36% among Hispanic births, 34% among non-Hispanic white births and 19% for black births from pre- to post-fortification. The

decline in the prevalence of anencephaly (AN) was similar among Hispanic births and non-Hispanic white births. No significant decline in AN was observed in non-Hispanic black births during this time.

In summary, these data demonstrate strong and consistent temporal reductions in NTD in children following mandatory folic acid fortification in the United States and Canada that took place in the late 1990s. In the United States, the reduction is between 23% to 54% for SB and 11% to 16% for AN. In Canada, the reduction is approximately 53% for SB and 31% for AN. It is important to note that it is possible that other factors could have contributed to the trends observed in these trials. Awareness of the importance of folic acid supplementation for women of childbearing years was heightened during this time. Similarly, women may have increased the consumption of other foods high in folate during this time. Due to the ecologic nature of mandatory folic acid fortification in the US and Canada, further analysis of the different contributions to the causes of the NTD decline will need to be established, to fully understand the unique contributions of folic acid fortification of flour and uncooked cereals.

Evidence summary paragraphs

Besser et al, 2007 (neutral quality), in a cross-sectional study, used data from the Metropolitan Atlanta Congenital Defects Program (MACDP) to identify birth defects among infants and fetuses of at least 20 weeks of gestation. Three periods were considered: 1) 1968 to 1981, when prenatal diagnosis was rarely used, 2) 1981 to 1993, when the use of prenatal diagnosis was increasing in Atlanta but MACDP did not ascertain prenatal diagnoses, and 3) 1994 to 2003, when prenatal diagnosis was used in Atlanta and MACDP during folic acid fortification. During January 1, 1968 to December 31, 2003, 434 infants and fetuses were identified with AN and 663 with SB. Total prevalence of both AN and SB declined during this time. Estimates of the annual percent change (APC) in prevalence of AN were: -6.9% (95% CI: -10.0, -3.6) for period 1; -2.9% (95% CI: -7.9, 2.3) for period 2; and -6.8% (95% CI: -12.6, -0.7) for period 3. Estimates of the APC in prevalence for SB were -7.1% for period 1, -7% for period 2 and -6.2% for period 3. The 95% confidence intervals around the APC for all three periods overlapped, indicating no significant (NS) variation in the point estimates of the slopes. This analysis suggested that changes in AN and SB surrounding folic acid fortification could be part of pre-existing trends.

Canfield et al, 2005 (neutral quality), in a trend study, assessed the effect of fortification on NTD rates. For 16 birth defects categories selected for the study, birth prevalence for two time periods was calculated with data submitted from 23 states in 1995 to 1996 (pre-fortification) and 1999 to 2000 (post-fortification). Of the 23 participating programs, eight conducted case ascertainment among pregnancy terminations. For most of the conditions studied, a decline in prevalence was observed comparing the 1999 to 2000 to the 1995 to 1996. Among other conditions AN (PR=0.84, 95% CI: 0.76, 0.94) and SB (PR=0.66, 95% CI: 0.61, 0.71) had statistically significant declines. The reductions in prevalence were two to three percentage points greater among the programs with prenatal data. Prevalence ratios appeared to vary for some defects depending on the programs' availability of prenatal ascertainment. The significant declines for SB and AN were observed in both groups of registries.

CDC Report, 2004 (neutral quality), conducted a noncomparative descriptive report

using data from 23 population-based surveillance systems that included prenatal ascertainment of these birth defects from two 24-month periods (pre-fortification period: 1995 to 1996 and post-fortification period: 1999 to 2000). The estimated number of NTD-affected pregnancies in the US declined from 4,000 in 1995 to 1996 to 3,000 in 1999 to 2000. After fortification, there was a 27% decline in NTD-affected pregnancies among systems with prenatal ascertainment and a 26% decline among systems without prenatal ascertainment. 1,180 fetal deaths (occurring at less than 20 weeks) or elective terminations occurred before fortification, compare with 840 after fortification.

Chen et al, 2008 (neutral quality), in a trend study, compared the slopes of two regression lines that summarized the annual change in NTD prevalence before (pre-fortification slope) and after (post-fortification slope). Data selected all deliveries in eight central California counties, reported as vital statistics and affected pregnancies identified by birth defects surveillance between January 1, 1989 and December 31, 2003. Two periods were considered: Pre-fortification period (January 1, 1989 to September 30, 1996) Post-fortification period (October 1, 1998 to December 31, 2003). From this data, 690 NTD cases were reported among 886,985 deliveries, as well as 420 SB and 270 AN cases. The average prevalence over the entire study period for all NTDs was 77.8 cases per 100,000 deliveries, and 30.4 and 47.4 cases per 100,000 deliveries for AN and SB respectively. For all NTD combined, the slopes showed that prevalence were decreasing by 7.5 (slope: -7.5; 95% CI: -12.4, -2.5) cases per 100,000 deliveries per year before fortification, whereas NTD prevalence were no longer decreasing after fortification. Comparison of the differences of the two slopes showed that the fortification slope exceeded the pre-fortification slope by 12.6 (95% CI: 2.6, 22.6) cases per 100,000 deliveries per year. Prevalence ratios for all NTDs combined and for AN and SB separately were less than one, suggesting that the post-fortification prevalence were lower than the pre-fortification prevalence. Estimates for NTDs overall and for AN were significant (upper confidence=1.00) and the estimate for SB was not significant (upper confidence limit=1.1).

De Wals et al, 2007 (neutral quality), in a retrospective cohort study evaluates baseline rates of NTDs on seven Canadian provinces from 1993 to 2002, and the magnitude of the decrease after folic acid fortification. From the data, 2,446 subjects with NTD were identified; 60% of pregnancies affected with NTDs were terminated after prenatal diagnosis (SB53% and AN 34%). The overall ratio of AN to SB was 0.65, and there was no significant (NS) variation of this ratio during the study years. Prevalence of NTDs showed a stable pattern rate from 1993 through 1997, followed by a decrease from 1998 through 2000 and stabilization thereafter. There was no significant downward trend during the pre-fortification years from 1993 through 1997, either in the whole data set or in any of the participating provinces. Overall prevalence of NTDs at birth decreased from 1.58 per 1000 births before fortification to 0.86 per 1,000 births during the full-fortification period, a 46% reduction (RR=0.54; 95% CI: 0.49, 0.60). The magnitude of the decrease was higher for SB (53%) than for either AN (38%, P=0.02) or encephalocele (31%, P=0.03). Also, the data showed a gradient between the east-to-west in the pre-fortification rates of defects and in the magnitude of rate reduction after fortification was fully implemented.

De Wals et al, 2008 (neutral quality), in a retrospective study, assessed the impact of fortification policy on the frequency of NTDs. The study included live-births, stillbirths, and termination of pregnancies because of fetal anomaly to women resident in seven

Canadian provinces, from 1993 to 2002. Data were divided in three periods: 1) all births ending before September 30, 1997 [belonging to the pre-fortification period (N=970,191)], 2) those between October 1, 1997 and March 31, 2000 [belonging to a partial fortification period (N=455,889)], and 3) those after this date [occurring during the full fortification period (N=487,034)]. A total of 1,286 SB cases were identified (51% live-births, 3% stillbirths and 46% terminations). The overall prevalence rate of SB decreased from 0.86 per 1,000 during the pre-fortification period to 0.57 per 1,000 during the partial fortification period and to 0.40 per 1,000 during full fortification period (P for linear trend <0.0001). The multivariate analysis showed the effect of fortification in reducing the proportion of upper defects remained while controlling for the region and for the type of birth (OR=0.56; 95% CI: 0.34, 0.91; P=0.02 for the partial fortification vs. pre-fortification period and for the full fortification period vs. pre-fortification period (OR=0.31, 95% CI: 0.16, 0.60; P<0.001).

Forrester et al, 2005 (neutral quality), in a trend study examined the potential impact of folic acid fortification on the rates of selected birth defects using data from a population-based birth defects registry in Hawaii. Data from 1986 to 2002 were divided in two periods, and two trends were examined. The first set was 1986 to 1996 (pre-fortification) and 1999 to 2002 (mandatory fortification). The second set was 1993 to 1996 (pre-fortification) and 1999 to 2002 (mandatory fortification), thus using equal lengths of time both before and after fortification. Results for the first set of data showed that birth defects rate had declined after folic acid fortification by 10% and 100% for all but three of the birth defects categories. The decline was not statistically significant for NTDs. For the second set, all but three of the defects categories showed a decline in rate after folic acid fortification. Among those, NTD (R=0.64; 95% CI: 0.44, 0.93), and SB (R=0.58; CI: 0.35, 0.96) were statistically significant.

Godwin et al, 2008 (neutral quality), in a trend study assessed changes in birth prevalence of select structural congenital anomalies between pre-fortification (1992 to 1996) and post-folic acid fortification (1999 to 2003) of grain products using data from Canada-based Alberta Congenital Anomalies Surveillance System (ACASS). Significant decreases in the birth prevalence of SB (OR=0.51, 95 % CI: 0.36, 0.73) during the post-fortification period. Birth prevalence decreases for AN were not statistically significant.

Honein et al, 2001 (neutral quality), in a trend study, evaluated the impact of food fortification with folic acid on NTD birth prevalence. Data from the National Study of Birth Certificate Data for live births to women in 45 US states and Washington, DC, between January 1990 and December 1999 were divided in two periods: Before fortification (October 1995 through December 1996) compared with after mandatory fortification (October 1998 through December 1999). The birth prevalence of NTDs reported on birth certificates decreased from 37.8 per 100,000 live births before fortification to 30.5 per 100,000 live births conceived after mandatory folic acid fortification, representing a 19% decline (PR=0.81; 95% CI: 0.75 to 0.87). During the same period, NTD birth prevalence declined from 53.4 per 100,000 to 46.5 per 100,000 (PR=0.87; 95% CI: 0.64, 1.18) for women who received only third-trimester or no prenatal care.

Mosley et al, 2007 (neutral quality), in a population-based longitudinal study, assessed the rates of NTDs in Arkansas per 10,000 live births. Data from the Arkansas Reproductive Health Monitoring System (ARHMS), which monitored birth defects among Arkansas women, showed that the use of supplements was 32%.

Rates of NTDs declined from 11.9 per 10,000 births in 1994 to 1995 to 7.2 per 10,000 live births in 2002 to 2003. In summary, NTDs in Arkansas has declined 40% since intervention programs (supplementation and fortification) were implemented.

Mosley et al, 2007 (neutral quality), in a population-based longitudinal cohort study, evaluated the rates of NTDs. Data from the Arkansas Reproductive Health Monitoring System (ARHMS) monitored birth defects among Arkansas women, and identified eligible birth defects among live-born or stillborn infants, miscarriages or electively terminated pregnancies. The data were divided in two periods: 1) 1994 to 1995 and 2) 2002 to 2003. Among Arkansas residents, supplement use was 32%; rates of NTDs declined from 11.9 per 10,000 births in 1994 to 1995 to 7.2 per 10,000 live births in 2002 to 2003. Among Hispanic births the most recent rate (10 per 10,000 births per year) was about half the rate (19.8 per 10,000 births per year) before public health interventions. Among whites, NTD rates per 10,000 births declined from 13.5 per year to 8.7. Rates per 10,000 births for blacks had increased slightly (5.8 to 6.6) but not statistically significant. In summary, NTDs in Arkansas have declined 40% since intervention programs (supplementation and fortification) were implemented.

Persad et al, 2002 (neutral quality) in a retrospective cohort study evaluated the annual incidence of all open NTDs, including those occurring in stillbirths and terminated pregnancies, in Nova Scotia over a 10-year period (1991 to 2000). The period spans times before and after folic acid supplementation initiatives and before and after folic acid fortification of grain products was implemented. Comparing pre- vs. post-fortification periods (1991 to 1997 vs. 1998 to 2000), incidence declined for open NTDs, including SB and AN. Open NTDs fell 54%, from 2.58 per 1,000 births on average during 1991 to 1997 to 1.17 per 1,000 births during 1998 to 2000 (RR=0.46, 95% CI: 0.32 to 0.66, P<0.001). Mean annual incidence of SB decreased from 1.51 before to 0.62 per 1,000 births after folic acid fortification (RR=0.40, 95% CI: 0.25 to 0.67, P<0.001). Mean annual incidence of AN decreased from 0.93 before to 0.38 per 1,000 births after folic acid fortification (RR=0.41, 95% CI: 0.22 to 0.77, P=0.004). In summary, fortification of grain products in Nova Scotia resulted in a significant reduction in the incidence of NTDs.

Williams et al, 2002 (neutral quality), in a trend study, evaluated data from 24 population-based birth defects surveillance programs (nine programs with and 13 without prenatal ascertainment). The study identified 5,630 cases of SB and AN. The data was divided in three categories: Before folic acid fortification (January 1995 to December 1996), optional fortification (January 1997 to September 1998) and mandatory fortification (October 1998 to December 1999). The prevalence of SB and AN during the pre- to the mandatory fortification period decreased 31% for SB (PR=0.69, 95% CI: 0.63, 0.74) and 16% for AN (PR=0.84, 95% CI: 0.75, 0.95). The prevalence of SB decreased 40% (PR=0.60, 95% CI: 0.51, 0.71) among the nine programs with prenatal ascertainment, and 28% (PR=0.72, 95% CI: 0.65, 0.80) among the 13 programs without prenatal ascertainment. No decline was observed from the optional to the mandatory fortification period. In conclusion, the decline in the prevalence of SB was temporally associated with folic acid fortification.

Williams et al, 2005 (neutral quality), in a trend study, evaluates prevalence of SB and AN among racial or ethnic groups during the transition to mandatory folic acid fortification in the US. The study included 4,468 cases of SB and 2,625 cases of AN from 21 population-based birth defects surveillance systems. Also, the data (1995 to 2002) were divided in three periods: Pre-fortification period (January 1995 to

December 1996), optional fortification period (January 1997 to September 1998) and the mandatory fortification period (October 1998-December 2002). Prevalence ratio (PR) were calculated by dividing the prevalence from the mandatory fortification by the prevalence in the pre-fortification period. The prevalence of SB decreased 36% among Hispanic births from the pre-fortification to the mandatory fortification period (PR=0.64; 95% CI: 0.56, 0.74), 34% among non-Hispanic white births (PR= 0.66; 95% CI: 0.60, 0.72) and 19% for black births (PR=0.81; 95% CI: 0.67, 1.00). The decline in the prevalence of AN was similar among Hispanic births (PR: 0.74; 95% CI: 0.62, 0.88) and non-Hispanic white births (PR=0.71; 95% CI: 0.63, 0.80). No significant decline was observed among non-Hispanic black births.

Overview table

Author, Year, Study Design, Class, Rating	Population/Sample Description	Measurements or Intervention	Significant Outcomes
<p>Besser LM, Williams LJ et al, 2003</p> <p>Study Design: Trend Study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>Data from the Metropolitan Atlanta Congenital Defects Program (MACDP) identified birth defects among infants and fetuses of at least 20 weeks of gestation.</p> <p>Periods considered:</p> <p>1968 to 1981 (prenatal diagnosis was rarely used)</p> <p>1981 to 1993 (use of prenatal diagnosis was increasing in Atlanta)</p> <p>1994 to 2003 (prenatal diagnosis was used during folic acid fortification).</p>	<p>Prevalence of AN and SB for three time periods (plotted number of infants and fetuses with AN or SB per 10,000 live-births and determined slope of line regression). The slope as defined as the annual percent Δ in AN or SB prevalence.</p> <p>Prevalence of AN and SB during each prenatal ascertainment period for the following: Pregnancy outcome, sex, mother's race, gravidity and mother's age.</p>	<p>During January 1, 1968 to December 31, 2003 434 infants and fetuses were identified with AN and 663 with SB.</p> <p>Total prevalence of both AN and SB \downarrow during this time. Estimates of the annual percent Δ (APC) in prevalence of AN were: -6.9% (95% CI: -10.0, -3.6) for period 1; -2.9% (95% CI: -7.9, 2.3) for period 2; and -6.8% (95% CI: -12.6, -0.7).</p> <p>Estimates of the APC in prevalence for SB were -7.1% for period 1, -7% for period 2 and -6.2% for period 3.</p> <p>The 95% CIs around the APC for all three periods overlapped, indicating NS variation in the point estimates of the slopes.</p>

<p>CDC, 2004</p> <p>Study Design: Non-comparative descriptive report</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>Total US births derived from National Vital Statistics System, and data from 23 population-based surveillance systems that include prenatal ascertainment of these birth defects from two 24-month periods:</p> <p>Pre-fortification period (1995 to 1996)</p> <p>Post-fortification period (1999 to 2000).</p>	<p>The number of NTD-affected pregnancies and births determined as prevalence multiplied by the average total number of U.S. births during pre-fortification and post-fortification years.</p> <p>Fetal deaths and elective pregnancies</p> <p>Systems with prenatal ascertainment: Estimated total number of pregnancies, including live births, stillbirths, prenatally diagnosed cases and elective terminations.</p>	<p>The estimated number of NTD-affected pregnancies in the US ↓ from 4,000 in 1995 to 1996 to 3,000 in 1999 to 2000.</p> <p>After fortification, there was a 27% ↓ in NTD-affected pregnancies among systems with prenatal ascertainment and a 26% decline among systems without prenatal ascertainment.</p> <p>1,180 fetal deaths (occurring at less than 20 weeks) or elective terminations occurred before fortification, compare with 840 after fortification.</p>
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<p>Canfield M, Collins J et al, 2005</p> <p>Study Design: Trend study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>Data from 23 state registries during the time periods: 1995 to 1996 1999 to 2000.</p>	<p>Δs in birth prevalence between the two time periods were assessed by calculating prevalence ratios and 95% CIs for 16 birth defects.</p>	<p>Of the 23 participating programs, eight conducted case ascertainment among pregnancy terminations.</p> <p>For most of the conditions studied, a ↓ in prevalence was observed comparing the 1999 to 2000 to the 1995 to 1996 date ranges. Among other conditions, AN (PR=0.84, 95% CI: 0.76 to 0.94) and SB (PR=0.66, 95% CI: 0.61 to 0.71) had statistically significant declines.</p> <p>The reductions in prevalence were two to three percentage points greater among the programs with prenatal data. Prevalence ratios appeared to vary for some defects, depending on the programs' availability of prenatal ascertainment. The significant declines for SB and AN were observed in both groups of registries.</p>
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<p>Chen B, Charmichael S et al, 2008</p> <p>Study Design: Trend study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>All deliveries in eight central California counties, reported as vital statistics and affected pregnancies identified by birth defects surveillance between January 1, 1989 and December 31, 2003.</p> <p>Two periods were considered:</p> <p>Pre-fortification period (January 1, 1989 to September 30, 1996)</p> <p>Post-fortification period (October 1, 1998 to December 31, 2003).</p>	<p>Compared the slopes of two regression lines that summarized the annual change in NTD prevalence before (pre-fortification slope) and after (post-fortification slope).</p> <p>Prevalence ratios (PR) were calculated by dividing the overall prevalence in the post-fortification period by that of the pre-fortification period.</p>	<p>690 NTD cases were reported among 886,985 deliveries, as well as 420 SB and 270 AN cases. The average prevalence over the entire study period for all NTDs was 77.8 cases per 100,000 deliveries and 30.4 and 47.4 cases per 100,000 deliveries for AN and SB, respectively.</p> <p>For all NTD combined, the slopes showed that prevalence were ↓ by 7.5 (slope: -7.5; 95% CI: -12.4, -2.5) cases per 100,000 deliveries per year before fortification, whereas NTD prevalence were no longer ↓ after fortification. Comparison of the differences of the two slopes showed that the fortification slope exceeded the pre-fortification slope by 12.6 (95% CI: 2.6, 22.6) cases per 100,000 deliveries per year.</p> <p>Prevalence ratios for all NTDs combined and for AN and SB separately were less than one, suggesting that the post-fortification prevalence were lower than the pre-fortification prevalence. Estimates for NTDs overall and for AN were significant (upper confidence = 1.00) and the estimate for SB was NS(upper confidence limit = 1.1)</p>
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<p>De Walls P, Tairou F et al, 2007</p> <p>Study Design: Trend Study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>Live-births, stillbirths and terminations of pregnancies because of fetal anomalies among women residing in seven of the 10 Canadian provinces from 1993 to 2002.</p>	<p>Baseline rates of NTDs on each province and the magnitude of the ↓ after folic acid fortification.</p>	<p>2,446 subjects with NTD were identified.</p> <p>60% of pregnancies affected with NTDs were terminated after prenatal diagnosis, as well as SB 53% and AN 34%. The overall ratio of AN to SB was 0.65, and there was NS variation of this ratio during the study years.</p> <p>Prevalence of NTDs showed a stable pattern rate from 1993 through 1997, followed by a ↓ from 1998 through 2000 and stabilization thereafter. There was a NS downward trend during the pre-fortification years from 1993 through 1997, either in the whole data set or in any of the participating provinces.</p> <p>Overall prevalence of NTDs at birth ↓ from 1.58 per 1,000 births before fortification to 0.86 per 1,000 births during the full-fortification period, a 46% reduction (RR=0.54; 95% CI: 0.49 to 0.60). The magnitude of the ↓ was higher for SB (53%) than for either AN (38%, P=0.02) or encephalocele (31%, P=0.03). Also, the data showed a gradient between the east-to-west rates of defects and in the magnitude of rate reduction after fortification was fully implemented.</p>
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<p>De Wals P, Tairou F et al, 2008</p> <p>Study Design: Retrospective cohort study</p> <p>Class: B</p> <p>Rating: Neutral</p>	<p>The study included live-births, stillbirths and termination of pregnancies because of fetal anomaly to women resident in seven Canadian provinces, from 1993 to 2002.</p> <p>Data were divided in three periods:</p> <p>Births ending before September 30, 1997 [belonging to the pre-fortification period (N=970, 191)]</p> <p>Those between October 1, 1997 and March 31, 2000 [belonging to a partial fortification period (N=455,889)]</p> <p>Those after this date [occurring during the full fortification period (N=487,034)].</p>	<p>Prevalence rates were calculated as the sum of SB cases in live-births, stillbirths and induced abortions, divided by total live- and stillbirths.</p> <p>Theoretical birth date was calculated for each NTD case assuming 40 weeks gestation [date of birth or abortion (gestation length in weeks + 40 weeks)], since a large proportion of NTD-affected pregnancies were terminated.</p>	<p>A total of 1,286 SB cases were identified (51% live-births, 3% stillbirths and 46% terminations).</p> <p>The overall prevalence rate of SB ↓ from 0.86 per 1,000 during the pre-fortification period, to 0.57 per 1,000 during the partial fortification period, and to 0.40 per 1,000 during full fortification period (P for linear trend < 0.0001).</p> <p>The multivariate analysis, the effect of fortification in reducing the proportion of upper defects remained while controlling for the region and for the type of birth (OR=0.56; 95% CI: 0.34, 0.91; P=0.02 for the partial fortification vs. pre-fortification period, and for the full fortification period vs. pre-fortification period (OR=0.31, 95% CI: 0.16, 0.60; P<0.00.1).</p>
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<p>Forrester MB and Merz RD, 2005</p> <p>Study Design: Trend study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>Data collected from the Hawaii Birth Defects Program (HBDP) and active statewide population-based birth defects registry.</p> <p>Two trends were examined:</p> <p>The first set was 1986 to 1996 (pre-fortification) and 1999 to 2002 (mandatory fortification)</p> <p>The second set was 1993 to 1996 (pre-fortification) and 1999-2002 (mandatory fortification).</p> <p>Thus, using equal lengths of time, both before and after fortification.</p>	<p>Rates for each birth defect were calculated for each time period, using denominators derived from birth certificates. Rates from mandatory fortification were compared to the corresponding pre-fortification rate by calculating rate ratios and 95% CIs.</p>	<p>Results for the first set of data showed that birth defect rate had ↓ after folic acid fortification by 10% and 100% for all but three of the birth defects categories. The decline was NS for NTDs.</p> <p>For the second set, the pre-fortification period was considered from 1993 to 1996, all but three of the defects categories showed a decline in rate after folic acid fortification. In this case, the reduction in NTDs (R=0.64; 95% CI: 0.44, 0.93) and SB (R=0.58; CI: 0.35, 0.96) was statistically significant.</p>
<p>Godwin KA, Sibbald B et al, 2008</p> <p>Study Design: Trend Study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>Data from the Canada-based Alberta Congenital Anomalies Surveillance System (ACASS) up to one year of age from numerous sources.</p> <p>Two periods were considered:</p> <p>1992 to 1996 (pre-fortification)</p> <p>1999 to 2003 (post-fortification).</p>	<p>Δs in birth prevalence of select structural congenital anomalies between pre- and post-folic acid fortification of grain products.</p>	<p>N=389,349 live-births and stillbirths (198,321 in 1992 to 1996 and 191,028 in 1999 to 2003).</p> <p>Significant ↓ in SB prevalence (OR 0.51; 95 % CI: 0.36, 0.73; P<0.003) were observed during the post-fortification period. Birth prevalence ↓ for AN were NS.</p> <p>Abortion data was excluded from the analysis.</p>

<p>Honein MA, Paulozzi LJ et al, 2001</p> <p>Study Design: Trend study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>National study of birth certificate data for live births to women in 45 US states and Washington, DC, between January 1990 and December 1999.</p>	<p>Birth certificate reports of SB and AN before fortification (October 1995 through December 1996), compared with after mandatory fortification (October 1998 through December 1999).</p>	<p>The birth prevalence of NTDs reported on birth certificates ↓ from 37.8 per 100,000 live births before fortification, to 30.5 per 100,000 live births conceived after mandatory folic acid fortification, representing a 19% ↓ (PR=0.81; 95% CI, 0.75 to 0.87).</p> <p>During the same period, NTD birth prevalence ↓ from 53.4 per 100,000 to 46.5 per 100,000 (PR=0.87; 95% CI: 0.64, 1.18) for women who received only third trimester or no prenatal care.</p>
<p>Mosley B, Hobbs C et al, 2007</p> <p>Study Design: Population-based longitudinal cohort study</p> <p>Class: B</p> <p>Rating: Neutral</p>	<p>Data from the Arkansas Reproductive Health Monitoring System (ARHMS), monitored birth defects among Arkansas women and identified eligible birth defects among live-born or stillborn infants, miscarriages or electively terminated pregnancies.</p> <p>The data were divided in two periods: 1994 to 1995 2002 to 2003.</p>	<p>Rates of NTDs in Arkansas cases per 10,000 live births. NTDs included SB and AN.</p>	<p>Among Arkansas residents, supplement use was 32%; rates of NTDs ↓ from 11.9 per 10,000 births in 1994 to 1995 to 7.2 per 10,000 live births in 2002 to 2003.</p> <p>Among Hispanic births, the most recent rate (10 per 10,000 births per year) was about half the rate (19.8 per 10,000 births per year) before public health interventions.</p> <p>Among whites, NTD rates per 10,000 births ↓ from 13.5 per year to 8.7. Rates per 10,000 births for blacks had ↑ slightly (5.8 to 6.6), but NS.</p>

<p>Persad VL, Van den Hoff MC et al, 2002</p> <p>Study Design: Retrospective cohort study</p> <p>Class: B</p> <p>Rating: Neutral</p>	<p>Ten-year period data from January 1, 1991 to December 31, 2000 from live-birth and stillbirth, with open NTDs from the Nova Scotia Atlee Perinatal database and the number of terminated pregnancies affected by NTDs from the Fetal Anomaly database.</p> <p>The data were divided in four periods based on:</p> <p>Canada's recommendation for pre-conceptional folic acid supplementation in 1994. Comparisons were made between periods before supplementation (1991 to 1994) and after supplementation (1995 to 1997);</p> <p>Canada's mandatory folic acid fortification of grain products in 1998. Comparison were made between before fortification (1991 to 1997) and after fortification (1998 to 2000).</p>	<p>Annual incidence of all open NTDs, including those occurring in stillbirths and terminated pregnancies. NTDs included SB, AN and encephaloceles.</p>	<p>Comparing pre- vs. post-supplementation periods (1991 to 1994 vs. 1995 to 1997), there were NS Δs in total annual incidence of open NTDs.</p> <p>The mean annual incidence of NTDs was 2.55 during 1991 to 1994 and 2.61 during 1995 to 1997 per 1,000 births (RR=1.02, 95% CI: 0.77 to 1.35, P=0.87). The mean annual incidence for SB was 1.44 during 1991 to 1994 and 1.60 during 1995 to 1997 per 1,000 births (RR=1.11, 95% CI: 0.79 to 1.60, P=0.64). The mean annual incidence for AN was 1.00 to 0.82 per 1,000 births (RR=0.82, 95% CI: 0.51 to 1.32, P=0.49).</p> <p>Comparing pre- vs. post-fortification periods (1991 to 1997 vs. 1998 to 2000), incidence \downarrow for open NTDs, including SB and AN. Open NTDs fell 54%, from 2.58 per 1,000 births on average during 1991 to 1997 to 1.17 per 1,000 births during 1998 to 2000 (RR=0.46, 95% CI: 0.32 to 0.66, P<0.001).</p> <p>Mean annual incidence of SB \downarrow from 1.51 before to 0.62 per 1,000 births after folic acid fortification (RR=0.40, 95% CI: 0.25 to 0.67, P<0.001). The mean annual incidence of AN \downarrow from 0.93 to 0.38 per 1,000 births after folic acid fortification (RR=0.41, 95% CI: 0.22, 0.77, P=0.004)</p>
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<p>Williams LJ, Mai CT et al, 2002</p> <p>Study Design: Trend study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>24 population-based birth defects surveillance programs (nine programs with and 13 without prenatal ascertainment), divided in three categories:</p> <p>Before folic acid fortification (January 1995 to December 1996)</p> <p>Optional fortification (January 1997 to September 1998)</p> <p>Mandatory fortification (October 1998 to December 1999).</p>	<p>Prevalence of SB and AN. Prevalence ratios (PR) calculated dividing prevalence from the mandatory fortification period by the pre-fortification period.</p>	<p>Prevalence of SB and AN from the pre- to the mandatory fortification period ↓: 31% for SB (PR=0.69, 95% CI: 0.63 to 0.74) and 16% for AN (PR=0.84, 95% CI: 0.75, 0.95).</p> <p>The prevalence of SB ↓ 40% (PR=0.60, 95% CI: 0.51, 0.71) among the nine programs with prenatal ascertainment, and 28% (PR=0.72, 95% CI: 0.65, 0.80) among the 13 programs without prenatal ascertainment.</p> <p>No ↓ was observed from the optional to the mandatory fortification period.</p> <p>The ↓ in the prevalence of AN remained significant among programs with prenatal ascertainment (PR=0.80, 95% CI: 0.66, 0.97), and programs without prenatal ascertainment showed NS decline (PR=0.85, 95% CI: 0.975, 1.02).</p>
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<p>Williams LJ, Rasmussen SA et al, 2005</p> <p>Study Design: Trend study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>Data from 21 population-based birth defects surveillance systems (1995 to 2002) were divided in three periods:</p> <p>Pre-fortification period (January 1995 to December 1996)</p> <p>Optional fortification period (January 1997 to September 1998)</p> <p>Mandatory fortification period (October 1998 to December 2002).</p>	<p>Prevalence ratios (PR) were calculated by dividing the prevalence from the mandatory fortification by the prevalence in the pre-fortification period.</p>	<p>The study included 4,468 cases of SB and 2,625 cases of AN.</p> <p>The prevalence of SB ↓ 36% among Hispanic births from the pre-fortification to the mandatory fortification period (PR=0.64; 95% CI: 0.56, 0.74), 34% among non-Hispanic white births (PR=0.66; 95% CI: 0.60, 0.72) and 19% for black births (PR=0.81; 95% CI: 0.67, 1.00).</p> <p>The ↓ in the prevalence of AN was similar among Hispanic births (PR=0.74; 95% CI: 0.62, 0.88) and non-Hispanic white births (PR=0.71; 95% CI: 0.63, 0.80).</p> <p>NS decline was observed among non-Hispanic black births.</p>
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Search plan and results

Inclusion criteria

- *Subjects/Population:* Human subjects
- *Age:* Men, women, and children
- *Setting:* US and Canada only
- *Health status:* Healthy and those with elevated chronic disease risk (CHD/CVD, type 2 diabetes, metabolic syndrome and obesity)
- *Nutrition related problem/Condition:* None.

Search Criteria

- *Study design preferences:* RCT or clinical controlled studies, large non-randomized observational studies, cohort and systematic reviews
- *Size of study groups:* The sample size must equal 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:* June 1999 to present
- *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-reviewed journal.

Exclusion criteria

- *Subjects/Population*: Populations outside the U.S. and Canada
- *Setting*: Hospitalized patients
- *Health status*: Medical treatment or therapy and diseased subjects (already diagnosed with disease related to study purpose).

Search Criteria

- *Size of study groups*: Sample sizes less than 10
- *Study dropout rate*: Dropout rate in a study of 20% or greater
- *Year range*: Prior to June 1999
- *Authorship*: Studies by same author similar in content
- *Languages*: Articles not in English
- *Other*: Abstracts or presentations and articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

Comparators

- Intake levels/consumption levels
- Fortification
- Supplementation

Health Outcomes/Clinical Disease

NTD

Other Terms

NHANES.

- PubMed:

("Neural Tube Defects"[Mesh] OR NTDs[All Fields] OR "Spinal Dysraphism"[Mesh] OR "Anencephaly"[Mesh]) AND ("Folic Acid"[Mesh] OR ("folic acid"[MeSH Terms] OR ("folic"[All Fields] AND "acid"[All Fields]) OR "folic acid"[All Fields] OR "folate"[All Fields])) AND "English and humans"[Filter]
Limits: published in the last 10 years. ("Folic Acid"[majr] OR folate) AND (fortification OR "Food, Fortified"[Mesh]) AND (serum OR plasma OR "red blood cell*" OR RBC*) AND ("Canada"[Mesh] OR "United States"[Mesh]) Limits: published in the last 10 years.

Date searched: 05/27/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 1099
- Total articles identified to review from electronic databases: 82
- Articles identified via handsearch or other means: 2

- Number of Primary Articles Identified: 24
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 24
- Number of Articles Reviewed but Excluded: 60

Included articles (References)

1. Besser LM, Williams LJ, Cragan JD. Interpreting changes in the epidemiology of anencephaly and spina bifida following folic acid fortification of the U.S. grain supply in the setting of long-term trends, Atlanta, Georgia, 1968-2003. *Birth Defects Res A Clin Mol Teratol.* 2007 Nov; 79(11): 730-736. PMID: 17990332.
2. Canfield MA, Collins JS, Botto LD, Williams LJ, Mai CT, Kirby RS, Pearson K, Devine O, Mulinare J; National Birth Defects Preventin Network. Changes in the birth prevalence of selected birth defects after grain fortification with folic acid in the United States: Findings from a multi-state population-based study. *Birth Defects Res A Clin Mol Teratol.* 2005 Oct; 73(10): 679-689. PMID: 16240378.
3. Centers for Disease Control and Prevention (CDC). Spina bifida and anencephaly before and after folic acid mandate: United States, 1995-1996 and 1999-2000. *MMWR Morb Mortal Wkly Rep.* 2004 May 7; 53(17): 362-365. PMID: 15129193.
4. Chen BH, Carmichael SL, Selvin S, Abrams B, Shaw GM. NTD prevalences in central California before and after folic acid fortification. *Birth Defects Res A Clin Mol Teratol.* 2008 Aug; 82(8): 547-552. PMID: 18496833.
5. De Wals P, Tairou F, Van Allen MI, Lowry RB, Evans JA, Van den Hof MC, Crowley M, Uh SH, Zimmer P, Sibbald B, Fernandez B, Lee NS, Niyonsenga T. Spina bifida before and after folic acid fortification in Canada. *Birth Defects Res A Clin Mol Teratol.* 2008 Sep; 82(9): 622-626. PMID: 18655127.
6. De Wals P, Tairou F, Van Allen MI, Uh SH, Lowry RB, Sibbald B, Evans JA, Van den Hof MC, Zimmer P, Crowley M, Fernandez B, Lee NS, Niyonsenga T. Reduction in neural-tube defects after folic acid fortification in Canada. *N Engl J Med.* 2007 Jul 12; 357(2): 135-142. PMID: 17625125.
7. Forrester MB, Merz RD. Rates of selected birth defects in relation to folic acid fortification, Hawaii, 1986-2002. *Hawaii Med J.* 2005 Dec; 64(12): 300, 302-305. PMID: 16438020.
8. Godwin KA, Sibbald B, Bedard T, Kuzeljevic B, Lowry RB, Arbour L. Changes in frequencies of select congenital anomalies since the onset of folic acid fortification in a Canadian birth defect registry. *Can J Public Health.* 2008 Jul-Aug; 99(4): 271-275. PMID: 18767269.
9. Honein MA, Paulozzi LJ, Mathews TJ, Erickson JD, Wong LY. Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects. *JAMA.* 2001 Jun 20; 285(23): 2, 981-2, 986. Erratum in: *JAMA.* 2001 Nov 14; 286(18): 2, 236. PMID: 11410096.
10. Mosley BS, Hobbs CA, Flowers BS, Smith V, Robbins JM. Folic acid and the decline in neural tube defects in Arkansas. *J Ark Med Soc.* 2007 Apr; 103(10): 247-250. PMID: 17487022.

11. Persad VL, Van den Hof MC, Dubé JM, Zimmer P. Incidence of open neural tube defects in Nova Scotia after folic acid fortification. *CMAJ*. 2002 Aug 6; 167(3): 241-245. PMID: 12186168 (HS).
12. Williams LJ, Rasmussen SA, Flores A, Kirby RS, Edmonds LD. Decline in the prevalence of spina bifida and anencephaly by race/ethnicity: 1995-2002. *Pediatrics*. 2005 Sep; 116(3): 580-586. PMID: 16140696.
13. Williams LJ, Mai CT, Edmonds LD, Shaw GM, Kirby RS, Hobbs CA, Sever LE, Miller LA, Meaney FJ, Levitt M. Prevalence of spina bifida and anencephaly during the transition to mandatory folic acid fortification in the United States. *Teratology*. 2002 Jul; 66(1): 33-39. PMID: 12115778.

Excluded articles

Excluded Articles	Reason for Exclusion
<p>Antoniades C, Antonopoulos AS, Tousoulis D, Marinou K, Stefanadis C. Homocysteine and coronary atherosclerosis: From folate fortification to the recent clinical trials. www.ncbi.nlm.nih.gov/pubmed/19029125 <i>Eur Heart J</i>. 2009 Jan; 30(1): 6-15. Epub 2008 Nov 23. Review. PMID: 19029125.</p>	<p>Does not answer the question; about homocysteine and CVD.</p>
<p>Bleys J, Miller ER 3rd, Pastor-Barriuso R, Appel LJ, Guallar E. Vitamin-mineral supplementation and the progression of atherosclerosis: a meta-analysis of randomized controlled trials. www.ncbi.nlm.nih.gov/pubmed/17023716 <i>Am J Clin Nutr</i>. 2006 Oct; 84(4): 880-887; quiz 954-955. PMID: 17023716.</p>	<p>Does not answer the question; about antioxidants and B vitamins.</p>
<p>Bor MV, Wulff AM, Nexø E, Krarup H. Clin Chem <u>Infrequency of low red blood cell (RBC) folate levels despite no folate fortification program: a study based on results from routine requests for RBC folate.</u> <i>Lab Med</i>. 2008; 46(3): 401-404. PMID: 18254711.</p>	<p>International study.</p>
<p>Bostom AG, Jacques PF, Liaugaudas G, Rogers G, Rosenberg IH, Selhub J. Total homocysteine lowering treatment among coronary artery disease patients in the era of folic acid-fortified cereal grain flour. www.ncbi.nlm.nih.gov/pubmed/11884295 <i>Arteriosclerosis Thromb Vasc Biol</i>. 2002 Mar 1; 22(3): 488-491. PMID: 11884295.</p>	<p>Does not answer the question; about homocysteine.</p>

<p>Botto LD, Lisi A, Bower C, Canfield MA, Dattani N, De Vigan C, De Walle H, Erickson DJ, Halliday J, Irgens LM, Lowry RB, McDonnell R, Metneki J, Poetzsch S, Ritvanen A, Robert-Gnansia E, Siffel C, Stoll C, Mastroiacovo P. <u>Trends of selected malformations in relation to folic acid recommendations and fortification: An international assessment.</u> <i>Birth Defects Res A Clin Mol Teratol.</i> 2006 Oct; 76(10): 693-705. PMID: 17029289.</p>	<p>International article.</p>
<p>Boulet SL, Yang Q, Mai C, Kirby RS, Collins JS, Robbins JM, Meyer R, Canfield MA, Mulinare J; National Birth Defects Prevention Network. <u>Trends in the postfortification prevalence of spina bifida and anencephaly in the United States.</u> <i>Birth Defects Res A Clin Mol Teratol.</i> 2008 Jul; 82(7): 527-532. PMID: 18481813.</p>	<p>Does not answer the question; evaluated only post-fortification.</p>
<p>Boushey CJ, Edmonds JW, Welshimer KJ. <u>Estimates of the effects of folic-acid fortification and folic-acid bioavailability for women.</u> <i>Nutrition.</i> 2001 Oct; 17(10): 873-879. PMID: 11684395.</p>	<p>Does not answer the research question</p>
<p>Byrne J, Carolan S, Arcement R, Kozlowski M, Taller I, Ried S, Keating R. <u>An intervention study to increase knowledge and use of folic acid among relatives in neural tube defect-affected families in Washington, D.C.</u> <i>Birth Defects Res A Clin Mol Teratol.</i> 2005 Jun; 73(6): 424-429. PMID: 15880789.</p>	<p>Does not answer the question; about knowledge and intake.</p>
<p>Canfield MA, Anderson JL, Waller DK, Palmer SE, Kaye CI. <u>Folic acid awareness and use among women with a history of a neural tube defect pregnancy: Texas, 2000-2001.</u> <i>MMWR Recomm Rep.</i> 2002 Sep 13; 51(RR-13): 16-19. PMID: 12353508.</p>	<p>Population with recurrent NTD.</p>
<p>Carlsson CM. Homocysteine lowering with folic acid and vitamin B supplements: effects on cardiovascular disease in older adults. www.ncbi.nlm.nih.gov/pubmed/16872232 <i>Drugs Aging.</i> 2006; 23(6): 491-502. Review. PMID: 16872232.</p>	<p>It doesn't answer the question. About B supplements and cardiovascular protection.</p>
<p>Caudill MA, Le T, Moonie SA, Esfahani ST, Cogger EA. <u>Folate status in women of childbearing age residing in Southern California after folic acid fortification.</u> <i>J Am Coll Nutr.</i> 2001 Apr; 20(2 Suppl): 129-134. Erratum in: <i>J Am Coll Nutr.</i> 2001 Jun; 20(3): 268. PMID: 11349935.</p>	<p>Does not answer the reseach question.</p>

<p>CDC, MMWR Weekly report, 2002. Folate Status in Women of Childbearing Age, by Race/Ethnicity: United States, 1999-2000. September 13, 2002; 51(36): 808-810. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5136a2.htm</p>	<p>Data used in this article was analyzed in the Quilivan et al., 2007 article, which was included.</p>
<p>CDC, MMWR Weekly report, 2009. Folate Status in Women of Childbearing Age, by Race/Ethnicity: United States, 1999-2000, 2001-2002 and 2003-2004. January 5, 2007; 55(51):1, 377-1, 380. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5551a2.htm</p>	<p>Data used in this article was analyzed in the Quilivan et al., 2007 study, which was included.</p>
<p>Cena ER, Joy AB, Heneman K, Espinosa-Hall G, Garcia L, Schneider C, Wooten Swanson PC, Hudes M, Zidenberg-Cherr S. <u>Folate intake and food-related behaviors in nonpregnant, low-income women of childbearing age.</u> <i>J Am Diet Assoc.</i> 2008 Aug; 108(8): 1, 364-1, 368. PMID: 18656578.</p>	<p>Does not answer the reseach question.</p>
<p>Clarke R, Collins R. Can dietary supplements with folic acid or vitamin B₆ reduce cardiovascular risk? Design of clinical trials to test the homocysteine hypothesis of vascular disease. www.ncbi.nlm.nih.gov/pubmed/9919473 <i>J Cardiovasc Risk.</i> 1998 Aug; 5(4): 249-255. PMID: 9919473.</p>	<p>Not a systematic review.</p>
<p>Choumenkovitch SF, Selhub J, Wilson PW, Rader JI, Rosenberg IH, Jacques PF. <u>Folic acid intake from fortification in United States exceeds predictions</u> <i>J Nutr.</i> 2002 Sep; 132(9): 2, 792-2, 798. PMID: 12221247</p>	<p>Does not answer the reseach question.</p>
<p>Cornel MC, de Smit DJ, de Jong-van den Berg LT. <u>Folic acid: The scientific debate as a base for public health policy.</u> <i>Reprod Toxicol.</i> 2005 Sep-Oct; 20(3): 411-415. Review. PMID: 15978774.</p>	<p>Commentary.</p>
<p>De Bree A, Mennen LI, Hercberg S, Galan P. Evidence for a protective (synergistic?) effect of B-vitamins and omega-3 fatty acids on cardiovascular diseases. www.ncbi.nlm.nih.gov/pubmed/15116076 <i>Eur J Clin Nutr.</i> 2004 May; 58(5): 732-744. PMID: 15116076.</p>	<p>Does not answer the question.</p>

<p>de Jong-Van den Berg LT, Hernandez-Diaz S, Werler MM, Louik C, Mitchell AA. <u>Trends and predictors of folic acid awareness and periconceptional use in pregnant women.</u> <i>Am J Obstet Gynecol.</i> 2005 Jan; 192(1): 121-128. PMID: 15672013.</p>	<p>Does not answer the question; about awareness.</p>
<p>DeWolfe J. Can J. <u>Folate intake of older adults before and after fortification of grain products.</u> <i>Diet Pract Res.</i> 2007 Winter; 68(4): 218-220. PMID: 18073005.</p>	<p>Measure intake not RBC or plasma folate.</p>
<p>Evans MI, Llurba E, Landsberger EJ, O'Brien JE, Harrison HH. <u>Impact of folic acid fortification in the United States: Markedly diminished high aternal serum alpha-fetoprotein values.</u> <i>Obstet Gynecol.</i> 2004 Mar; 103(3): 474-479. PMID: 14990409.</p>	<p>Does not answer the question; addresses alpha-fetoprotein values.</p>
<p>Goh YI, Bollano E, Einarson TR, Koren G. Prenatal multivitamin supplementation and rates of congenital anomalies: A meta-analysis. www.ncbi.nlm.nih.gov/pubmed/17022907 <i>J Obstet Gynaecol Can.</i> 2006 Aug; 28(8): 680-689. Review. PMID: 17022907.</p>	<p>Folic acid intake is not quantified.</p>
<p>Grosse SD, Collins JS. <u>Folic acid supplementation and neural tube defect recurrence revention.</u> <i>Birth Defects Res A Clin Mol Teratol.</i> 2007 Nov; 79(11): 737-742. PMID: 17990333.</p>	<p>Does not answer the question; about recurrence.</p>
<p>Kannan S, Menotti E, Scherer HK, Dickinson J, Larson K. <u>Folic acid and the prevention of neural tube defects: A survey of awareness among Latina women of childbearing age residing in southeast Michigan.</u> <i>Health Promot Pract.</i> 2007 Jan; 8(1): 60-68. Epub 2006 Jul 13. PMID: 16840767.</p>	<p>Does not answer the question; about awareness.</p>
<p>Klerk M, Durga J, Schouten EG, Kluff C, Kok FJ, Verhoef P. No effect of folic acid supplementation in the course of one year on haemostasis markers and C-reactive protein in older adults. www.ncbi.nlm.nih.gov/pubmed/16113791 <i>Thromb Haemost.</i> 2005 Jul; 94(1): 96-100. PMID: 16113791.</p>	<p>Does not answer the question; about supplementation and homocysteine.</p>
<p>Lambert-Messerlian G, Halliday J, Williams J, Cain R, Msall ME, Palomaki GE, Canick JA. <u>Effect of folic acid fortification on prevalence of neural tube defects in Rhode Island.</u> <i>J Med Screen.</i> 2004; 11(2): 106-107. PMID: 15153328.</p>	<p>Letter to the editor.</p>

<p>Lewis SJ, Ebrahim S, Davey Smith G. Meta-analysis of MTHFR 677C-T polymorphism and coronary heart disease: Does totality of evidence support causal role for homocysteine and preventive potential of folate? www.ncbi.nlm.nih.gov/pubmed/16216822 <i>BMJ</i>. 2005 Nov 5; 33 1(7, 524): 1, 053. Epub 2005 Oct 10. Review. PMID: 16216822.</p>	<p>Not a systematic review; does not answer the question; about genotype.</p>
<p>Lumley J, Watson L, Watson M, Bower C. Cochrane <u>Periconceptional supplementation with folate and/or multivitamins for preventing neural tube defects</u>. <i>Database Syst Rev</i>. 2001;(3): CD001056. Review. PMID: 11686974.</p>	<p>Does not answer the question; about NTD and supplementation.</p>
<p>Malinow MR, Duell PB, Irvin-Jones A, Upson BM, Graf EE. Increased plasma homocyst(e)ine after withdrawal of ready-to-eat breakfast cereal from the diet: Prevention by breakfast cereal providing 200 microg folic acid. www.ncbi.nlm.nih.gov/pubmed/10963464 <i>J Am Coll Nutr</i>. 2000 Aug; 19(4): 452-457. PMID: 10963464.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>Mark L, Erdei F, Markizay J, Kondacs A, Katona A. Effect of treatment with folic acid and vitamin B₆ on lipid and homocysteine concentrations in patients with coronary artery disease. www.ncbi.nlm.nih.gov/pubmed/11985950 <i>Nutrition</i>. 2002 May; 18(5): 428-429. No abstract available. PMID: 11985950.</p>	<p>Does not answer the question; about supplementation and homocysteine.</p>
<p>McCully KS. Homocysteine, vitamins, and vascular disease prevention. www.ncbi.nlm.nih.gov/pubmed/17991676 <i>Am J Clin Nutr</i>. 2007 Nov; 86(5): 1, 563S-1, 568S. Review. PMID: 17991676.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>McEligot AJ, Rock CL, Gilpin EA, Pierce JP. Responsiveness of homocysteine concentrations to food and supplemental folate intakes in smokers and never-smokers enrolled in a diet intervention trial. www.ncbi.nlm.nih.gov/pubmed/16497600 <i>Nicotine Tob Res</i>. 2006 Feb; 8(1): 57-66. PMID: 16497600.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>McKay DL, Perrone G, Rasmussen H, Dallal G, Blumberg JB. Multivitamin/mineral supplementation improves plasma B-vitamin status and homocysteine concentration in healthy older adults consuming a folate-fortified diet. www.ncbi.nlm.nih.gov/pubmed/11110875</p>	<p>Does not answer the question; about supplementation and homocysteine.</p>

<p>Mills JL, Signore C. <u>Neural tube defect rates before and after food fortification with folic acid.</u> <i>Birth Defects Res A Clin Mol Teratol.</i> 2004 Nov; 70(11): 844-845. Review. PMID: 15468072</p>	<p>Review of four articles; three primary articles were included.</p>
<p>Moats C, Rimm EB. Vitamin intake and risk of coronary disease: observation versus intervention. <i>Curr Atheroscler Rep.</i> 2007 Dec; 9(6): 508-514. Review. www.ncbi.nlm.nih.gov/pubmed/18377792 PMID: 18377792</p>	<p>Not a systematic review; does not answer the question.</p>
<p>Mosley BS, Cleves MA, Siega-Riz AM, Shaw GM, Canfield MA, Waller DK, Werler MM, Hobbs CA; National Birth Defects Prevention Study. <u>Neural tube defects and maternal folate intake among pregnancies conceived after folic acid fortification in the United States.</u> <i>Am J Epidemiol.</i> 2009 Jan 1; 169(1): 9-17. Epub 2008 Oct 25. PMID: 18953063.</p>	<p>Does not address the question; evaluated the relation of NTD and maternal folic acid consumption after folic acid fortification.</p>
<p>Muskiet FA. The importance of (early) folate status to primary and secondary coronary artery disease prevention. www.ncbi.nlm.nih.gov/pubmed/15964170 <i>Reprod Toxicol.</i> 2005 Sep-Oct; 20(3): 403-410. Review. PMID: 15964170.</p>	<p>Not a systematic review.</p>
<p>Ntaios GC, Savopoulos CG, Chatzinikolaou AC, Kaiafa GD, Hatzitolios A. Vitamins and stroke: The homocysteine hypothesis still in doubt. <i>Neurologist.</i> 2008 Jan; 14(1): 2-4. Review. www.ncbi.nlm.nih.gov/pubmed/18195649 PMID: 18195649.</p>	<p>Not a systematic review; about vitamins and CVD.</p>
<p>Palomaki GE, Williams J, Haddow JE. <u>Comparing the observed and predicted effectiveness of folic acid fortification in preventing neural tube defects.</u> <i>J Med Screen.</i> 2003; 10(1): 52-53. PMID: 12790316.</p>	<p>Letter to the editor.</p>
<p>Quinlivan EP, McPartlin J, McNulty H, Ward M, Strain JJ, Weir DG, Scott JM. Importance of both folic acid and vitamin B₁₂ in reduction of risk of vascular disease. <i>Lancet.</i> 2002 Jan 19; 359(9, 302): 227-228. PMID: 11812560.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>Rader JI, Schneeman BO. <u>Prevalence of neural tube defects, folate status, and folate fortification of enriched cereal-grain products in the United States.</u> <i>Pediatrics.</i> 2006 Apr; 117(4): 1, 394-1, 399. PMID: 16585338.</p>	<p>Not a systematic review.</p>

<p>Ramos MI, Allen LH, Mungas DM, Jagust WJ, Haan MN, Green R, Miller JW. <u>Low folate status is associated with impaired cognitive function and dementia in the Sacramento Area Latino Study on Aging.</u> <i>Am J Clin Nutr.</i> 2005 Dec; 82(6): 1, 346-1, 352. PMID: 16332669.</p>	<p>Does not answer the question; about dementia and folate status.</p>
<p>Ray JG, Vermeulen MJ, Boss SC, Cole DE. Declining rate of folate insufficiency among adults following increased folic acid food fortification in Canada. <i>Can J Public Health.</i> 2002 Jul-Aug; 93(4): 249-253. PMID: 12154524.</p>	<p>Does not address the question; investigates the changes in folate and vitamin B₁₂ insufficiency after folic acid fortification.</p>
<p>Rydlewicz A, Simpson JA, Taylor RJ, Bond CM, Golden MH. The effect of folic acid supplementation on plasma homocysteine in an elderly population. <i>QJM.</i> 2002 Jan; 95(1): 27-35. PMID: 11834770.</p>	<p>Does not answer the question; about supplementation and homocysteine.</p>
<p>Sauer J, Mason JB, Choi SW. Too much folate: A risk factor for cancer and cardiovascular disease? www.ncbi.nlm.nih.gov/pubmed/19057184 <i>Curr Opin Clin Nutr Metab Care.</i> 2009 Jan; 12(1): 30-36. Review. PMID: 19057184.</p>	<p>Not a systematic review.</p>
<p>Smolková B, Dusinská M, Raslová K, Barancoková M, Kazimírová A, Horská A, Spustová V, Collins A. Folate levels determine effect of antioxidant supplementation on micronuclei in subjects with cardiovascular risk. <i>Mutagenesis.</i> 2004 Nov; 19(6): 469-476. PMID: 15548759.</p>	<p>Does not answer the question; about antioxidants.</p>
<p>Stevenson RE, Allen WP, Pai GS, Best R, Seaver LH, Dean J, Thompson S. <u>Decline in prevalence of neural tube defects in a high-risk region of the United States.</u> <i>Pediatrics.</i> 2000 Oct; 106(4): 677-683. PMID: 11015508.</p>	<p>Does not address the question; evaluates the recurrence prevention effort and public awareness campaign of folic acid supplementation for all women of childbearing age.</p>
<p>Suarez L, Hendricks KA, Cooper SP, Sweeney AM, Hardy RJ, Larsen RD. <u>Neural tube defects among Mexican Americans living on the US-Mexico border: effects of folic acid and dietary folate.</u> <i>Am J Epidemiol.</i> 2000 Dec 1; 152(11): 1, 017-1, 023. PMID: 11117610.</p>	<p>Does not measure plasma, RBC or serum folate; about NTD.</p>

<p>Thompson SJ, Torres ME, Stevenson RE, Dean JH, Best RG. <u>Periconceptional multivitamin folic acid use, dietary folate, total folate and risk of neural tube defects in South Carolina.</u> <i>Ann Epidemiol.</i> 2003 Jul; 13(6): 412-418. PMID: 12875798.</p>	<p>Does not answer the question; about supplementation treatment.</p>
<p>Tucker KL, Olson B, Bakun P, Dallal GE, Selhub J, Rosenberg IH. Breakfast cereal fortified with folic acid, vitamin B-6, and vitamin B-12 increases vitamin concentrations and reduces homocysteine concentrations: A randomized trial. <i>Am J Clin Nutr.</i> 2004 May; 79(5): 805-811. PMID: 15113718.</p>	<p>Does not answer the question; about supplementation and homocysteine.</p>
<p>Van Beynum IM, den Heijer M, Blom HJ, Kapusta L. The MTHFR 677C-T polymorphism and the risk of congenital heart defects: A literature review and meta-analysis. www.ncbi.nlm.nih.gov/pubmed/17965089 <i>QJM.</i> 2007 Dec; 100(12): 743-753. Epub 2007 Oct 26. Review. PMID: 17965089.</p>	<p>Does not answer the question.</p>
<p>Villa P, Perri C, Suriano R, Cucinelli F, Panunzi S, Ranieri M, Mele C, Lanzone A. L-folic acid supplementation in healthy postmenopausal women: Effect on homocysteine and glycolipid metabolism. <i>J Clin Endocrinol Metab.</i> 2005 Aug;90(8):4622-4.629. Epub 2005 May 17. PMID: 15899950.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>Villa P, Suriano R, Costantini B, Macrì F, Ricciardi L, Campagna G, Lanzone A. Hyperhomocysteinemia and cardiovascular risk in postmenopausal women: the role of Folate supplementation. www.ncbi.nlm.nih.gov/pubmed/17311496 <i>Clin Chem Lab Med.</i> 2007; 45(2): 130-135. Review. PMID: 17311496.</p>	<p>Does not answer the question.</p>
<p>Wald DS, Bishop L, Wald NJ, Law M, Hennessy E, Weir D, McPartlin J, Scott J. Randomized trial of folic acid supplementation and serum homocysteine levels. <i>Arch Intern Med.</i> 2001 Mar 12; 161(5): 695-700. PMID: 11231701.</p>	<p>Does not answer the question; about supplementation and homocysteine.</p>
<p>Yang QH, Carter HK, Mulinare J, Berry RJ, Friedman JM, Erickson JD. <u>Race-ethnicity differences in folic acid intake in women of childbearing age in the United States after folic acid fortification: Findings from the National Health and Nutrition Examination Survey, 2001-2002.</u> <i>Am J Clin Nutr.</i> 2007 May; 85(5): 1, 409-1, 416. PMID: 17490980.</p>	<p>Does not answer the research question.</p>

Werler MM, Louik C, Mitchell AA. Achieving a public health recommendation for preventing neural tube defects with folic acid. *Am J Public Health.* 1999 Nov; 89(11): 1, 637-1, 640. PMID: 10553381

Does not answer the question; about supplementation.

CHAPTER 6. DIETARY BEHAVIORS AND NUTRIENT INTAKE – FOLIC ACID FORTIFICATION POLICY AND SERUM FOLATE, PLASMA AND RED BLOOD CELL FOLATE STATUS

WHAT EFFECT HAS FOLIC ACID FORTIFICATION POLICY HAD ON SERUM FOLATE, PLASMA, AND RED BLOOD CELL FOLATE STATUS OF US CANADA WOMEN, MEN, AND CHILDREN?

Conclusion statement

Strong and consistent evidence demonstrates serum, plasma and red blood cell (RBC) folate concentrations have increased in the United States and Canada, following mandatory folate fortification.

Grade

Strong

Evidence summary overview

Of the eleven studies reviewed, seven were from the US, one from the US/Mexico border counties, and two from Canada. A third study from Canada of negative quality was not considered in forming the conclusion. Given the ecological nature of mandatory fortification, it was impossible to conduct a controlled trial during this time.

Five of the US studies (Dietrich, 2005; Dowd, 2008; Ganji, 2006; Pfeiffer, 2007; Quinlivan, 2007) used National Health and Nutrition Examination Surveys (NHANES) data for analysis; therefore, these studies are nationally representative. All of the NHANES database studies showed an increase in serum and red blood cell (RBC) folate status and a reduction in low folate concentrations. The study of Dietrich et al (2005) compared men and women aged 20 and older (non-supplement users) from NHANES III (pre-fortification) and NHANES 1999 to 2000 (post-fortification). In comparison to pre-fortification values, both serum and RBC folate levels increased significantly. Mean serum levels more than doubled (136%), and mean RBC folate levels increased 57%. The prevalence of low RBC folate decreased significantly from 39% to 3.7% between the two surveys. The NHANES studies of Ganji et al (2006), Pfeiffer et al (2007) and Quinlivan et al (2007) added additional time periods, collectively covering 1999 to 2004. In all three studies, serum and RBC folate concentrations increased significantly in the first fortification time period and then declined slightly (5% to 13% and 6% to 9%, respectively) in most age groups between the first and second or third fortification periods. The decrease in folate concentrations observed following the initial folate fortification is small in comparison to the initial increase observed and is mostly likely a result of over-fortification during the initial fortification period.

The studies of Jacques et al, 1999, and Kalmbach et al, 2008 used the Framingham database to address this question. Both studies showed increases in folate concentrations and decreases in low folate concentrations following folate fortification. In the study of Kalmbach et al, 2008, supplement users were 2.28 (95% CI: 1.7 to 3.01) times more likely to have high circulating folate concentrations than were non-supplement users.

The two Canadian studies also showed increases in folate concentrations following

mandatory fortification. Bar-Oz et al, 2008 examined women of childbearing years from four general practices and two hospitals in Ontario. They demonstrated that RBC folate levels rose significantly over the years, since fortification with fewer women of childbearing years at risk for low folate concentrations. Despite these improvements, a small but significant portion of women of childbearing years are still at risk for low folate concentrations following mandatory folate fortification.

Evidence summary paragraphs

Bar-Oz et al, 2008 (neutral quality). This trend study examined the RBCs of women of childbearing age from four general practice laboratories and two hospitals in Ontario, Canada. The results showed that RBC folic acid levels have risen significantly over the years since fortification. Also, no significant (NS) difference in the medians between 2002 (1,207nmol per L) and 2004 (928nmol per L) and between 2004 (928nmol per L) and 2005 (910nmol per L). There was a significant difference in the medians between 2005 (910nmol per L) and 2006 (972nmol per L) ($P=<0.01$). Overall, there was a significant decrease in the population at risk (RBC folate below either 700 or 900nmol per L) ($P<0.001$) from 1998 to 2002. After 2002, this trend reversed with an increase in the proportion of women with levels below 900nmol per L from 24% in 2005 to 40% in 2006. After folic acid fortification, a considerable proportion of pregnant women are still at risk of having a baby with neural tube defects (NTD).

Dietrich et al, 2005 (neutral quality) This trend study measured changes in serum and erythrocyte folate status pre- and post-fortification. The data was taken from the NHANES III and NHANES 1999 to 2000 of healthy men and women 20 years old and older and non-supplement-using. In comparison to pre-fortification values, both serum and erythrocyte folate concentrations increased significantly ($P<0.0001$ for all age-sex groups) post-fortification. Mean serum folate increased more than double from NHANES III to NHANES 1999 to 2000 (136%), from 11.4nmol per L to 26.9nmol per L. Mean erythrocyte folate, a marker of long-term folate status, increased 57%, (from 375nmol per L to 590nmol per L) overall. Prevalence of inadequate serum folate concentrations (less than 7nmol per L) decreased significantly from 25.77% to 0.93% ($P<0.0001$). Prevalence of low erythrocyte folate (less than 305nmol per L) decreased significantly from 39.07% to 3.70% ($P<0.0001$) between the two surveys. Mean total folate intake increased 28%, from 275ug per day to 351ug per day. In conclusion, mandatory folic acid fortification led to significant increases in both serum and erythrocyte folate concentrations; however, women of childbearing age may take supplements to reach levels associated with decreased risk of NTDs.

Dowd et al, 2008 (neutral quality), in this trend study examined the RBC of adults aged 25 years old or older. Data from NHANES survey were divided into two periods: 1) Pre-fortification [NHANES III (1991 to 1994)], and 2) Post-fortification (NHANES 1999 to 2000 and 2001 to 2002). The results showed that following fortification, the rate per 1,000 of low RBC folate status dropped from 95% CI: 528 (507, 549)nmol per L to 110 (91, 128) for the lowest income quartile, and from 374 (351, 396) to 42 (34 to 50) in the highest income quartile. The rate per 1,000 of low folate status in non-Hispanic blacks dropped from 95% CI: 647 (626, 667) to 171 (152, 190) following fortification, for Hispanics fell from 484(461, 507) to 58 (48, 67) and for non-Hispanics whites fell from 327 (310, 344) to 38 (32, 44).

Felkner et al, 2002 (neutral quality) This cross-sectional study examined the RBC of randomly selected women who delivered in a hospital or birthing center in 14 border

counties from Texas-Mexico. They were controls in a population-based case-control NTD study from 1995 through 1999. Calculations showed that the median serum folate concentration increased modestly from 8.5ng per ml in 1996 to 12.4ng per ml in 1999 (46% higher). Also, the median RBC folate level increase from 272ng per ml in 1996 to 393ng per ml in 1999 (44% higher). The median RBC folate concentration in women, who were not prenatal vitamin users was 254ng per ml in 1996 and 378ng per ml in 1999 (49% increase). In conclusion, serum and RBC folate levels appear to have risen in this postpartum Texas-Mexico border population from 1996 through 1999. (Test for statistical difference is not mentioned.)

Ganji et al, 2006 (neutral quality) This trend study examined the serum and RBC folate of three NHANES survey periods: 1) NHANES III (1988 to 1994); 2) NHANES 1999 to 2000; and 3) NHANES 2001 to 2002. Serum and RBC folate concentrations were significantly higher and the prevalence of low serum and RBC folate concentrations were significantly lower in period 2 and 3 than in period 1, in all demographic groups of the US. Overall, mean serum folate concentrations were higher in period 2 (149.6%) and in period 3 (129.8%) than in period 1. From period 2 to 3, serum folate concentration significantly decline in men (7.3%, $P=0.0012$), in women (8.5%, $P=0.0028$), in non-Hispanic whites (NHW) (9.7%, $P=0.0037$), in those 18 years old (7.3%, $P=0.0081$), in those 31 to 50 years old (7.6%, $P=0.0021$), in those 51 to 70 years old (10.8%, $P=0.0146$) and in those with poverty income ratio (PIR) 1.0 (12.5%, $P=0.0063$) and $\$4.0$ (9.9%, $P=0.0068$). When the data were adjusted for sex, age and race-ethnicity, there was a reduction of 10.4% in serum folate concentrations from period 2 to 3 ($P<0.0002$). Overall, mean RBC folate concentrations were 58.2% higher in period 2 and 56.5% higher in period 3 than in period 1. When the data were adjusted for sex, age and race-ethnicity, similar trends were present for RBC folate.

Jacques et al, 1999 (positive quality) This trend study assessed the effect of folic acid fortification on folate status. Plasma folate and total homocysteine concentrations were measured in a cohort of participants from the fifth and sixth examination Framingham study. The data were divided in two groups: 1) Baseline (fifth examination before fortification policy); 2) Follow-up (sixth examination after fortification policy); and 3) Control group (sixth examination before fortification policy began). Among the subjects who did not use vitamin supplements, the mean folate concentrations increased from the baseline to the follow-up visit, from 4.6 to 10.0ng per ml (11 to 23nmol per L) ($P<0.001$), increasing by 117% after fortification. The prevalence of low folate concentrations decreased from 22.0% to 1.7% ($P<0.001$), decreasing by 92% [less than 3ng per ml (7nmol per L)]. In the control group, there were no statistically significant changes in concentrations of folate or homocysteine. The fortification of enriched grain products with folic acid was associated with a substantial improvement in folate status in a population of middle-aged and older adults.

Kalmbach et al, 2008 (positive quality) This cross-sectional study assessed the effect of folic acid fortification implementation on total plasma folate, circulation concentration of folic acid and 5-methyltetrahydrofolate (5MeTHF) in the Framingham Offspring Cohort. Among nonsupplement users, median circulating concentrations of folic acid increased after fortification (from 0.25 to 0.50nmol per L, $P<0.001$). The prevalence of detectable circulating folic acid was 55% before and 74.7% after fortification ($P<0.001$). The prevalence of high circulating folic acid was 9.4% before and 19.1% after fortification ($P=0.002$). Plasma folate concentrations were 91% higher after fortification ($P<0.001$) and 5MeTHF concentrations were 92% higher after fortification ($P<0.001$).

Among B-vitamin supplements users, median circulating concentrations of folic acid increased after fortification from 0.54 to 0.68 ($P=0.001$). The prevalence of detectable circulating folic acid was 72.5% before fortification and 80.7% after fortification ($P=0.13$). The prevalence of high circulating folic acid increased from 15.9% to 24.3% after fortification ($P=0.02$). Total plasma folate concentration was 29.9% higher after fortification ($P<0.001$) and 5MeTHF concentrations were 28.7% higher ($P<0.001$) after fortification. A trend was observed for an increased prevalence of high circulating folic acid as the total folate intake increased ($P<0.001$). After adjusted for age, sex, vitamin intakes and total energy intake, folic acid intake, total folate intake, use of B-vitamin supplements and total plasma folate were the only significant determinants identified. Supplements users were 2.28 (95% CI: 1.7, 3.01) times more likely to have high circulating folic acid than were non-supplement users.

Pfeiffer et al, 2007 (positive quality) This trend study evaluated data from participants in the pre-fortification NHANES III (1988 to 1994), and participants in three post-fortification NHANES periods (covering 1999 to 2004). Measurements were comparing for serum folate for 1988 to 1994 and 1999 to 2004, vitamin B₁₂ for 1991 to 1994 and 1999 to 2004, and RBC folate for 1988 to 1994 and 1999 to 2004. Serum and RBC folate concentrations increased substantially (by 119% to 161 % and 44% to 64%, respectively) in each age group in the first post-fortification survey period and then declined slightly (by 5% to 13% and 6% to 9%, respectively) in most age groups between the first and third post-fortification survey periods. Serum vitamin B₁₂ concentrations did not change appreciably. Prevalence estimates of low serum and RBC folate concentration declined in women of childbearing age from before to after fortification (from 31% to less than 1% and from 38% to 5%, respectively) but remained unchanged thereafter. Prevalence estimates of high serum folate concentrations increased in children and older persons from before to after fortification (from 5% to 42% and from 7% to 38%, respectively) but decreased later after fortification. The authors concluded that decrease in folate concentrations observed longer after fortification is small compared with the increased soon after the introduction of fortification.

Quinlivan et al, 2007 (neutral quality), in this trend study used NHANES data to quantify changes in folate intake after folic acid fortification and estimated the effect on NTD occurrence. Three waves of NHANES data were divided in two periods: Pre-fortification (1988 to 1994) and post-fortification (1999 to 2000 and 2001 to 2004). Red blood cell and serum folate concentrations increased between 1988 to 1994 and 1999 to 2000, and then they decreased each year from 1999 to 2000 to 2003 to 2004. Between 1988 to 1994 and 1999 to 2000, the percentage increase in serum and RBC folate concentration was smallest in the women with the highest folate status. Median folate consumption of the study population increased by 529µg dietary folate equivalent (DFE) per day between before fortification and after fortification; then decreased by 135µg DFE per day between 1999 to 2000 and 2003 to 2004. The overall decrease in folate consumption was primarily due to changes in subjects with the highest folate status. Total folate consumption increased in the year after mandatory fortification. However, by 2003 to 2004, total folate consumed by subjects in the 90th percentile had decreased to 1,249µg DFE per day.

Ray et al, 2002 (neutral quality), This cross-sectional study examined the changes in rates of serum folate, RBC folate and vitamin B₁₂ insufficiency among Canadian adults after the mandatory folic acid food fortification program was implemented. Data from

8,884 individuals who underwent evaluation were evaluated, organized on the following periods: 1) Period 1 (April 1, 1997 to July 31, 1998); 2) Period 2 (August 1, 1998 to January 30, 1999); and 3) Period 3 (February 1, 1999 to March 31, 2000). The prevalence of serum folate insufficiency (less than 3.4nmol per L) fell from 0.52% in period 1 to 0.22% in period 3 [prevalence ratio (RR) 0.41%, 95% CI: 0.18, 0.93]. The prevalence of RBC folate insufficiency (less than 215nmol per L) declined from 1.78% during period 1 to 0.41% in period 3 (RR 0.23, 95% CI: 0.14 to 0.40). No significant difference was observed between periods in the prevalence of B₁₂ insufficiency below 120nmol per L (3.93% vs. 3.11%, respectively; RR 0.79, 95% CI: 0.62, 1.01).

Shuaibi et al, 2008 (negative quality) In this cross-sectional study of 95 women, the University of Manitoba assessed descriptive statistics for serum and RBC folate and total homocysteine. Also, assessed total folate intake (from natural food folate, folic acid added to food and folic acid supplements) and used T-tests to assess differences in folate intake between supplement users and non-users ($P < 0.05$). The intake of natural food folate, expressed as micrograms, was 1.6 times more than the total folic acid from food and supplements intake expressed as micrograms, and almost the same when expressed as Dietary Folate Equivalents (DFEs). The total intakes for folate were significantly higher for supplement users compared to supplement non-users. The mean \pm SD, median and the range (10th and 90th percentile) for serum folate were, respectively, 14.6 \pm 3.5, 14.1 and 10.0 to 19.3ng per ml (33.0 \pm 7.9, 32.0 and 22.6 to 43.8nmol per L); for RBC folate, the values were 312.0 \pm 137.2, 286.8 and 180.5 to 462.9ng per ml (707 \pm 311, 650 and 409 to 1,049nmol per L), respectively. Also, no women were folate deficient and 14% reached RBC folate higher than 400ug per day. Finally, intakes of folic acid from fortified foods are within the level originally predicted for the fortification efforts but only 17% of participants met the special recommendation for women of childbearing age (400ug folic acid daily from supplements, fortified foods or both in addition to consuming food folate from diet). This data suggest that women of childbearing age are increasing RBC folate status but it may not be sufficient to achieve values associated with reduction of NTD risk.

Overview table

Author, Year, Study Design, Class, Rating	Population/Sample Description	Measurements or Intervention	Significant Outcomes
<p>Bar-Oz B, Koren G et al, 2008</p> <p>Study Design: Trend study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>Data from women of childbearing age from four general practice laboratories and two hospitals in Ontario were divided in three periods:</p> <p>1) 1995 to 1997 (pre-fortification)</p> <p>2) 1998 (start of fortification)</p> <p>3) 2000 to 2006 (post-fortification).</p>	<p>RBC folate.</p>	<p>NS difference in RBC folate medians between 2002 (1,207nmol per L) and 2004 (928nmol per L).</p> <p>NS difference in the medians between 2004 (928nmol per L) and 2005 (910nmol per L).</p> <p>Significant difference in the medians between 2005 (910nmol per L) and 2006 (972nmol per L) $P \leq 0.01$.</p> <p>Significant ↓ in the population at risk (RBC folate <700 or 900nmol per L) ($P < 0.001$) from 1998 to 2002.</p> <p>After 2002, this trend reversed with an ↑ in the proportion of women with levels <900nmol per L from 24% in 2005 to 40% in 2006.</p>

<p>Dietrich M, Brown C et al, 2005</p> <p>Study Design: Trend study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>N=9,919 from NHANES III and 2,121 from NHANES 1999 to 2000</p> <p>Age: ≥20 years.</p>	<p>Serum folate concentrations.</p> <p>Erythrocyte folate concentrations (marker of long-term folate status).</p> <p>Total dietary folate intake.</p> <p>Dietary folate sources.</p>	<p>In comparison to pre-fortification values, both serum and erythrocyte folate concentrations ↑ significantly (P<0.0001 for all age-sex groups) post-fortification.</p> <p>Mean serum folate ↑ from NHANES III to NHANES 1999 to 2000 (136%), from 11.4nmol per L to 26.9nmol per L.</p> <p>Mean erythrocyte folate ↑ 57% (from 375nmol per L to 590nmol per L).</p> <p>Prevalence of:</p> <p>Inadequate serum folate concentrations (<7nmol per L) ↓ significantly from 25.77% to 0.93% (P<0.0001).</p> <p>Low erythrocyte folate (<305nmol per L) ↓ significantly from 39.07% to 3.70% (P<0.0001).</p>
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<p>Dowd JB and Aiello AE, 2008</p> <p>Study Design: Trend study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>Three waves of NHANES were divided into two periods:</p> <p>1) Pre-fortification [NHANES III (1991 to 1994)]</p> <p>2) Post-fortification (NHANES 1999 to 2000 and 2001 to 2002).</p> <p>Age: ≥25 years.</p>	<p>RBC folate.</p>	<p>Following fortification, the rate per 1,000 (number of cases) of low RBC folate status (<362.6nmol):</p> <p>↓ from 528 (95% CI: 507, 549) to 110 (95% CI: 91,128) for the lowest income quartile</p> <p>↓ from 374 (95% CI: 351, 396) to 42 (95% CI: 34 to 50) in the highest income quartile.</p> <p>Following fortification, the rate per 1,000 of low folate status:</p> <p>↓ from 647 (95% CI: 626, 667) to 171 (95% CI: 152, 190) in non-Hispanic blacks</p> <p>↓ from 484 (95% CI: 461, 507) to 58 (95% CI: 48, 67) in Hispanics</p> <p>↓ from 327 (95% CI: 310, 344) to 38 (95% CI: 32, 44) in non-Hispanics whites.</p>
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<p>Felkner M, Suarez L et al, 2002</p> <p>Study Design: Cross-sectional study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>Data from a population-based case-control NTD study done in 14 border counties of Texas-Mexico, from 1995 through 1999.</p> <p>N=93 women (51 were for 1996, 27 for 1997, 44 for 1998 and 48 for 1999) randomly selected from the control group.</p>	<p>RBC folate, mean and median.</p>	<p>About half of the women were born in Mexico; ~half had annual family incomes <\$15,000 and <12 years of education.</p> <p>Median serum folate concentration ↑ modestly from 8.5ng per ml in 1996 to 12.4ng per ml in 1999 (46% higher).</p> <p>Median RBC folate level ↑ from 272ng per ml in 1996 to 393ng per ml in 1999 (44% ↑).</p> <p>Median RBC folate concentration in women without prenatal vitamin users was 254ng per ml in 1996 and 378ng per ml in 1999 (49% ↑).</p>
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<p>Ganji V and Kafai MR, 2006</p> <p>Study Design: Trend study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>Data were measured at three periods:</p> <p>1) NHANES III 1988 to 1994</p> <p>2) NHANES 1999 to 2000</p> <p>3) NHANES 2001 to 2002.</p>	<p>Serum, RBC folate.</p> <p>Circulation total homocysteine concentrations.</p>	<p>Overall, mean serum folate concentrations in period 1, 2 and 3 were 12.1 ± 0.3, 30.2 ± 0.7 and 27.8 ± 0.5 nmol per L, respectively.</p> <p>When data were adjusted for sex, age and race-ethnicity, there was a ↓ of 10.4% in serum folate concentrations from period 2 to 3 ($P < 0.0002$).</p> <p>Overall, for all mean RBC folate concentrations in period 1, 2 and 3, 391 ± 5.4, 318 ± 11.7 and 611 ± 9.3 nmol per L, respectively.</p> <p>When data were adjusted for sex, age and race-ethnicity, similar trends were present for RBC folate.</p>
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<p>Jacques PF, Selhub J et al, 1999</p> <p>Study Design: Trend study.</p> <p>Class: D</p> <p>Rating: Positive</p>	<p>Data from the Framingham Offspring Cohort were divided in three groups:</p> <ol style="list-style-type: none"> 1) Baseline (fifth examination, pre-fortification) 2) Control group [sixth examination occurred before fortification began (January 1995 to September 1996)] 3) Study group (sixth examination, post-fortification). <p>Data were examined for those who used vitamin supplements and those who did not.</p>	<p>Plasma homocysteine.</p> <p>Folate.</p> <p>Vitamin B₁₂.</p> <p>Pyridoxal 5'-phosphate (active, circulating form of vitamin B₆).</p> <p>Dietary intake of folate assessed with a FFQ.</p>	<p>For subjects in the study group, not using supplements, the mean folate concentrations ↑ from 4.6 to 10.0ng per ml (11 to 23nmol per L) (P<0.001) from baseline.</p> <p>The prevalence of low folate concentrations [<3ng per ml (7nmol per liter)] ↓ from 22.0% to 1.7% (P<0.001).</p> <p>In the control group, NS Δ in concentrations of folate or homocysteine.</p> <p>Study and control groups, who used B-vitamin supplements, significantly ↑ plasma folate concentrations from baseline to follow-up.</p> <p>↑ 62% in the study group (P<0.001) and 24% control group (P<0.001).</p>
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<p>Kalmbach RD, Choumenkovitch SF et al, 2008</p> <p>Study Design: Cross-sectional study (data from a longitudinal study)</p> <p>Class: D</p> <p>Rating: Positive</p>	<p>Data from the Offspring cohort of the Framingham Heart Study was divided in four groups:</p> <p><i>Not exposed to fortification:</i></p> <p>1) N=705 non-supplement users</p> <p>2) N=398 supplement users.</p> <p><i>Exposed to fortification:</i></p> <p>3) N=355 non-supplement users</p> <p>4) N=245 supplement users.</p>	<p>Plasma folic acid (residual folic acid is a minor constituent of plasma folate that is not always detectable).</p> <p>Folic acid.</p> <p>5MeTHF concentrations.</p> <p>Folate activity.</p> <p>Dietary intake assessed by FFQ.</p>	<p>Total plasma folate for no B-vitamin supplements users was 32.4ug per day before fortification and 241.4ug per day after fortification.</p> <p>For vitamin supplements users, the total plasma folate, before and after fortification, was 399.4 and 601.4ug per day, respectively.</p>
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<p>Pfeiffer CM, Johnson CL et al, 2007</p> <p>Study Design: Trend study</p> <p>Class: C</p> <p>Rating: Positive</p>	<p>Participants in the pre-fortification NHANES III (1988 to 1994) and participants in three post-fortification NHANES periods (covering 1999 to 2004).</p>	<p>Folate for 1988 to 1994 and 1999 to 2004.</p> <p>Vitamin B₁₂ for 1991 to 1994 and 1999 to 2004.</p> <p>RBC folate for 1988 to 1994 and 1999 to 2004.</p>	<p>Serum and RBC folate concentrations ↑ substantially (by 119% to 161% and 44% to 64%, respectively) in each age group in the first post-fortification survey period and then ↓ (by 5% to 13% and 6% to 9%, respectively) in most age groups between the first and third post-fortification survey periods.</p> <p>Serum vitamin B₁₂ concentrations did not Δ.</p> <p>Prevalence of RBC folate concentration ↓ significantly in women of childbearing age from before to after fortification (from 38% to 5%), but no Δ thereafter.</p>
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<p>Quinlivan E and Gregory J, 2007</p> <p>Study Design: Trend study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>Three waves of NHANES data were divided into two periods:</p> <p>1) Pre-fortification (1988 to 1994)</p> <p>2) Post-fortification (1999 to 2000 and 2001 to 2004).</p>	<p>Serum and RBC folate concentrations.</p> <p>Linear relationship between Δ in serum or plasma folate concentration and daily folate equivalents was determined.</p>	<p>RBC folate and serum folate concentrations \uparrow between 1988 to 1994 and 1999 to 2000 and then \downarrow each year from 1999 to 2000 to 2003 to 2004.</p> <p>Values for the 90th percentile of RBC concentration were:</p> <p>296ng per ml in 1988 to 1994</p> <p>409ng per ml in 1999 to 2000</p> <p>395ng per ml in 2001 to 2002</p> <p>367ng per ml in 2003 to 2004.</p>
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<p>Ray JG, Vermeulen MJ et al, 2002</p> <p>Study Design: Cross-sectional study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>Data from 8,884 individuals who underwent evaluation of serum folate, red cell folate and serum vitamin B₁₂ between:</p> <p>1) Period 1 (April 1, 1997 to July 31, 1998)</p> <p>2) Period 2 (August 1, 1998 to January 30, 1999)</p> <p>3) Period 3 (February 1, 1999 to March 31, 2000).</p>	<p>All consecutive, concomitant and non-redundant:</p> <p>Serum folate</p> <p>RBC folate</p> <p>B₁₂.</p>	<p>Prevalence of serum folate insufficiency (<3.4nmol per L) ↓ from 0.52% in period 1 to 0.22% in period 3 [prevalence ratio (RR) 0.41%, 95% CI: 0.18, 0.93].</p> <p>Prevalence of RBC folate insufficiency (<215nmol per L) ↓ from 1.78% during period 1 to 0.41% in period 3 (RR 0.23, 95% CI: 0.14 to 0.40).</p> <p>NS difference observed between periods in the prevalence of B₁₂ insufficiency <120pmol per L (3.93% vs. 3.11%, respectively; RR 0.79, 95% CI: 0.62,1.01).</p>
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<p>Shuaibi A, House J et al, 2008</p> <p>Study Design: Cross-sectional</p> <p>Class: D</p> <p>Rating: Negative</p>	<p>N=95 healthy and non-pregnant college students were recruited from the University of Manitoba.</p> <p>Age: 18 to 25 years.</p>	<p>RBC folate.</p> <p>Dietary folate from natural food folate.</p> <p>Folic acid added to food.</p> <p>Folic acid supplements.</p> <p>Supplemental folate in the post-folic acid fortification era.</p>	<p>No women were folate deficient.</p> <p>14% reached RBC folate >400ug per day.</p> <p>Mean serum folate concentration for all participants = 14.6ng per ml (33.1nmol per L) and for RBC folate concentration = 311.9ng per ml (706.7nmol per L).</p> <p>Mean dietary intake of folic acid = 96±64ug per day.</p> <p>Supplemental folic acid intake = 94±189ug per day.</p> <p>Natural folate was 314±134ug per day and total dietary intake measured as DFEs = 646±368ug per day.</p>
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Search plan and results

Inclusion criteria

- *Subjects/Population:* Human subjects
- *Age:* Men, women, and children
- *Setting:* US and Canada only
- *Health status:* Healthy and those with elevated chronic disease risk (CHD/CVD, type 2 diabetes, metabolic syndrome and obesity)
- *Nutrition related problem/Condition:* None.

Search Criteria

- *Study design preferences:* RCT or clinical controlled studies, large non-randomized observational studies, cohort and systematic reviews
- *Size of study groups:* The sample size must equal 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:* June 1999 to present
- *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-reviewed journal.

Exclusion criteria

- *Subjects/Population:* Populations outside the U.S. and Canada
- *Setting:* Hospitalized patients
- *Health status:* Medical treatment or therapy and diseased subjects (already diagnosed with disease related to study purpose).

Search Criteria

- *Size of study groups:* Sample sizes less than 10
- *Study dropout rate:* Dropout rate in a study of 20% or greater
- *Year range:* Prior to June 1999
- *Authorship:* Studies by same author similar in content
- *Languages:* Articles not in English
- *Other:* Abstracts or presentations and articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

Comparators

- Intake levels/consumption levels
- Fortification
- Supplementation.

Health Outcomes/Clinical Disease

NTD.

Other Terms

NHANES.

- PubMed:

("Neural Tube Defects"[Mesh] OR NTDs[All Fields] OR "Spinal Dysraphism"[Mesh] or "Anencephaly"[Mesh]) AND ("Folic Acid"[Mesh] OR ("folic acid"[MeSH Terms] OR ("folic"[All Fields] AND "acid"[All Fields]) OR "folic acid"[All Fields] OR "folate"[All Fields])) AND "English and humans"[Filter]
Limits: published in the last 10 years. ("Folic Acid"[majr] OR folate) AND (fortification OR "Food, Fortified"[Mesh]) AND (serum OR plasma OR "red blood cell*" OR RBC*) AND ("Canada"[Mesh] OR "United States"[Mesh]) Limits: published in the last 10 years.

Date searched: 5/27/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 1099
- Total articles identified to review from electronic databases: 82
- Articles identified via handsearch or other means: 2
- Number of Primary Articles Identified: 24
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 24
- Number of Articles Reviewed but Excluded: 60

Included articles (References)

1. Bar-Oz B, Koren G, Nguyen P, Kapur BM. Folate fortification and supplementation: Are we there yet? *Reprod Toxicol*. 2008 Aug; 25(4): 408-412. Epub 2008 May 3. PMID: 18550330.
2. Dietric M, Brown CJ, Block G. The effect of folate fortification of cereal-grain products on blood folate status, dietary folate intake, and dietary folate sources among adult non-supplement users in the United States. *J Am Coll Nutr*. 2005 Aug; 24(4): 266-274. PMID: 16093404.
3. Dowd JB, Aiello AE. Did national folic acid fortification reduce socioeconomic and racial disparities in folate status in the US? *Int J Epidemiol*. 2008 Oct; 37(5): 1, 059-1, 066. Epub 2008 May 2. PMID: 18456713.
4. Felkner M, Suarez L, Hendricks K, Gunter EW. Blood folate levels on the Texas-Mexico border. *Tex Med*. 2002 Nov; 98(11): 58-60. PMID: 12448957.
5. Ganji V, Kafai MR. Trends in serum folate, RBC folate, and circulating total homocysteine concentrations in the United States: Analysis of data from National Health and Nutrition Examination Surveys, 1988-1994, 1999-2000, and 2001-2002. *J Nutr*. 2006 Jan; 136(1): 153-158. PMID: 16365075.
6. Jacques PF, Selhub J, Bostom AG, Wilson PW, Rosenberg IH. The effect of folic acid fortification on plasma folate and total homocysteine concentrations. *N Engl J Med*. 1999 May 13; 340(19): 1, 449-1, 454. PMID: 10320382 (HS).
7. Kalmbach RD, Choumenkovitch SF, Troen AM, D'Agostino R, Jacques PF, Selhub J. Circulating folic acid in plasma: Relation to folic acid fortification. *Am J Clin Nutr*. 2008 Sep; 88(3): 763-768. PMID: 18779294.
8. Pfeiffer CM, Johnson CL, Jain RB, Yetley EA, Picciano MF, Rader JI, Fisher KD, Mulinare J, Osterloh JD. Trends in blood folate and vitamin B-12 concentrations in the United States, 1988 2004. *Am J Clin Nutr*. 2007 Sep; 86(3): 718-727. PMID: 17823438.
9. Quinlivan EP, Gregory JF 3rd. Reassessing folic acid consumption patterns in the United States (1999 2004): Potential effect on neural tube defects and overexposure to folate. *Am J Clin Nutr*. 2007 Dec;86(6):1773-9. PMID: 18065598.
10. Ray JG, Vermeulen MJ, Boss SC, Cole DE. Declining rate of folate insufficiency among adults following increased folic acid food fortification in Canada. *J Public Health*. 2002 Jul-Aug; 93(4): 249-253. PMID: 12154524.
11. Shuaibi AM, House JD, Sevenhuysen GP. Folate status of young Canadian women after folic acid fortification of grain products. *J Am Diet Assoc*. 2008 Dec; 108(12): 2, 090-2, 094. PMID: 19027414.

Excluded articles

Excluded Articles	Reason for Exclusion
<p>Antoniades C, Antonopoulos AS, Tousoulis D, Marinou K, Stefanadis C. Homocysteine and coronary atherosclerosis: From folate fortification to the recent clinical trials. www.ncbi.nlm.nih.gov/pubmed/19029125 Eur Heart J. 2009 Jan; 30(1): 6-15. Epub 2008 Nov 23. Review. PMID: 19029125.</p>	<p>Does not answer the question; about homocysteine and CVD.</p>
<p>Bleys J, Miller ER 3rd, Pastor-Barriuso R, Appel LJ, Guallar E. Vitamin-mineral supplementation and the progression of atherosclerosis: a meta-analysis of randomized controlled trials. www.ncbi.nlm.nih.gov/pubmed/17023716 Am J Clin Nutr. 2006 Oct; 84(4): 880-887; quiz 954-955. PMID: 17023716.</p>	<p>Does not answer the question; about antioxidants and B vitamins.</p>
<p>Bor MV, Wulff AM, Nexø E, Krarup H. Clin Chem Infrequency of low red blood cell (RBC) folate levels despite no folate fortification program: a study based on results from routine requests for RBC folate. Lab Med. 2008; 46(3): 401-404. PMID: 18254711.</p>	<p>International study.</p>
<p>Bostom AG, Jacques PF, Liaugaudas G, Rogers G, Rosenberg IH, Selhub J. Total homocysteine lowering treatment among coronary artery disease patients in the era of folic acid-fortified cereal grain flour. www.ncbi.nlm.nih.gov/pubmed/11884295 Arterioscler Thromb Vasc Biol. 2002 Mar 1; 22(3): 488-491. PMID: 11884295.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>Botto LD, Lisi A, Bower C, Canfield MA, Dattani N, De Vigan C, De Walle H, Erickson DJ, Halliday J, Irgens LM, Lowry RB, McDonnell R, Metneki J, Poetzsch S, Ritvanen A, Robert-Gnansia E, Siffel C, Stoll C, Mastroiacovo P. Trends of selected malformations in relation to folic acid recommendations and fortification: An international assessment. Birth Defects Res A Clin Mol Teratol. 2006 Oct; 76(10): 693-705. PMID: 17029289.</p>	<p>International article.</p>
<p>Boulet SL, Yang Q, Mai C, Kirby RS, Collins JS, Robbins JM, Meyer R, Canfield MA, Mulinare J; National Birth Defects Prevention Network. Trends in the postfortification prevalence of spina bifida and anencephaly in the United States. Birth Defects Res A Clin Mol Teratol. 2008 Jul; 82(7): 527-532. PMID: 18481813.</p>	<p>Does not answer the question; evaluated only post-fortification.</p>

<p>Boushey CJ, Edmonds JW, Welshimer KJ. Estimates of the effects of folic-acid fortification and folic-acid bioavailability for women. <i>Nutrition</i>. 2001 Oct; 17(10): 873-879. PMID: 11684395.</p>	<p>Does not answer the research question</p>
<p>Byrne J, Carolan S, Arcement R, Kozlowski M, Taller I, Ried S, Keating R. An intervention study to increase knowledge and use of folic acid among relatives in neural tube defect-affected families in Washington, D.C. <i>Birth Defects Res A Clin Mol Teratol</i>. 2005 Jun; 73(6): 424-429. PMID: 15880789.</p>	<p>Does not answer the question; about knowledge and intake.</p>
<p>Canfield MA, Anderson JL, Waller DK, Palmer SE, Kaye CI. Folic acid awareness and use among women with a history of a neural tube defect pregnancy: Texas, 2000-2001. <i>MMWR Recomm Rep</i>. 2002 Sep 13; 51(RR-13): 16-19. PMID: 12353508.</p>	<p>Population with recurrent NTD.</p>
<p>Carlsson CM. Homocysteine lowering with folic acid and vitamin B supplements: effects on cardiovascular disease in older adults. www.ncbi.nlm.nih.gov/pubmed/16872232 <i>Drugs Aging</i>. 2006; 23(6): 491-502. Review. PMID: 16872232.</p>	<p>It doesn't answer the question. About B supplements and cardiovascular protection.</p>
<p>Caudill MA, Le T, Moonie SA, Esfahani ST, Cogger EA. Folate status in women of childbearing age residing in Southern California after folic acid fortification. <i>J Am Coll Nutr</i>. 2001 Apr; 20(2 Suppl): 129-134. Erratum in: <i>J Am Coll Nutr</i>. 2001 Jun; 20(3): 268. PMID: 11349935.</p>	<p>Does not answer the research question.</p>
<p>CDC, MMWR Weekly report, 2002. Folate Status in Women of Childbearing Age, by Race/Ethnicity: United States, 1999-2000. September 13, 2002; 51(36): 808-810. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5136a2.htm</p>	<p>Data used in this article was analyzed in the Quilivan et al., 2007 article, which was included.</p>
<p>CDC, MMWR Weekly report, 2009. Folate Status in Women of Childbearing Age, by Race/Ethnicity: United States, 1999-2000, 2001-2002 and 2003-2004. January 5, 2007; 55(51):1, 377-1, 380. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5551a2.htm</p>	<p>Data used in this article was analyzed in the Quilivan et al., 2007 study, which was included.</p>

<p>Cena ER, Joy AB, Heneman K, Espinosa-Hall G, Garcia L, Schneider C, Wooten Swanson PC, Hudes M, Zidenberg-Cherr S. <u>Folate intake and food-related behaviors in nonpregnant, low-income women of childbearing age.</u> <i>J Am Diet Assoc.</i> 2008 Aug; 108(8): 1, 364-1, 368. PMID: 18656578.</p>	<p>Does not answer the research question.</p>
<p>Clarke R, Collins R. Can dietary supplements with folic acid or vitamin B₆ reduce cardiovascular risk? Design of clinical trials to test the homocysteine hypothesis of vascular disease. www.ncbi.nlm.nih.gov/pubmed/9919473 <i>J Cardiovasc Risk.</i> 1998 Aug; 5(4): 249-255. PMID: 9919473.</p>	<p>Not a systematic review.</p>
<p>Choumenkovitch SF, Selhub J, Wilson PW, Rader JI, Rosenberg IH, Jacques PF. <u>Folic acid intake from fortification in United States exceeds predictions</u> <i>J Nutr.</i> 2002 Sep; 132(9): 2, 792-2, 798. PMID: 12221247</p>	<p>Does not answer the research question.</p>
<p>Cornel MC, de Smit DJ, de Jong-van den Berg LT. <u>Folic acid: The scientific debate as a base for public health policy.</u> <i>Reprod Toxicol.</i> 2005 Sep-Oct; 20(3): 411-415. Review. PMID: 15978774.</p>	<p>Commentary.</p>
<p>De Bree A, Mennen LI, Hercberg S, Galan P. Evidence for a protective (synergistic?) effect of B-vitamins and omega-3 fatty acids on cardiovascular diseases. www.ncbi.nlm.nih.gov/pubmed/15116076 <i>Eur J Clin Nutr.</i> 2004 May; 58(5): 732-744. PMID: 15116076.</p>	<p>Does not answer the question.</p>
<p>de Jong-Van den Berg LT, Hernandez-Diaz S, Werler MM, Louik C, Mitchell AA. <u>Trends and predictors of folic acid awareness and periconceptional use in pregnant women.</u> <i>Am J Obstet Gynecol.</i> 2005 Jan; 192(1): 121-128. PMID: 15672013.</p>	<p>Does not answer the question; about awareness.</p>
<p>DeWolfe J. Can J. <u>Folate intake of older adults before and after fortification of grain products.</u> <i>Diet Pract Res.</i> 2007 Winter; 68(4): 218-220. PMID: 18073005.</p>	<p>Measure intake not RBC or plasma folate.</p>
<p>Evans MI, Llurba E, Landsberger EJ, O'Brien JE, Harrison HH. <u>Impact of folic acid fortification in the United States: Markedly diminished high paternal serum alpha-fetoprotein values.</u> <i>Obstet Gynecol.</i> 2004 Mar; 103(3): 474-479. PMID: 14990409.</p>	<p>Does not answer the question; addresses alpha-fetoprotein values.</p>

<p>Goh YI, Bollano E, Einarson TR, Koren G. Prenatal multivitamin supplementation and rates of congenital anomalies: A meta-analysis. www.ncbi.nlm.nih.gov/pubmed/17022907 <i>J Obstet Gynaecol Can.</i> 2006 Aug; 28(8): 680-689. Review. PMID: 17022907.</p>	<p>Folic acid intake is not quantified.</p>
<p>Grosse SD, Collins JS. <u>Folic acid supplementation and neural tube defect recurrence revention.</u> <i>Birth Defects Res A Clin Mol Teratol.</i> 2007 Nov; 79(11): 737-742. PMID: 17990333.</p>	<p>Does not answer the question; about recurrence.</p>
<p>Kannan S, Menotti E, Scherer HK, Dickinson J, Larson K. <u>Folic acid and the prevention of neural tube defects: A survey of awareness among Latina women of childbearing age residing in southeast Michigan.</u> <i>Health Promot Pract.</i> 2007 Jan; 8(1): 60-68. Epub 2006 Jul 13. PMID: 16840767.</p>	<p>Does not answer the question; about awareness.</p>
<p>Klerk M, Durga J, Schouten EG, Kluff C, Kok FJ, Verhoef P. No effect of folic acid supplementation in the course of one year on haemostasis markers and C-reactive protein in older adults. www.ncbi.nlm.nih.gov/pubmed/16113791 <i>Thromb Haemost.</i> 2005 Jul; 94(1): 96-100. PMID: 16113791.</p>	<p>Does not answer the question; about supplementation and homocysteine.</p>
<p>Lambert-Messerlian G, Halliday J, Williams J, Cain R, Msall ME, Palomaki GE, Canick JA. <u>Effect of folic acid fortification on prevalence of neural tube defects in Rhode Island.</u> <i>J Med Screen.</i> 2004; 11(2): 106-107. PMID: 15153328.</p>	<p>Letter to the editor.</p>
<p>Lewis SJ, Ebrahim S, Davey Smith G. Meta-analysis of MTHFR 677C-T polymorphism and coronary heart disease: Does totality of evidence support causal role for homocysteine and preventive potential of folate? www.ncbi.nlm.nih.gov/pubmed/16216822 <i>BMJ.</i> 2005 Nov 5; 33 1(7, 524): 1, 053. Epub 2005 Oct 10. Review. PMID: 16216822.</p>	<p>Not a systematic review; does not answer the question; about genotype.</p>
<p>Lumley J, Watson L, Watson M, Bower C. Cochrane <u>Periconceptional supplementation with folate and/or multivitamins for preventing neural tube defects.</u> <i>Database Syst Rev.</i> 2001;(3): CD001056. Review. PMID: 11686974.</p>	<p>Does not answer the question; about NTD and supplementation.</p>

<p>Malinow MR, Duell PB, Irvin-Jones A, Upson BM, Graf EE. Increased plasma homocyst(e)ine after withdrawal of ready-to-eat breakfast cereal from the diet: Prevention by breakfast cereal providing 200 microg folic acid. www.ncbi.nlm.nih.gov/pubmed/10963464 <i>J Am Coll Nutr.</i> 2000 Aug; 19(4): 452-457. PMID: 10963464.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>Mark L, Erdei F, Markizay J, Kondacs A, Katona A. Effect of treatment with folic acid and vitamin B₆ on lipid and homocysteine concentrations in patients with coronary artery disease. www.ncbi.nlm.nih.gov/pubmed/11985950 <i>Nutrition.</i> 2002 May; 18(5): 428-429. No abstract available. PMID: 11985950.</p>	<p>Does not answer the question; about supplementation and homocysteine.</p>
<p>McCully KS. Homocysteine, vitamins, and vascular disease prevention. www.ncbi.nlm.nih.gov/pubmed/17991676 <i>Am J Clin Nutr.</i> 2007 Nov; 86(5): 1, 563S-1, 568S. Review. PMID: 17991676.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>McEligot AJ, Rock CL, Gilpin EA, Pierce JP. Responsiveness of homocysteine concentrations to food and supplemental folate intakes in smokers and never-smokers enrolled in a diet intervention trial. www.ncbi.nlm.nih.gov/pubmed/16497600 <i>Nicotine Tob Res.</i> 2006 Feb; 8(1): 57-66. PMID: 16497600.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>McKay DL, Perrone G, Rasmussen H, Dallal G, Blumberg JB. Multivitamin/mineral supplementation improves plasma B-vitamin status and homocysteine concentration in healthy older adults consuming a folate-fortified diet. www.ncbi.nlm.nih.gov/pubmed/11110875</p>	<p>Does not answer the question; about supplementation and homocysteine.</p>
<p>Mills JL, Signore C. <u>Neural tube defect rates before and after food fortification with folic acid.</u> <i>Birth Defects Res A Clin Mol Teratol.</i> 2004 Nov; 70(11): 844-845. Review. PMID: 15468072</p>	<p>Review of four articles; three primary articles were included.</p>
<p>Moats C, Rimm EB. Vitamin intake and risk of coronary disease: observation versus intervention. <i>Curr Atheroscler Rep.</i> 2007 Dec; 9(6): 508-514. Review. www.ncbi.nlm.nih.gov/pubmed/18377792 PMID: 18377792</p>	<p>Not a systematic review; does not answer the question.</p>

<p>Mosley BS, Cleves MA, Siega-Riz AM, Shaw GM, Canfield MA, Waller DK, Werler MM, Hobbs CA; National Birth Defects Prevention Study. <u>Neural tube defects and maternal folate intake among pregnancies conceived after folic acid fortification in the United States.</u> <i>Am J Epidemiol.</i> 2009 Jan 1; 169(1): 9-17. Epub 2008 Oct 25. PMID: 18953063.</p>	<p>Does not address the question; evaluated the relation of NTD and maternal folate consumption after folic acid fortification.</p>
<p>Muskiet FA. The importance of (early) folate status to primary and secondary coronary artery disease prevention. www.ncbi.nlm.nih.gov/pubmed/15964170 <i>Reprod Toxicol.</i> 2005 Sep-Oct; 20(3): 403-410. Review. PMID: 15964170.</p>	<p>Not a systematic review.</p>
<p>Ntaios GC, Savopoulos CG, Chatzinikolaou AC, Kaiafa GD, Hatzitolios A. Vitamins and stroke: The homocysteine hypothesis still in doubt. <i>Neurologist.</i> 2008 Jan; 14(1): 2-4. Review. www.ncbi.nlm.nih.gov/pubmed/18195649 PMID: 18195649.</p>	<p>Not a systematic review; about vitamins and CVD.</p>
<p>Palomaki GE, Williams J, Haddow JE. <u>Comparing the observed and predicted effectiveness of folic acid fortification in preventing neural tube defects.</u> <i>J Med Screen.</i> 2003; 10(1): 52-53. PMID: 12790316.</p>	<p>Letter to the editor.</p>
<p>Quinlivan EP, McPartlin J, McNulty H, Ward M, Strain JJ, Weir DG, Scott JM. Importance of both folic acid and vitamin B₁₂ in reduction of risk of vascular disease. <i>Lancet.</i> 2002 Jan 19; 359(9, 302): 227-228. PMID: 11812560.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>Rader JI, Schneeman BO. <u>Prevalence of neural tube defects, folate status, and folate fortification of enriched cereal-grain products in the United States.</u> <i>Pediatrics.</i> 2006 Apr; 117(4): 1, 394-1, 399. PMID: 16585338.</p>	<p>Not a systematic review.</p>
<p>Ramos MI, Allen LH, Mungas DM, Jagust WJ, Haan MN, Green R, Miller JW. <u>Low folate status is associated with impaired cognitive function and dementia in the Sacramento Area Latino Study on Aging.</u> <i>Am J Clin Nutr.</i> 2005 Dec; 82(6): 1, 346-1, 352. PMID: 16332669.</p>	<p>Does not answer the question; about dementia and folate status.</p>

<p>Ray JG, Vermeulen MJ, Boss SC, Cole DE. Declining rate of folate insufficiency among adults following increased folic acid food fortification in Canada. <i>Can J Public Health</i>. 2002 Jul-Aug; 93(4): 249-253. PMID: 12154524.</p>	<p>Does not address the question; investigates the changes in folate and vitamin B₁₂ insufficiency after folic acid fortification.</p>
<p>Rydlewicz A, Simpson JA, Taylor RJ, Bond CM, Golden MH. The effect of folic acid supplementation on plasma homocysteine in an elderly population. <i>QJM</i>. 2002 Jan; 95(1): 27-35. PMID: 11834770.</p>	<p>Does not answer the question; about supplementation and homocysteine.</p>
<p>Sauer J, Mason JB, Choi SW. Too much folate: A risk factor for cancer and cardiovascular disease? www.ncbi.nlm.nih.gov/pubmed/19057184 <i>Curr Opin Clin Nutr Metab Care</i>. 2009 Jan; 12(1): 30-36. Review. PMID: 19057184.</p>	<p>Not a systematic review.</p>
<p>Smolková B, Dusinská M, Raslová K, Barancoková M, Kazimírová A, Horská A, Spustová V, Collins A. Folate levels determine effect of antioxidant supplementation on micronuclei in subjects with cardiovascular risk. <i>Mutagenesis</i>. 2004 Nov; 19(6): 469-476. PMID: 15548759.</p>	<p>Does not answer the question; about antioxidants.</p>
<p>Stevenson RE, Allen WP, Pai GS, Best R, Seaver LH, Dean J, Thompson S. <u>Decline in prevalence of neural tube defects in a high-risk region of the United States.</u> <i>Pediatrics</i>. 2000 Oct; 106(4): 677-683. PMID: 11015508.</p>	<p>Does not address the question; evaluates the recurrence prevention effort and public awareness campaign of folic acid supplementation for all women of childbearing age.</p>
<p>Suarez L, Hendricks KA, Cooper SP, Sweeney AM, Hardy RJ, Larsen RD. <u>Neural tube defects among Mexican Americans living on the US-Mexico border: effects of folic acid and dietary folate.</u> <i>Am J Epidemiol</i>. 2000 Dec 1; 152(11): 1, 017-1, 023. PMID: 11117610.</p>	<p>Does not measure plasma, RBC or serum folate; about NTD.</p>
<p>Thompson SJ, Torres ME, Stevenson RE, Dean JH, Best RG. <u>Periconceptional multivitamin folic acid use, dietary folate, total folate and risk of neural tube defects in South Carolina.</u> <i>Ann Epidemiol</i>. 2003 Jul; 13(6): 412-418. PMID: 12875798.</p>	<p>Does not answer the question; about supplementation treatment.</p>

<p>Tucker KL, Olson B, Bakun P, Dallal GE, Selhub J, Rosenberg IH. Breakfast cereal fortified with folic acid, vitamin B-6, and vitamin B-12 increases vitamin concentrations and reduces homocysteine concentrations: A randomized trial. <i>Am J Clin Nutr.</i> 2004 May; 79(5): 805-811. PMID: 15113718.</p>	<p>Does not answer the question; about supplementation and homocysteine.</p>
<p>Van Beynum IM, den Heijer M, Blom HJ, Kapusta L. The MTHFR 677C-T polymorphism and the risk of congenital heart defects: A literature review and meta-analysis. www.ncbi.nlm.nih.gov/pubmed/17965089 <i>QJM.</i> 2007 Dec; 100(12): 743-753. Epub 2007 Oct 26. Review. PMID: 17965089.</p>	<p>Does not answer the question.</p>
<p>Villa P, Perri C, Suriano R, Cucinelli F, Panunzi S, Ranieri M, Mele C, Lanzone A. L-folic acid supplementation in healthy postmenopausal women: Effect on homocysteine and glycolipid metabolism. <i>J Clin Endocrinol Metab.</i> 2005 Aug;90(8):4622-4.629. Epub 2005 May 17. PMID: 15899950.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>Villa P, Suriano R, Costantini B, Macrì F, Ricciardi L, Campagna G, Lanzone A. Hyperhomocysteinemia and cardiovascular risk in postmenopausal women: the role of Folate supplementation. www.ncbi.nlm.nih.gov/pubmed/17311496 <i>Clin Chem Lab Med.</i> 2007; 45(2): 130-135. Review. PMID: 17311496.</p>	<p>Does not answer the question.</p>
<p>Wald DS, Bishop L, Wald NJ, Law M, Hennessy E, Weir D, McPartlin J, Scott J. Randomized trial of folic acid supplementation and serum homocysteine levels. <i>Arch Intern Med.</i> 2001 Mar 12; 161(5): 695-700. PMID: 11231701.</p>	<p>Does not answer the question; about supplementation and homocysteine.</p>
<p>Yang QH, Carter HK, Mulinare J, Berry RJ, Friedman JM, Erickson JD. <u>Race-ethnicity differences in folic acid intake in women of childbearing age in the United States after folic acid fortification: Findings from the National Health and Nutrition Examination Survey, 2001-2002.</u> <i>Am J Clin Nutr.</i> 2007 May; 85(5): 1, 409-1, 416. PMID: 17490980.</p>	<p>Does not answer the research question.</p>
<p>Werler MM, Louik C, Mitchell AA. <u>Achieving a public health recommendation for preventing neural tube defects with folic acid.</u> <i>Am J Public Health.</i> 1999 Nov; 89(11): 1, 637-1, 640. PMID: 10553381</p>	<p>Does not answer the question; about supplementation.</p>

CHAPTER 7. DIETARY BEHAVIORS AND NUTRIENT INTAKE – MANDATORY FOLIC ACID FORTIFICATION AND INCIDENCE OF CVD AND STROKE

WHAT IMPACT HAS MANDATORY FOLIC ACID FORTIFICATION HAD ON THE INCIDENCE OF CVD AND STROKE IN THE US AND CANADA?

Conclusion statement

A limited body of evidence suggest stroke mortality has declined in US and Canadian populations following mandatory folate fortification.

Grade

Limited

Evidence summary overview

The population-based cohort study of Yang et al, 2006, examined national stroke mortality data from the United States (US) and Canada to evaluate trends in stroke-related mortality before and after folic acid fortification in the US and Canada and, as a comparison, during the same period in England and Wales, where fortification is not required. The ongoing decline in stroke mortality observed in the US between 1990 and 1997 accelerated in the period 1998 to 2002 in nearly all population strata, with an overall change from -0.3% (95% CI: -0.7 to -0.08) to -2.9 (95% CI: -3.5 to -2.3) per year ($P=0.0005$). The fall in stroke mortality in Canada averaged -1.0% (95% CI: -1.4 to -0.6) per year from 1990 to 1997 and accelerated to -5.4% (95% CI: -6.0 to -4.7) per year in 1998 to 2002 ($P\leq 0.0001$). In contrast, the decline in stroke mortality in England and Wales did not change significantly between 1990 and 2002.

Evidence summary paragraphs

The population-based cohort study, **Yang et al, 2006** (neutral quality), study examined national stroke mortality data from the US and Canada, using segmented log-linear regression to evaluate trends in stroke-related mortality before and after folic acid fortification in the US and Canada and, as a comparison, during the same period in England and Wales, where fortification is not required. After folic acid fortification in the US, blood folate concentration increased and total homocysteine concentration decreased significantly. The ongoing decline in stroke mortality observed in the US between 1990 and 1997 accelerated in the period 1998 to 2002 in nearly all population strata, with an overall change from -0.3% (95% CI: -0.7,0.08) to -2.9 (95% CI: -3.5,-2.3) per year ($P=0.0005$). The fall in stroke mortality in Canada averaged -1.0% (95% CI: -1.4,-0.6) per year from 1990 to 1997 and accelerated to -5.4% (95% CI: -6.0,-4.7) per year in 1998 to 2002 ($P\leq 0.0001$). In contrast, the decline in stroke mortality in England and Wales did not change significantly between 1990 and 2002.

Overview table

Author, Year, Study Design, Class, Rating	Population/Sample Description	Measurements or Intervention	Significant Outcomes
<p>Yang Q, Botto LD et al, 2006</p> <p>Study Design: Population-based cohort study</p> <p>Class: B</p> <p>Rating: Neutral</p>	<p>Data were taken from the Center for Health Statistics Multiple cause Mortality Files of the CDC. Similar data were provided from the Canadian Mortality database at Canada and the from the UK office for National Statistics for England and Wales.</p> <p>Study period: 1990 through 2002.</p> <p>Subjects were ≥ 40 years and who experienced greater than 95% of death associated with stroke.</p>	<p>Age-adjusted stroke mortality rates were per 100,000-resident population.</p>	<p>After folic acid fortification in the US, blood folate concentration \uparrow and total homocysteine concentration \downarrow significantly. The ongoing \downarrow in stroke mortality observed in the US between 1990 and 1997 accelerated in 1998 to 2002 in nearly all population strata, with an overall Δ from -0.3% (95% CI, -0.7 to 0.08) to -2.9 (95% CI, -3.5 to -2.3) per year ($P=0.0005$).</p> <p>The fall in stroke mortality in Canada averaged -1.0% (95% CI, -1.4 to -0.6) per year from 1990 to 1997 and accelerated to -5.4% (95% CI, -6.0 to -4.7) per year in 1998 to 2002 ($P\leq 0.0001$).</p> <p>In contrast, the \downarrow in stroke mortality in England and Wales did not Δ significantly between 1990 and 2002.</p>

Search plan and results**Inclusion criteria**

- *Subjects/Population:* Human subjects.
- *Age:* Children, men and women of all ages.

- *Setting*: US and Canada only.
- *Health Status*: Healthy and those with elevated chronic disease risk (CHD/CVD, Type 2 diabetes, metabolic syndrome and obesity).
- *Nutrition Related Problem/Condition*: None.

Search Criteria

- *Study Design Preferences*: RCT or clinical controlled studies, large non-randomized observational studies, cohort, case-control studies, systematic reviews and meta-analysis.
- *Size of study Groups*: The sample size must equal 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 Drop Out Rate*: Less than 20%; preference for smaller dropout rates.
- *Year Range*: June 1999 to June 2009.
- *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-reviewed journal.

Exclusion criteria

- *Subjects/Population*:
 - Animal and in vitro studies
 - Malnourished/third-world populations or disease incidence not relative to US population (e.g. malaria).
- *Age*: Not applicable.
- *Setting*: Hospitalized patients.
- *Health Status*: Medical treatment/therapy and diseased subjects (already diagnosed with disease related to study purpose).
- *Nutrition Related Problem/Condition*: All conditions.

Search Criteria

- *Study Design Preferences*: Not applicable.
- *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 June 1999.
- *Authorship*: Studies by same author similar in content.
- *Languages*: Articles not in English.
- *Other*: Abstracts or presentations and articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed:
("Coronary Disease"[Mesh] OR "Cerebrovascular Disorders"[Mesh:NoExp] OR

"Stroke"[Mesh:NoExp] OR "Heart Diseases"[Mesh] OR "Cardiovascular Diseases"[Mesh:NoExp]) AND ("folic acid"[mh] OR folate) AND ("Food, Fortified"[Mesh] OR fortification)

Date searched: 6/25/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 48
- Total articles identified to review from electronic databases: 13
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 1
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 1
- Number of Articles Reviewed but Excluded: 12

Included articles (References)

- Yang Q, Botto LD, Erickson JD, Berry RJ, Sambell C, Johansen H, Friedman JM. Improvement in stroke mortality in Canada and the United States, 1990 to 2002. *Circulation.* 2006 Mar 14; 113 (10): 1, 335-1, 343. PMID: 16534029.

Excluded articles

Excluded Articles	Reason for Exclusion
Anderson JL, Horne BD, Carlquist JF, Bair TL, Habashi J, Hart NI, Jones SK, Muhlestein JB; Intermountain Heart Collaborative Study Group <u>Effect of implementation of folic acid fortification of food on homocysteine concentrations in subjects with coronary artery disease.</u> <i>Am J Cardiol.</i> 2002 Sep 1; 90 (5): 536-539. No abstract available. PMID: 12208419.	It does not answer the question. About homocysteine.
Anderson JL, Jensen KR, Carlquist JF, Bair TL, Horne BD, Muhlestein JB. <u>Effect of folic acid fortification of food on homocysteine-related mortality.</u> <i>Am J Med.</i> 2004 Feb 1; 116 (3): 158-164. PMID: 14749159.	It does not answer the question. About homocysteine.
Bostom AG, Jacques PF, Liaugaudas G, Rogers G, Rosenberg IH, Selhub J. <u>Total homocysteine lowering treatment among coronary artery disease patients in the era of folic acid-fortified cereal grain flour.</u> <i>Arterioscler Thromb Vasc Biol.</i> 2002 Mar 1; 22 (3): 488-491. PMID: 11884295.	It does not answer the question. About homocysteine.

<p>Brilakis ES, McConnell JP, Ballman KV, Klee GG, Berger PB <u>Lack of association between plasma homocysteine and angiographic coronary artery disease in the era of fortification of cereal grain flour with folic acid.</u> <i>Atherosclerosis</i>. 2002 Dec; 165 (2): 375-381. PMID: 12417290.</p>	<p>It does not answer the question.</p>
<p>Dalmeijer GW, Olthof MR, Verhoef P, Bots ML, van der Schouw YT. <i>Eur J Clin Nutr</i>. 2008 Mar; 62 (3): 386-394. Epub 2007 Mar 21. <u>Prospective study on dietary intakes of folate, betaine and choline and cardiovascular disease risk in women.</u> PMID: 17375117.</p>	<p>International study.</p>
<p>Dhonukshe-Rutten RA, de Vries JH, de Bree A, van der Put N, van Staveren WA, de Groot LC. <u>Dietary intake and status of folate and vitamin B12 and their association with homocysteine and cardiovascular disease in European populations.</u> <i>Eur J Clin Nutr</i>. 2009 Jan; 63 (1): 18-30. Epub 2007 Sep 12. PMID: 17851461.</p>	<p>International study.</p>
<p>Hoey L, McNulty H, Askin N, Dunne A, Ward M, Pentieva K, Strain J, Molloy AM, Flynn CA, Scott JM. <u>Effect of a voluntary food fortification policy on folate, related B vitamin status and homocysteine in healthy adults.</u> <i>Am J Clin Nutr</i>. 2007 Nov; 86 (5): 1, 405-1, 413. PMID: 17991653.</p>	<p>It does not answer the question. About dietary intake and biomarker status of folate.</p>
<p>Ionescu-Iltu R, Marelli AJ, Mackie AS, Pilote L. <u>Prevalence of severe congenital heart disease after folic acid fortification of grain products: Time trend analysis in Quebec, Canada.</u> <i>BMJ</i>. 2009 May 12; 338: b1, 673. doi: 10.1, 136/bmj. b1, 673., PMID: 19436079.</p>	<p>It does not answer the question. About congenital heart disease.</p>
<p>Lutsep HL, Campbell S, Chambless LE, Howard VJ, Toole JF. <u>Plasma total homocysteine levels in stroke patients screened for the vitamin intervention for stroke prevention clinical trial in the era of folate fortification.</u> <i>Neuroepidemiology</i>. 2006; 26 (1): 45-51. Epub 2005 Oct 25. PMID: 16254453.</p>	<p>It does not answer the question. It evaluated homocysteine.</p>
<p>Malinow MR, Duell PB, Irvin-Jones A, Upson BM, Graf EE. <u>Increased plasma homocyst(e)ine after withdrawal of ready-to-eat breakfast cereal from the diet: Prevention by breakfast cereal providing 200 microg folic acid.</u> <i>J Am Coll Nutr</i>. 2000 Aug; 19 (4): 452-457. PMID: 10963464.</p>	<p>It does not answer the question. About homocysteine.</p>

<p>Neal B, MacMahon S, Ohkubo T, Tonkin A, Wilcken D; PACIFIC Study Group. <u>Dose-dependent effects of folic acid on plasma homocysteine in a randomized trial conducted among 723 individuals with coronary heart disease.</u> <i>Eur Heart J.</i> 2002 Oct; 23 (19): 1, 509-1, 515. PMID: 12395803.</p>	<p>It does not answer the question. About homocysteine.</p>
<p>Shirodaria C, Antoniades C, Lee J, Jackson CE, Robson MD, Francis JM, Moat SJ, Ratnatunga C, Pillai R, Refsum H, Neubauer S, Channon KM. <u>Global improvement of vascular function and redox state with low-dose folic acid: Implications for folate therapy in patients with coronary artery disease.</u> <i>Circulation.</i> 2007 May 1; 115 (17): 2, 262-2, 270. Epub 2007 Apr 9. PMID: 17420345.</p>	<p>It does not answer the question. About effects of folic acid on human vessels.</p>

CHAPTER 8. DIETARY BEHAVIORS AND NUTRIENT INTAKE – MANDATORY FOLIC ACID FORTIFICATION AND INCIDENCE OF COLON CANCER

WHAT IMPACT HAS MANDATORY FOLIC ACID FORTIFICATION HAD ON THE INCIDENCE OF COLON CANCER?

Conclusion statement

A limited body of evidence demonstrates that mandatory folic acid fortification has increased the incidence of colorectal cancer (CRC) in the US and Canada.

Grade

Limited

Evidence summary overview

Mason et al, 2007 used the nationwide Surveillance, Epidemiology and End Result Registry, which collected data in the US and Canada from 1986 to 2002, to address the question. In the US the absolute rates of colorectal cancer (CRC) began to increase in 1996 and peaked in 1998. In Canada the absolute rates of CRC began to increase in 1997 and peaked in 2000. The sudden increase in CRC incidence represents a significant deviation from the time period just prior to folate fortification in the US by four to six additional cases per 100,000 individuals. It does not appear that changes in colorectal endoscopic procedures accounted for the increase in CRC incidence.

The study of Hirsch et al (2009) compared rates of hospital discharges due to CRC in Chile before (1992 to 1996) and after (2001 to 2004) mandatory folic acid fortification (220mcg per 100g wheat flour). The results were described in two groups: 1) Adults aged 45 to 64 and 2) adults aged 65 to 70. In age group 1, the rate ratio of hospital discharges due to CRC was 2.6 (CI: 99% 2.93 to 2.58) for an overall increase of 162%. In age group 2, the rate ratio was 2.9 (CI: 99% 3.25 to 2.86). The authors conclude that mandatory folate fortification may be associated with an increased risk of colon cancer.

Evidence summary paragraphs

Hirsch et al, 2009 (neutral quality). This trend study compared the rates of hospital discharges owing to colon cancer in Chile before (1992 to 1996) and after (2001 to 2004) mandatory fortification with 220mcg folic acid per 100g wheat flour. Results were described for two groups: 1) 45 to 64 years and 2) 65 to 79 years old. In Group 1, the rate of hospital discharges owing to colon cancer increased by 162%. The highest rate ratio between the two periods was for colon cancer in Group 1 (rate ratio, 2.6, CI: 99% 2.93, 2.58) and in Group 2 (rate ratio, 2.9, CI: 99% 3.25, 2.86). These data provide new evidence that a folate fortification program could be associated with risk of colon cancer.

Mason et al, 2007 (neutral quality). This research hypothesis highlights a temporal association between folic acid fortification of enriched cereal grains in the US and Canada and an increase in the incidence of colorectal cancer (CRC) in these two countries. This paper presents a hypothetical foundation on which further research will

be required to determine whether causality exists. In the US the absolute rates of CRC began to increase in 1996 and peaked in 1998. In Canada the absolute rates of CRC began to increase in 1997 and peaked in 2000. The sudden increase in CRC incidence represents a statistically significant deviation from the pre-1996 to 1997 trends by four to six additional cases per 100,000 individuals.

Overview table

Author, Year, Study Design, Class, Rating	Population/Sample Description	Measurements or Intervention	significant Outcomes
<p>Hirsch S, Sanchez H et al, 2009</p> <p>Study Design: Trend Study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>Number of hospital discharges of two groups:</p> <p>1) Before (1992 to 1996)</p> <p>2) After (2001 to 2004) mandatory fortification policy in Chile.</p> <p>Data set collected by Chilean Ministry of Health and National Institute of Statistics.</p>	<p>Hospital discharge rates for colorectal, breast and gastric cancer and ischemic, hypertensive and cerebrovascular disease.</p> <p>Discharge rates were compared using Rate Ratios.</p>	<p>Rates of hospital discharge causes per 100,000 inhabitants:</p> <p>Group 1: (45 to 64 years old) rate ratio 2.6 (CI: 99%, 2.93 to 2.58); 1992=24.4; 1993=21.6; 1996=24.5; 2002=56.1; 2003=60.8; 2004=67.3</p> <p>Group 2 (65 to 79 years old) rate ratio 2.9 (CI: 99% 3.25, 2.86); 1992=62.7; 1993=65.8; 1996=78.4; 2002=178.9; 2003=208.0; 2004=214.5.</p>

<p>Mason J, Dickstein A et al, 2007</p> <p>Study Design: Trend study</p> <p>Class: D</p> <p>Rating: Neutral</p>	<p>Nationally representative data collected from the nationwide Surveillance, Epidemiology and End Result registry [which collects cancer incidence and survival data from population-based cancer registries covering ~26% of the US population and the Canadian Cancer Statistics (from 1986 to 2002)].</p>	<p>Colorectal endoscopic procedures.</p>	<p>In the US, absolute rates of CRC began to ↑ in 1996 and peaked in 1998.</p> <p>In Canada, absolute rates of CRC began to ↑ in 1997 and peaked in 2000.</p> <p>The sudden ↑ in CRC incidence represents a highly statistically significant deviation from pre-1996 to 1997 trends by four to six additional cases per 100,000 individuals.</p> <p>↑ in rates remain statistically significant when data from each country were analyzed separately for men and women.</p> <p>Δ in colorectal endoscopic procedures do not seem to account for this ↑ in CRC incidence.</p>
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Search plan and results

Inclusion criteria

- *Subjects/population:* Human subjects
- *Age:* Children, men and women of all ages
- *Setting:* US and Canada and other countries with fortification policy
- *Health status:* Healthy and those with elevated chronic disease risk (coronary heart disease or cardiovascular disease, type 2 diabetes, metabolic syndrome and obesity)
- *Nutrition related problem/condition:* None.

Search Criteria

- *Study design preferences:* Randomized controlled trials or clinical controlled studies, large non-randomized observational studies, cohorts, case-control studies, systematic reviews and meta-analyses

- *Size of study groups:* The sample size must equal 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:* June 2004 to June 2009
- *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

Exclusion criteria

- *Subjects/population:* Populations outside of the US and Canada
- *Age:* Not applicable
- *Setting:* Hospitalized patients
- *Health status:* Medical treatment or therapy and diseased subjects (already diagnosed with disease related to study purpose)
- *Nutrition related problem/condition:* All conditions.

Search Criteria

- *Study design preferences:* Not applicable
- *Size of study groups:* Sample sizes less than 10
- *Study dropout rate:* If the dropout rate in a study is 20% or greater, the study will be rejected
- *Year range:* Prior to June 2004
- *Authorship:* Studies by same author similar in content
- *Languages:* Articles not in English
- *Other:* Abstracts or presentations and articles not peer reviewed (Web sites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

Comparators

- Intake levels and consumption levels
- Fortification
- Supplementation.

Intermediate Biomarkers/Physiological Effects

Polyps.

Health Outcomes/Clinical Disease

Colon cancer.

Other Terms

NHANES.

Electronic databases used:

Pubmed:

("Folic Acid"[Mesh] OR "folate"[All Fields]) AND ("Food, Fortified"[Mesh] OR "Dietary Supplements"[Mesh] OR "diet"[MeSH Terms] OR intake[All Fields]) AND "english and humans"[Filter] AND ("Colorectal Neoplasms"[mesh] OR "polyps"[MeSH Terms])

Date searched: 6/18/09

Summary of articles identified to review

- Total hits from all electronic database searches: 570
- Total articles identified to review from electronic databases: 29
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 2
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 2
- Number of Articles Reviewed but Excluded: 27

Included articles (References)

1. Mason JB, Dickstein A, Jacques PF, Haggarty P, Selhub J, Dallal G, Rosenberg IH. A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: A hypothesis. *Cancer Epidemiol Biomarkers Prev.* 2007 Jul; 16(7): 1, 325-1, 329. PMID: 17626997.
2. Hirsch S, Sanchez H, Albala C, de la Maza MP, Barrera G, Leiva L, Bunout D. Colon cancer in Chile before and after the start of the flour fortification program with folic acid. *Eur J Gastroenterol Hepatol.* 2009 Apr; 21(4): 436-439. PMID: 19190501.

Excluded articles

Article	Reason for Exclusion
Ashktorab H, Begum R, Akhgar A, Smoot DT, Elbedawi M, Daremipouran M, Zhao A, Momen B, Giardiello FM. Folate status and risk of colorectal polyps in African Americans. www.ncbi.nlm.nih.gov/pubmed/17372834 <i>Dig Dis Sci.</i> 2007 Jun; 52(6): 1, 462-1, 470. Epub 2007 Mar 20. PMID: 17372834	Does not answer question. About gene-promoter.
Bird CL, Swendseid ME, Witte JS, Shikany JM, Hunt IF, Frankl HD, Lee ER, Longnecker MP, Haile RW. Red cell and plasma folate, folate consumption, and the risk of colorectal adenomatous polyps. <i>Cancer Epidemiol Biomarkers Prev.</i> 1995 Oct-Nov; 4(7): 709-714. PMID: 8672986	Article from 1995.

<p>Bollheimer LC, Buettner R, Kullmann A, Kullmann F. <u>Folate and its preventive potential in colorectal carcinogenesis. How strong is the biological and epidemiological evidence?</u> <i>Crit Rev Oncol Hematol</i>. 2005 Jul; 55(1): 13-36. Review. PMID: 15927841</p>	<p>Not a systematic review.</p>
<p>Cole BF, Baron JA, Sandler RS, Haile RW, Ahnen DJ, Bresalier RS, McKeown-Eyssen G, Summers RW, Rothstein RI, Burke CA, Snover DC, Church TR, Allen JI, Robertson DJ, Beck GJ, Bond JH, Byers T, Mandel JS, Mott LA, Pearson LH, Barry EL, Rees JR, Marcon N, Saibil F, Ueland PM, Greenberg ER; Polyp Prevention Study Group. Folic acid for the prevention of colorectal adenomas: A randomized clinical trial. www.ncbi.nlm.nih.gov/pubmed/17551129 <i>JAMA</i>. 2007 Jun 6; 297(21): 2, 351-2, 359. PMID: 17551129</p>	<p>Does not answer question. About folic acid supplementation intervention.</p>
<p>Coogan PF, Rosenberg L. <u>The use of folic acid antagonists and the risk of colorectal cancer.</u> <i>Pharmacoepidemiol Drug Saf</i>. 2007 Oct; 16(10): 1, 111-1, 119. PMID: 17600846</p>	<p>Does not answer question. About folic acid antagonists.</p>
<p>Figueiredo JC, Levine AJ, Grau MV, Barry EL, Ueland PM, Ahnen DJ, Byers T, Bresalier RS, Summers RW, Bond J, McKeown-Eyssen GE, Sandler RS, Haile RW, Baron JA. Colorectal adenomas in a randomized folate trial: The role of baseline dietary and circulating folate levels. www.ncbi.nlm.nih.gov/pubmed/18843003 <i>Cancer Epidemiol Biomarkers Prev</i>. 2008 Oct; 17(10): 2, 625-2, 631. PMID: 18843003</p>	<p>Does not answer question. About folic acid supplementation intervention.</p>
<p>Flood A, Caprario L, Chatterjee N, Lacey JV Jr, Schairer C, Schatzkin A. Folate, methionine, alcohol, and colorectal cancer in a prospective study of women in the United States. <i>Cancer Causes Control</i>. 2002 Aug; 13(6): 551-561. PMID: 12195645</p>	<p>Does not answer question. About association between alcohol and folic acid consumption.</p>
<p>Fuchs CS, Willett WC, Colditz GA, Hunter DJ, Stampfer MJ, Speizer FE, Giovannucci EL. The influence of folate and multivitamin use on the familial risk of colon cancer in women. www.ncbi.nlm.nih.gov/pubmed/11895870 <i>Cancer Epidemiol Biomarkers Prev</i>. 2002 Mar; 11(3): 227-234. PMID: 11895870</p>	<p>Does not answer question. Evaluated association of folic acid with colon cancer risk.</p>

<p>Harnack L, Jacobs DR Jr, Nicodemus K, Lazovich D, Anderson K, Folsom AR. Relationship of folate, vitamin B-6, vitamin B-12, and methionine intake to incidence of colorectal cancers. www.ncbi.nlm.nih.gov/pubmed/12588695 <i>Nutr Cancer</i>. 2002; 43(2): 152-158. PMID: 12588695</p>	<p>Does not answer question. Assessed the relationship of folate, methionine and vitamins B₆ and B₁₂ to occurrence of cancers of the colon.</p>
<p>Jaszewski R, Misra S, Tobi M, Ullah N, Naumoff JA, Kucuk O, Levi E, Axelrod BN, Patel BB, Majumdar AP. Folic acid supplementation inhibits recurrence of colorectal adenomas: a randomized chemoprevention trial. www.ncbi.nlm.nih.gov/pubmed/18680228 <i>World J Gastroenterol</i>. 2008 Jul 28; 14(28): 4, 492-4, 498. PMID: 18680228</p>	<p>Does not answer question. About folic acid supplementation intervention. Measure recurrence of polyps.</p>
<p>Kato I, Dnistrian AM, Schwartz M, Toniolo P, Koenig K, Shore RE, Akhmedkhanov A, Zeleniuch-Jacquotte A, Riboli E. Serum folate, homocysteine and colorectal cancer risk in women: A nested case-control study. http://www.ncbi.nlm.nih.gov/pubmed/10206314 <i>Br J Cancer</i>. 1999 Apr; 79(11-12): 1, 917-1, 922. PMID: 10206314</p>	<p>Does not answer question. As assessed the relation of plasma folate and homocysteine and colorectal adenoma recurrence</p>
<p>Khosraviani K, Weir HP, Hamilton P, Moorehead J, Williamson K. Effect of folate supplementation on mucosal cell proliferation in high-risk patients for colon cancer. <i>Gut</i>. www.ncbi.nlm.nih.gov/pubmed/12117879 2002 Aug; 51(2): 195-199. PMID: 12117879</p>	<p>Lab study.</p>
<p>Kim YI, Baik HW, Fawaz K, Knox T, Lee YM, Norton R, Libby E, Mason JB. Effects of folate supplementation on two provisional molecular markers of colon cancer: A prospective, randomized trial. www.ncbi.nlm.nih.gov/pubmed/11197251 <i>Am J Gastroenterol</i>. 2001 Jan; 96(1): 184-195. PMID: 11197251</p>	<p>Does not answer question. Study of folate supplementation on genomic DNA methylation.</p>
<p>Kim YI. <u>Folate and colorectal cancer: An evidence-based critical review</u>. <i>Mol Nutr Food Res</i>. 2007 Mar; 51(3): 267-292. PMID: 17295418</p>	<p>Not a systematic review.</p>
<p>Kim YI. <u>Role of folate in colon cancer development and progression</u>. <i>J Nutr</i>. 2003 Nov; 133(11 Suppl 1): 3731S-3739S. Review. PMID: 14608107</p>	<p>Not a systematic review.</p>

<p>Konings EJ, Goldbohm RA, Brants HA, Saris WH, van den Brandt PA. Intake of dietary folate vitamers and risk of colorectal carcinoma: Results from The Netherlands Cohort Study. www.ncbi.nlm.nih.gov/pubmed/12237910 <i>Cancer</i>.2002 Oct 1; 95(7): 1, 421-1, 433. PMID: 12237910</p>	<p>International.</p>
<p>Kune G, Watson L. Colorectal cancer protective effects and the dietary micronutrients folate, methionine, vitamins B6, B12, C, E, selenium, and lycopene. http://www.ncbi.nlm.nih.gov/pubmed/17176213 <i>Nutr Cancer</i>. 2006; 56(1): 11-21. PMID: 17176213</p>	<p>Does not answer question. International study (Australia) that assessed relationship of folate, methionine and vitamins B₆ and B₁₂ to occurrence of colon cancers.</p>
<p>Luebeck EG, Moolgavkar SH, Liu AY, Boynton A, Ulrich CM. Does folic acid supplementation prevent or promote colorectal cancer? Results from model-based predictions. www.ncbi.nlm.nih.gov/pubmed/18539928 <i>Cancer Epidemiol Biomarkers Prev</i>. 2008 Jun; 17(6): 1, 360-1, 367. Epub 2008 Jun 6. PMID: 18539928</p>	<p>Does not answer question. Mathematical model.</p>
<p>Martínez ME, Giovannucci E, Jiang R, Henning SM, Jacobs ET, Thompson P, Smith-Warner SA, Alberts DS. Folate fortification, plasma folate, homocysteine and colorectal adenoma recurrence. http://www.ncbi.nlm.nih.gov/pubmed/16615116?ordinalpos=39&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVDocSum <i>Cancer</i>.2006 Sep 15; 119(6): 1, 440-1, 446. PMID: 16615116</p>	<p>Does not answer question. Assessed the relation of plasma folate and homocysteine and colorectal adenoma recurrence.</p>
<p>Martínez ME, Henning SM, Alberts DS. Folate and colorectal neoplasia: Relation between plasma and dietary markers of folate and adenoma recurrence. www.ncbi.nlm.nih.gov/pubmed/15051616 <i>Am J Clin Nutr</i>.2004 Apr; 79(4): 691-697. PMID: 15051616</p>	<p>Does not answer question. Assessed dietary markers of folate status and colorectal adenoma recurrence.</p>
<p>Murphy G, Sansbury LB, Cross AJ, Stolzenberg-Solomon R, Laiyemo A, Albert PS, Wang Z, Schatzkin A, Lehman T, Kalidindi A, Modali R, Lanza E. Folate and MTHFR: Risk of adenoma recurrence in the Polyp Prevention Trial. <i>Cancer Causes Control</i>. 2008 Sep; 19(7): 751-758. Epub 2008 Mar 6. PMID: 18322814</p>	<p>Does not answer question. About the association between MTHFR, total folate and the risk of colorectal adenoma recurrence.</p>

<p>Otani T, Iwasaki M, Sasazuki S, Inoue M, Tsugane S; Japan Public Health Center-based Prospective Study Group. Plasma folate and risk of colorectal cancer in a nested case-control study: the Japan Public Health Center-based prospective study. www.ncbi.nlm.nih.gov/pubmed/17943453 <i>Cancer Causes Control</i>. 2008 Feb; 19(1): 67-74. Epub 2007 Oct 18. PMID: 17943453</p>	<p>International.</p>
<p>Sanjoaquin MA, Allen N, Couto E, Roddam AW, Key TJ. Folate intake and colorectal cancer risk: A meta-analytical approach. www.ncbi.nlm.nih.gov/pubmed/15499620 <i>Int J Cancer</i>. 2005 Feb 20; 113(5): 825-828. PMID: 15499620</p>	<p>Does not answer question. Examined the association between folate consumption and colorectal cancer risk.</p>
<p>Terry P, Jain M, Miller AB, Howe GR, Rohan TE. Dietary intake of folic acid and colorectal cancer risk in a cohort of women. www.ncbi.nlm.nih.gov/pubmed/11857369 <i>Int J Cancer</i>. 2002 Feb 20; 97(6): 864-867. PMID: 11857369</p>	<p>Does not answer question. Evaluated association between dietary folate intake and reduced colorectal cancer risk.</p>
<p>Sauer J, Mason JB, Choi SW. Too much folate: A risk factor for cancer and cardiovascular disease? <i>Curr Opin Clin Nutr Metab Care</i>. 2009 Jan; 12(1): 30-36. Review. PMID: 19057184</p>	<p>Does not answer question. Examined role of folate in chronic diseases, focusing on cancer and CVD.</p>
<p>Van Guelpen B, Hultdin J, Johansson I, Hallmans G, Stenling R, Riboli E, Winkvist A, Palmqvist R. Low folate levels may protect against colorectal cancer. www.ncbi.nlm.nih.gov/pubmed/16638790 <i>Gut</i>. 2006 Oct; 55(10): 1, 461-1, 466. Epub 2006 Apr 25. PMID: 16638790</p>	<p>International.</p>
<p>Zhang SM, Moore SC, Lin J, Cook NR, Manson JE, Lee IM, Buring JE. Folate, vitamin B6, multivitamin supplements, and colorectal cancer risk in women. www.ncbi.nlm.nih.gov/pubmed/16339055 <i>Am J Epidemiol</i>. 2006 Jan 15; 163(2): 108-115. Epub 2005 Dec 7. PMID: 16339055</p>	<p>Does not answer question. Evaluated associations between intakes of folate and vitamin B6 and colorectal cancer risk among women enrolled in a randomized trial.</p>

CHAPTER 9. DIETARY BEHAVIORS AND NUTRIENT INTAKE –FOLIC ACID SUPPLEMENTATION AND RISK OF CVD

WHAT EFFECT DOES FOLIC ACID SUPPLEMENTATION (WITH OR WITHOUT ADDITIONAL B VITAMIN SUPPLEMENTATION) HAVE ON RISK OF CVD AMONG PERSONS WITH OR WITHOUT PRE-EXISTING VASCULAR DISEASE?

Conclusion statement

Strong evidence demonstrates that folic acid supplementation with or without additional B vitamins in adult men and women with pre-existing vascular disease, does not appear to reduce risk of cardiovascular disease, and may increase risk slightly.

Grade

Strong

Evidence summary overview

Four large randomized placebo controlled trials (CT) and one meta-analysis study examined the relationship between folic acid supplementation and risk of cardiovascular disease (CVD) in adults with pre-existing vascular disease.

Albert et al (2008) (positive quality) conducted an CT as part of an ongoing antioxidant vitamin trial with health professionals in the US. Women aged 40 and older were randomized to either placebo or a supplement containing folic acid (2.5mg), vitamin B₁₂ (mg) and vitamin B₆ (50mg). All women had a history of CVD or three or more coronary risk factors (average age. 62.8 years). The average follow-up was 7.3 years. The primary outcome was composite of myocardial infarction, stroke, coronary revascularization or CVD mortality. Again, despite significant homocysteinelowering, the folic acid, B₁₂ and B₆ vitamin supplement did not reduce cardiovascular events (RR 1.03; 95% CI: 0.90 to 1.19; P=0.65). The authors noted that a limitation of the study was that the research subjects were health professionals and at low risk for folate deficiency. In addition, all subjects were exposed to universal folate fortification of grain at the time the study. Therefore, one cannot rule out the benefit of folate supplementation in a folate-deficient population.

Ebbing et al (2008) (positive quality) conducted an CT in Norway as part of the Western Norway B-Vitamin Intervention Trial. Men and women aged 18 or older from two hospitals in western Norway who where undergoing coronary artery angiography for suspected CVD or aortic valve stenosis were included in the trial. A total of 3,096 patients were randomized (mean age 61.7 years, 20.5% female). A total of 2,121 patients completed the trial. The researchers used a 2 x 2 factorial design. Patients were randomized to a placebo or one of three different daily supplements: 1) Folic acid (0.8mg), plus vitamin B₁₂ (0.4mg) and B₆ (40mg); 2) Folic acid (0.8mg), plus B₁₂ (0.4mg); vitamin B₆ (40mg). The median follow-up was 38 months. The primary outcome was a composite of all-cause death, non-fatal acute myocardial infarction (MI), acute hospitalization or unstable angina pectoris, and non-fatal thromboembolic stroke. Mean plasma homocysteine concentration decreased by 30% after one year of treatment. Despite these reductions, overall there was no effect of the treatment with folic acid and vitamin B₁₂ or vitamin B₆ on total mortality or cardiovascular events. If anything there was a slight but significant increase in risk

using post-hoc overall survival analysis of the composite primary endpoint in the group receiving folic acid plus vitamin B₁₂ (HR, 1.43; 95% CI: 1.03 to 1.75; P=0.03) compared to placebo.

Ray et al (2007) (positive quality) conducted a placebo-controlled clinical trial using data from the Heart Outcomes Prevention Evaluation 2 (HOPE-2), a large (N=5,522), five-year randomized study, to determine whether decreasing homocysteine levels alters the risk for symptomatic venous thromboembolism. The vitamin therapy group received a daily supplement containing 2.5mg of folic acid, 50mg of vitamin B₆, and mg of vitamin B₁₂. The incidence rate of venous thromboembolism was the same in the vitamin therapy group and the placebo group (0.35 per 100 person-years; hazard ratio (HR), 1.01; 95% CI: 0.66, 1.53). Vitamin therapy did not reduce the risk for deep venous thrombosis (HR, 1.04; 95% CI: 0.63, 1.72), pulmonary embolism (HR, 1.14; 95% CI: 0.57, 2.28), or unprovoked venous thromboembolism (HR, 1.21; 95% CI: 0.66, 2.23). Decreasing homocysteine levels with folic acid and vitamins B₆ and B₁₂ did not reduce the risk for symptomatic venous thromboembolism.

Bonaa et al (2006) (positive quality) conducted a randomized controlled trial (RCT), double-blind, 2 x 2 factorial design evaluated data from men and women 30 to 85 years of age who had had an acute MI from the Norwegian Vitamin (NORVIT) trial. Vitamin B treatments had no significant (NS) effect on the primary end point (risk ratio, 1.08; 95% CI: 0.93, 1.25; P=0.31). Treatment with vitamin B₆ was not associated with any significant benefit with regard to the primary end point [relative risk (RR) of the primary end point, 1.14; 95% CI: 0.98, 1.32; P=0.09]. In the group given folic acid, vitamin B₁₂ and vitamin B₆, there was a trend toward an increased risk (RR, 1.22; 95% CI: 1.00, 1.50; P=0.05). Treatment with B-vitamins did not lower the risk of recurrent cardiovascular disease after acute MI. In this trial, a harmful effect from combined B-vitamin treatment was suggested.

Bazzano et al (2006) (positive quality) was a meta-analysis. The objective of the meta-analysis was to evaluate the effects of folic acid supplementation on risk of CVD and all-cause mortality among adults with pre-existing CVD or renal disease. The researchers only evaluated RCTs. Studies were retrieved by searching Medline from January 1966 to July 2006. Out of a total of 165 studies reviewed, 12 studies met the criteria for inclusion, representing 16,958 men and women. The studies were conducted around the world (two in the US, one in Australia and New Zealand, one in Canada and eight in Europe). Dosage of folic acid supplementation ranged from 0.5mg per day to 15mg per day and study durations ranged from six months to five years. In this meta-analysis, folic acid supplementation did not reduce risk of CVD or all-cause mortality in persons with prior history of disease. The overall RR of outcomes for subjects receiving folic acid supplementation compared to controls were 0.95 (95% CI: 0.88 to 1.03) for CVD, 1.04 (95% CI: 0.92 to 1.17) for coronary heart disease (CHD) and 0.96 (95% CI: 0.88 to 1.04) for all-cause mortality.

These data taken together demonstrate consistent outcomes showing that folic acid supplementation does not reduce risk of CVD in men and women with existing disease. There is some limited evidence that there may be increased risk. For this reason, adults with pre-existing vascular disease should not be encouraged to take a folic acid supplementation. One question that still remains is whether there are any differences in response due to race or ethnicity with folic acid supplementation.

Evidence summary paragraphs

Albert et al, 2008 (positive quality). This RCT (individually randomized) tested whether a combination of 2.5mg of folic acid, 50mg of vitamin B₆ and mg of vitamin B₁₂ lowers risk of CVD among high-risk women with and without CVD. The study participants were from the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS), aged 40 years or older, post-menopausal or with no intention of becoming pregnant, and had a reported history of CVD or had at least three cardiac risk factors. The results showed that 796 participants (14.6%) from a total of 5,442, experienced a confirmed CVD event (139 MIs, 148 strokes, 508 coronary revascularization procedures and 190 cardiovascular deaths). There was no difference in the cumulative incidence of the primary combined endpoint in the active vs. placebo treatment groups at any time during study follow-up. In addition, 406 women (14.9%) in the active treatment group and 390 (14.3%) in the placebo group experienced at least one cardiovascular event included in the primary endpoint (226.9 per 10,000 person-years vs. 219.2 per 10,000 person-years). The overall RR was 1.03 (95% CI: 0.90,1.19; P=0.65) after controlling for age and antioxidant treatment assignment. In conclusion, after 7.3 years of treatment and follow-up, a combination pill of folic acid, vitamin B₆ and vitamin B₁₂ did not reduce a combined endpoint of total cardiovascular events among high-risk women.

Bazzano et al, 2006 (positive quality). This meta-analysis study evaluated the effects of folic acid supplementation on risk of CVD and all-cause mortality using a random-effects model. The 12 RCTs represented 16,958 men and women. The overall RR CIs of outcomes for patients treated with folic acid supplementation compared with controls were 0.95 (0.88,1.03) for CVD, 1.04 (0.92,1.17) for CHD, 0.86 (0.71,1.04) for stroke and 0.96 (0.88,1.04) for all-cause mortality. The RR was consistent among participants with pre-existing CVD or renal disease. Folic acid supplementation has not been shown to reduce risk of CVD or all-cause mortality among participants with prior history of vascular disease. Studies included US, Canadian and European subjects.

Bonaa et al, 2006 (positive quality). This RCT, double-blind, 2 x 2 factorial design evaluated data from men and women 30 to 85 years of age who had had an acute MI from the Norwegian Vitamin (NORVIT) trial. Vitamin-B treatments had NSeffect on the primary end point (RR, 1.08; 95% CI: 0.93, 1.25; P=0.31). Also, treatment with vitamin B₆ was not associated with any significant benefit with regard to the primary end point (RR of the primary end point, 1.14; 95% CI: 0.98, 1.32; P=0.09). In the group gimetalfolic acid, vitamin B₁₂ and vitamin B₆, there was a trend toward an increased risk (RR, 1.22; 95% CI: 1.00, 1.50; P=0.05). Treatment with B vitamins did not lower the risk of recurrent CVD after acute MI. In this trial a harmful effect from combined B-vitamin treatment was suggested.

Ebbing et al, 2009 (positive quality). This randomized double blind controlled trial assessed the effect of treatment with folic acid and vitamin B₁₂ and the effect of treatment with vitamin B₆ as secondary prevention. Data from the Western Norway B-vitamin intervention Trial (WENBIT) was used; it included men and women 18 years old or older undergoing coronary artery angiography for suspected coronary artery disease (CAD) or aortic valve stenosis from two university hospitals in Western Norway. Intervention treatment consisted of daily oral dose of one of the following: 1) Folic acid, 0.8mg, plus vitamin B₁₂ (cyanocobalamin), 0.4mg and vitamin B₆ (pyridoxine), 40mg; 2) Folic acid, 0.8mg, plus vitamin B₁₂, 0.4mg; 3) Vitamin B₆, 40mg; or 4) Placebo. Mean follow-up was 38 months. Results after one year showed

mean serum folate concentration increased seven-fold and mean serum cobalamin concentration increased by 65% in the groups receiving folic acid plus vitamin B₁₂. Mean plasma total homocysteine level was decreased by 30%, from 10.8 (SD, 4.5) μ mol per L at baseline to 7.6 (SD, 2.2) μ mol per L in the groups receiving folic acid and vitamin B₁₂ ($P < 0.001$). In the final results, 422 participants (13.7% of all) experienced an event in the composite primary end point of death, acute MI(AMI), unstable angina pectoris or thromboembolic stroke. A total of 219 participants (14.2%) in the groups receiving folic acid vs. 203 participants (13.1%) in the groups not receiving folic acid experienced the primary end point (HR=1.09; 95% CI: 0.90,1.32; $P=0.36$). 157 participants (12.2%) in the groups receiving folic acid groups vs. 146 (11.8%) of those not receiving folic acid experienced the primary end point (HR, 1.04; 95% CI: 0.83,1.30; $P=0.75$). There were no differences in treatment response for the separate end points of death, total AMI (fatal and non-fatal, including procedure-related), or unstable angina pectoris. The incidence of total stroke (fatal and non-fatal, including hemorrhagic) was NS lower in the groups receiving folic acid. The incidence of acute hospitalization due to angina pectoris was lower in the folic acid groups (HR= 0.82; 95% CI: 0.67,1.00; $P=.05$). Post-hoc overall survival analysis showed no differences between the groups ($P=0.07$), but there was an increased risk of the composite primary end point in the group receiving folic acid plus vitamin B₁₂ (HR= 1.34; 95% CI: 1.03,1.75; $P=0.03$) compared with placebo. Daily supplements: 1) Folic acid (0.8mg), plus vitamin B₁₂ (0.4mg) and B₆ (40mg); 2) Folic acid (0.8mg), plus B₁₂ (0.4mg); vitamin B₆ (40mg). The median follow-up was 38 months. The primary outcome was a composite of all-cause death, non-fatal AMI, acute hospitalization or unstable angina pectoris and non-fatal thromboembolic stroke. Mean plasma homocysteine concentration decreased by 30% after one year of treatment. Despite these reductions, overall there was no effect of the treatment with folic acid and vitamin B₁₂ or vitamin B₆ on total mortality or cardiovascular events. If anything, there was a slight but significant increase in risk using post-hoc overall survival analysis of the composite primary end point in the group receiving folic acid plus vitamin B₁₂ (HR=1.43; 95% CI: 1.03,1.75; $P=0.03$) compared to placebo.

Ray et al, 2007 (positive quality). This placebo-controlled clinical trial used data from the Heart Outcomes Prevention Evaluation 2 (HOPE-2), a large, randomized study, to determine whether decreasing homocysteine levels alters the risk for symptomatic venous thromboembolism. The incidence rate of venous thromboembolism was the same in the vitamin therapy group and the placebo group (0.35 per 100 person-years; HR, 1.01 95% CI: 0.66, 1.53). Vitamin therapy did not reduce the risk for deep venous thrombosis (HR, 1.04; 95% CI: 0.63, 1.72), pulmonary embolism (HR, 1.14; 95% CI: 0.57, 2.28), or unprovoked venous thromboembolism (HR, 1.21; 95% CI: 0.66, 2.23). Decreasing homocysteine levels with folic acid and vitamins B₆ and B₁₂ did not reduce the risk for symptomatic venous thromboembolism.

Overview table

Author, Year, Study Design, Class, Rating	Population/Sample Description	Measurements or Intervention	Significant Outcomes
<p>Albert CM, Cook NR et al, 2008</p> <p>Study Design: Randomized controlled trial (individual randomized)</p> <p>Class: A</p> <p>Rating: Postive</p>	<p>Participants from the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS), age ≥ 42 years, post-menopausal or had no intention of becoming pregnant and had reported history of CVD or had at least three cardiac risk factors.</p>	<p>Daily placebo or a combination pill containing 2.5mg folic acid, 50mg vitamin B₆ and 1mg vitamin B₁₂.</p> <p>Dietary folic acid intake.</p>	<p>N=796 participants (14.6%) from a total of 5,442 experienced a confirmed combined endpoint of cardiovascular morbidity and mortality event (139 MIs, 148 strokes, 508 coronary revascularization procedures and 190 cardiovascular deaths).</p> <p>No difference in cumulative incidence of primary combined end point in active vs. placebo treatment groups at any time during study follow-up.</p> <p>N=406 women (14.9%) in active treatment group and 390 (14.3%) in placebo group experienced at least one cardiovascular event included in the primary end point (226.9 of 10,000 person-years vs. 219.2 of 10,000 person-years).</p> <p>RR was 1.03 (95% CI: 0.90,1.19; P =0.65) after controlling for age and antioxidant treatment assignment.</p> <p>In separate analysis: NS differences between groups for each of the components of the primary outcome including CVD mortality (50.3/10,000 person-years vs. 49.6/10,000 person-years; RR= 1.01; 95% CI: 0.76,1.35; P = 0.93).</p> <p>No difference between groups for risk of death from any cause (RR= 0.97; 95% CI: 0.81,1.15; P =0.73).</p>

<p>Bazzano I, Reynolds K et al, 2006</p> <p>Study Design: Meta-analysis</p> <p>Class: M</p> <p>Rating: Positive</p>	<p>N=12 RCTs, representing 16,958 participants, both men and women.</p> <p>Studies were conducted in:</p> <p>US (two)</p> <p>Australia and New Zealand (one)</p> <p>Canada (one)</p> <p>European countries (eight).</p>	<p>Clinical CVD events reported as an end point.</p> <p>Folic acid supplementation with either placebo or usual care.</p> <p>Intervention ranged from 0.5mg per day to 15mg per day, for a duration ranging from six months to five years.</p>	<p>RR for folic acid supplemental patients vs. control were 0.95 CI: 0.88,1.03 for CVD.</p> <p>RR consistent among participants with pre-existing CVD or renal disease.</p>
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<p>Bønaa K, Njølstad I et al, 2006</p> <p>Study Design: Randomized controlled trial</p> <p>Class: A</p> <p>Rating: Positive</p>	<p>Men and women 30 to 85 years of age who had had an acute MI within seven days before randomization from the Norwegian Vitamin (NORVIT) trial, which was a multicenter, prospective, randomized, double-blind, placebo-controlled trial.</p>	<p>Intervention:</p> <ol style="list-style-type: none"> 1) Combination group: 0.8mg of folic acid, 0.4mg of vitamin B₁₂ and 40mg of vitamin B₆ per day 2) 0.8mg of folic acid plus 0.4mg of vitamin B₁₂ per day 3) 40mg of vitamin B₆ per day 4) Placebo. <p>Measurements: Primary end point included composite of new non-fatal and fatal MI, non-fatal and fatal stroke and sudden death attributed to CHD.</p> <p>Secondary end points included MI, unstable angina pectoris requiring hospitalization, coronary revascularization with percutaneous coronary intervention or coronary-artery bypass grafting, stroke and death from any cause.</p> <p>Blood samples for plasma total homocysteine serum folate and serum cobalamin.</p> <p>Adjustments for: Study center, age, sex, SBP, TC level and smoking status and warfarin use.</p>	<p>Treatment with folic acid in combination with vitamin B₁₂, with or without vitamin B₆, did not significantly ↓ risk of the primary end point, as compared with placebo.</p> <p>Both treatment regimens were associated with a NS ↑ in risk, mainly driven by an event rate that was 22% ↑ in the combination-therapy group than in the placebo group (P=0.05).</p> <p>Cumulative HR for the combination-therapy group, as compared with the other three groups, was 1.20 (95% CI: 1.02 to 1.41; P=0.03).</p> <p>Risk of the secondary end points was NS influenced by treatment with folic acid and vitamin B₁₂.</p> <p>Vitamin B₆ therapy associated with a 17% ↑ in the risk of MI (P=0.05) and combination therapy associated with a 30% ↑ in the risk of non-fatal MI (P=0.05).</p>
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<p>Ebbing M, Bleie O et al, 2008</p> <p>Study Design: Randomized double-blind controlled trial</p> <p>Class: A</p> <p>Rating: Postive</p>	<p>The Western Norway B-vitamin intervention Trial (WENBIT) was used.</p> <p>Data included men and women ≥18 years undergoing coronary artery angiography for suspected CAD or aortic valve stenosis from two university hospitals in Western Norway.</p>	<p>Intervention treatment consisted of daily oral dose of one of the following:</p> <ol style="list-style-type: none"> 1) Folic acid, 0.8mg, plus vitamin B₁₂ (cyanocobalamin), 0.4mg, and vitamin B₆ (pyridoxine), 40mg 2) Folic acid, 0.8mg, plus vitamin B₁₂, 0.4mg 3) Vitamin B₆, 40mg 4) Placebo. 	<p>Mean follow-up: 38 months.</p> <p>Results after one year showed mean serum folate concentration ↑ seven-fold and mean serum cobalamin concentration ↑ by 65% in the groups receiving folic acid plus vitamin B₁₂.</p> <p>Mean plasma total homocysteine level was ↓ by 30%, from 10.8 (SD, 4.5) μmol per L at baseline to 7.6 (SD,2.2) μmol per L in the groups receiving folic acid and vitamin B₁₂ (P<0.001).</p> <p>In the final results, 422 participants (13.7% of all) experienced an event in the composite primary end point of death, AMI, unstable angina pectoris or thromboembolic stroke.</p> <p>A total of 219 participants (14.2%) in the groups receiving folic acid vs. 203 participants (13.1%) in the groups not receiving folic acid experienced the primary end point (HR= 1.09; 95% CI: 0.90-1.32; P=0.36).</p> <p>157 participants (12.2%) in the groups receiving folic acid groups vs. 146 (11.8%) of those not receiving folic acid experienced the primary end point (HR= 1.04; 95% CI: 0.83,1.30; P= 0.75).</p> <p>No differences in treatment response for the separate end points of death, total AMI (fatal and nonfatal, including procedure-related) or unstable angina pectoris.</p> <p>Incidence of total stroke (fatal and nonfatal, including hemorrhagic) was not significantly ↓ in groups receiving folic acid.</p> <p>Incidence of acute hospitalization due to angina pectoris was ↓ in the folic acid groups (HR= 0.82; 95% CI: 0.67,1.00; P= 0.05).</p> <p>Post hoc overall survival analysis showed no differences between the groups (P= 0.07), but there was an ↑ risk of the composite primary end point in the group receiving folic acid plus vitamin B₁₂ (HR=1.34; 95% CI: 1.03,1.75; P= 0.03) compared with placebo.</p>
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<p>Ray JG, Kearon C et al, 2007</p> <p>Study Design: Secondary analysis of data from a randomized trial</p> <p>Class: A</p> <p>Rating: Positive</p>	<p>Data from the Heart Outcomes Prevention Evaluation 2 (HOPE-2), a large randomized study, were analyzed.</p> <p>N=5,522.</p> <p>Individuals (≥55 years of age with known CVD or DM and at least one other risk factor for vascular disease) were recruited from 145 centers in 13 countries:</p> <p>Canada (N=3,568)</p> <p>US (N=414)</p> <p>Brazil (N=265)</p> <p>Western European countries (N=426)</p> <p>Slovakia (N=849).</p>	<p>Intervention: Daily supplement of 2.5mg of folic acid, 50mg of vitamin B₆, and 1mg of vitamin B₁₂ or matching placebo for five years.</p> <p>Measurement: Prospectively diagnosed and confirmed symptomatic deep venous thrombosis or pulmonary embolism.</p>	<p>N=88 episodes of venous thromboembolism, of which about two-thirds were deep venous thrombosis and 47% were unprovoked.</p> <p>N=17 events (19.3%) recorded in the first 18 months after randomization and 71 recorded thereafter.</p> <p>N=44 episodes of venous thromboembolism occurred in each group, corresponding to an incidence rate of 0.35 per 100 person-years in each group [HR, 1.01 (95% CI: 0.66 to 1.53); P=0.97].</p> <p>No benefit observed from the therapy in any subgroup.</p>
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Search plan and results

Inclusion criteria

- *Subjects/Population:* Human subjects.
- *Age:* Children, men and women of all ages.
- *Setting:* International.
- *Health Status:* Healthy and those with elevated chronic disease risk (CHD/CVD, Type 2 diabetes, metabolic syndrome and obesity).
- *Nutrition Related Problem/Condition:* None.

Search Criteria

- *Study Design Preferences:* RCT or clinical controlled studies, large non-randomized observational studies, cohort, case-control studies, systematic reviews and meta-analysis.
- *Size of Study Groups:* The sample size must equal 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 Drop Out Rate:* Less than 20%; preference for smaller dropout rates.
- *Year Range:* May 2004 to July 2009.
- *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-reviewed journal.

Exclusion criteria

- *Subjects/Population*
 - Animal and in vitro studies
 - Malnourished/third-world populations or disease incidence not relative to US population (e.g., malaria).
- *Age:* Not applicable.
- *Setting:* Hospitalized patients.
- *Health Status:* Medical treatment/therapy and diseased subjects (already diagnosed with disease related to study purpose).
- *Nutrition Related Problem/Condition:* All conditions.
- *Search Criteria*
- *Study Design Preferences:* Not applicable.
- *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 May 2004.
- *Authorship:* Studies by same author similar in content.
- *Languages:* Articles not in English.

- *Other*: Abstracts or presentations and articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

Comparators

- Intake levels/consumption levels
- Fortification
- Supplementation.

Health outcomes/clinical disease: CVD (morbidity and mortality)

Other terms: NHANES.

- PubMed:

("Folic Acid"[Mesh] OR "folate"[All Fields]) AND ("Food, Fortified"[Mesh] OR "Dietary Supplements"[Mesh] OR diet[Mesh] OR intake[All Fields]) AND "english and humans"[Filter] AND "cardiovascular diseases"[MeSH Terms] ("Folic Acid"[Mesh] OR "folate"[All Fields]) AND "english and humans"[Filter] AND "cardiovascular diseases"[MeSH Terms] AND meta ("Folic Acid"[Mesh] OR "folate"[All Fields]) AND "english and humans"[Filter] AND "cardiovascular diseases"[MeSH Terms] Limits: Meta-Analysis

("Folic Acid" OR "folate"[All Fields]) AND (supplement* OR "Dietary Supplements"[Mesh]) AND (stroke[mh] OR "Vascular Diseases"[mh]) AND "cardiovascular diseases"[MeSH Terms]

Date searched: 1) 2/09/09, 2) 2/20/09, 3) 7/21/09

Summary of articles identified to review

- Total hits from all electronic database searches: 741
- Total articles identified to review from electronic databases: 63
- Articles identified via handsearch or other means: 1
- Number of Primary Articles Identified: 4
- Number of Review Articles Identified: 1
- Total Number of Articles Identified: 5
- Number of Articles Reviewed but Excluded: 59

Included articles (References)

Meta-analysis

1. Bazzano LA, Reynolds K, Holder KN, He J. Effect of folic acid supplementation on risk of cardiovascular diseases: A meta-analysis of randomized controlled trials. www.ncbi.nlm.nih.gov/pubmed/17164458 *JAMA*. 2006 Dec 13; 296 (22): 2, 720-2, 726. Erratum in: *JAMA*. 2007 Mar 7; 297 (9): 952. PMID: 17164458.

Primary Articles

2. Albert CM, Cook NR, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, Buring JE, Manson JE. Effect of folic acid and B vitamins on risk of

cardiovascular events and total mortality among women at high risk for cardiovascular disease: A randomized trial. www.ncbi.nlm.nih.gov/pubmed/18460663 *JAMA*. 2008 May 7; 299 (17): 2, 027-2, 036. PMID: 18460663.

3. Bønaa KH, Njølstad I, Ueland PM, Schirmer H, Tverdal A, Steigen T, Wang H, Nordrehaug JE, Arnesen E, Rasmussen K; NORVIT Trial Investigators. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med*. 2006 Apr 13; 354 (15): 1, 578-1, 588. Epub 2006 Mar 12. (Hand search) PMID: 16531614.
4. Ebbing M, Bleie Ø, Ueland PM, Nordrehaug JE, Nilsen DW, Vollset SE, Refsum H, Pedersen EK, Nygård O. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: A randomized controlled trial. *JAMA*. 2008 Aug 20; 300(7): 795-804. PMID: 18714059 (HS).
5. Ray JG, Kearon C, Yi Q, Sheridan P, Lonn E; Heart Outcomes Prevention Evaluation 2 (HOPE-2) Investigators. Homocysteine-lowering therapy and risk for venous thromboembolism: A randomized trial. *Ann Intern Med*. 2007 Jun 5; 146 (11): 761-767. Epub 2007 Apr 30. PMID: 17470822.

Excluded articles

Excluded Articles	Reason for Exclusion
<p>Antoniades C, Antonopoulos AS, Tousoulis D, Marinou K, Stefanadis C. Homocysteine and coronary atherosclerosis: From folate fortification to the recent clinical trials. www.ncbi.nlm.nih.gov/pubmed/19029125 <i>Eur Heart J</i>. 2009 Jan; 30 (1): 6-15. Epub 2008 Nov 23. Review. PMID: 19029125.</p>	<p>It does not answer the question. About Hcy and CVD.</p>
<p>Bleys J, Miller ER 3rd, Pastor-Barriuso R, Appel LJ, Guallar E. Vitamin-mineral supplementation and the progression of atherosclerosis: A meta-analysis of randomized controlled trials. www.ncbi.nlm.nih.gov/pubmed/17023716 <i>Am J Clin Nutr</i>. 2006 Oct; 84 (4): 880-887; quiz 954-955. PMID: 17023716.</p>	<p>It does not answer the question. About antioxidants and B vitamins.</p>
<p>Bostom AG, Jacques PF, Liaugaudas G, Rogers G, Rosenberg IH, Selhub J. Total homocysteine lowering treatment among coronary artery disease patients in the era of folic acid-fortified cereal grain flour. www.ncbi.nlm.nih.gov/pubmed/11884295 <i>Arterioscler Thromb Vasc Biol</i>. 2002 Mar 1; 22 (3): 488-491. PMID: 11884295.</p>	<p>It does not answer the question. About homocysteine.</p>

<p>Carlsson CM. Homocysteine lowering with folic acid and vitamin B supplements: Effects on cardiovascular disease in older adults. www.ncbi.nlm.nih.gov/pubmed/16872232 <i>Drugs Aging</i>. 2006; 23 (6): 491-502. Review. PMID: 16872232.</p>	<p>It does not answer the question. About B supplements and cardiovascular protection.</p>
<p>Clarke R, Collins R. Can dietary supplements with folic acid or vitamin B6 reduce cardiovascular risk? Design of clinical trials to test the homocysteine hypothesis of vascular disease. www.ncbi.nlm.nih.gov/pubmed/9919473 <i>J Cardiovasc Risk</i>. 1998 Aug; 5 (4): 249-255. No abstract available. PMID: 9919473.</p>	<p>Not a systematic review.</p>
<p>De Bree A, Mennen LI, Hercberg S, Galan P. Evidence for a protective (synergistic?) effect of B-vitamins and omega-3 fatty acids on cardiovascular diseases. www.ncbi.nlm.nih.gov/pubmed/15116076 <i>Eur J Clin Nutr</i>. 2004 May; 58 (5): 732-744. PMID: 15116076.</p>	<p>It does not answer the question.</p>
<p>Goh YI, Bollano E, Einarson TR, Koren G. Prenatal multivitamin supplementation and rates of congenital anomalies: A meta-analysis. www.ncbi.nlm.nih.gov/pubmed/17022907 <i>J Obstet Gynaecol Can</i>. 2006 Aug; 28 (8): 680-689. Review. PMID: 17022907.</p>	<p>It does not answer the question. Folic acid intake is not quantify in this article.</p>
<p>Kang JH, Cook N, Manson J, Buring JE, Albert CM, Grodstein F. A trial of B vitamins and cognitive function among women at high risk of cardiovascular disease. www.ncbi.nlm.nih.gov/pubmed/19064521 <i>Am J Clin Nutr</i>. 2008 Dec; 88 (6): 1, 602-1, 610. PMID: 19064521.</p>	<p>It does not answer the question. About cognitive function.</p>
<p>Klerk M, Durga J, Schouten EG, Kluit C, Kok FJ, Verhoef P. No effect of folic acid supplementation in the course of one year on haemostasis markers and C-reactive protein in older adults. www.ncbi.nlm.nih.gov/pubmed/16113791 <i>Thromb Haemost</i>. 2005 Jul; 94 (1): 96-100. PMID: 16113791.</p>	<p>It does not answer the question. About supplementation and homocysteine.</p>
<p>Lewis SJ, Ebrahim S, Davey Smith G. Meta-analysis of MTHFR 677C->T polymorphism and coronary heart disease: Does totality of evidence support causal role for homocysteine and preventive potential of folate? www.ncbi.nlm.nih.gov/pubmed/16216822 <i>BMJ</i>. 2005 Nov 5;331 (7524): 1, 053. Epub 2005 Oct 10. Review. PMID: 16216822.</p>	<p>It does not answer the question. About genotype. Not a systematic review.</p>

<p>Malinow MR, Duell PB, Irvin-Jones A, Upson BM, Graf EE. Increased plasma homocyst(e)ine after withdrawal of ready-to-eat breakfast cereal from the diet: Prevention by breakfast cereal providing 200 microg folic acid. www.ncbi.nlm.nih.gov/pubmed/10963464 <i>J Am Coll Nutr.</i> 2000 Aug; 19 (4): 452-457. PMID: 10963464.</p>	<p>It does not answer the question. About homocysteine.</p>
<p>McCully KS. Homocysteine, vitamins and vascular disease prevention. www.ncbi.nlm.nih.gov/pubmed/17991676 <i>Am J Clin Nutr.</i> 2007 Nov; 86 (5): 1, 563S-1, 568S. Review. PMID: 17991676.</p>	<p>It does not answer the question. About homocysteine.</p>
<p>McEligot AJ, Rock CL, Gilpin EA, Pierce JP. Responsiveness of homocysteine concentrations to food and supplemental folate intakes in smokers and never-smokers enrolled in a diet intervention trial. www.ncbi.nlm.nih.gov/pubmed/16497600 <i>Nicotine Tob Res.</i> 2006 Feb; 8 (1): 57-66. PMID: 16497600.</p>	<p>It does not answer the question. About homocysteine.</p>
<p>McKay DL, Perrone G, Rasmussen H, Dallal G, Blumberg JB. Multivitamin/mineral supplementation improves plasma B-vitamin status and homocysteine concentration in healthy older adults consuming a folate-fortified diet. www.ncbi.nlm.nih.gov/pubmed/11110875.</p>	<p>It does not answer the question. About supplementation and homocysteine.</p>
<p>Moats C, Rimm EB. Vitamin intake and risk of coronary disease: Observation vs. intervention. <i>Curr Atheroscler Rep.</i> 2007 Dec; 9 (6): 508-514. Review. www.ncbi.nlm.nih.gov/pubmed/18377792 PMID: 18377792.</p>	<p>*Not a systematic review. It doesn't answer the question.</p>
<p>Muskiet FA. The importance of (early) folate status to primary and secondary coronary artery disease prevention. www.ncbi.nlm.nih.gov/pubmed/15964170 <i>Reprod Toxicol.</i> 2005 Sep-Oct; 20 (3): 403-410. Review. PMID: 15964170.</p>	<p>*Not a systematic review.</p>
<p>Ntaios GC, Savopoulos CG, Chatzinikolaou AC, Kaiafa GD, Hatzitolios A. Vitamins and stroke: The homocysteine hypothesis still in doubt. <i>Neurologist.</i> 2008 Jan; 14 (1): 2-4. Review. www.ncbi.nlm.nih.gov/pubmed/18195649 PMID: 18195649.</p>	<p>It does not answer the question. Not a systematic review. About vitamins and CVD.</p>
<p>Quinlivan EP, McPartlin J, McNulty H, Ward M, Strain JJ, Weir DG, Scott JM. Importance of both folic acid and vitamin B12 in reduction of risk of vascular disease. <i>Lancet.</i> 2002 Jan 19; 359(9302): 227-228. PMID: 11812560.</p>	<p>It does not answer the question. About homocysteine.</p>

<p>Rydlewicz A, Simpson JA, Taylor RJ, Bond CM, Golden MH. The effect of folic acid supplementation on plasma homocysteine in an elderly population. <i>QJM</i>. 2002 Jan; 95 (1): 27-35. PMID: 11834770.</p>	<p>It does not answer the question. About supplementation and homocysteine.</p>
<p>Sauer J, Mason JB, Choi SW. Too much folate: A risk factor for cancer and cardiovascular disease? www.ncbi.nlm.nih.gov/pubmed/19057184 <i>Curr Opin Clin Nutr Metab Care</i>. 2009 Jan; 12 (1): 30-36. Review. PMID: 19057184.</p>	<p>*Not a systematic review.</p>
<p>Smolková B, Dusinská M, Raslová K, Barancoková M, Kazimírová A, Horská A, Spustová V, Collins A. Folate levels determine effect of antioxidant supplementation on micronuclei in subjects with cardiovascular risk. <i>Mutagenesis</i>. 2004 Nov; 19 (6): 469-476. PMID: 15548759.</p>	<p>It does not answer the question. About antioxidants.</p>
<p>Tucker KL, Olson B, Bakun P, Dallal GE, Selhub J, Rosenberg IH. Breakfast cereal fortified with folic acid, vitamin B-6, and vitamin B-12 increases vitamin concentrations and reduces homocysteine concentrations: a randomized trial. <i>Am J Clin Nutr</i>. 2004 May; 79 (5): 805-811. PMID: 15113718.</p>	<p>It does not answer the question. About supplementation and homocysteine.</p>
<p>Van Beynum IM, den Heijer M, Blom HJ, Kapusta L. The MTHFR 677C->T polymorphism and the risk of congenital heart defects: A literature review and meta-analysis. www.ncbi.nlm.nih.gov/pubmed/17965089 <i>QJM</i>. 2007 Dec; 100 (12): 743-753. Epub 2007 Oct 26. Review. PMID: 17965089.</p>	<p>It does not answer the question.</p>
<p>Villa P, Perri C, Suriano R, Cucinelli F, Panunzi S, Ranieri M, Mele C, Lanzone A. L-folic acid supplementation in healthy postmenopausal women: Effect on homocysteine and glycolipid metabolism. <i>J Clin Endocrinol Metab</i>. 2005 Aug; 90 (8): 4, 622-4, 629. Epub 2005 May 17. PMID: 15899950.</p>	<p>It does not answer the question. About homocysteine.</p>
<p>Villa P, Suriano R, Costantini B, Macrì F, Ricciardi L, Campagna G, Lanzone A. Hyperhomocysteinemia and cardiovascular risk in postmenopausal women: The role of Folate supplementation. www.ncbi.nlm.nih.gov/pubmed/17311496 <i>Clin Chem Lab Med</i>. 2007; 45 (2): 130-135. Review. PMID: 17311496.</p>	<p>It does not answer the question.</p>

<p>Wald DS, Bishop L, Wald NJ, Law M, Hennessy E, Weir D, McPartlin J, Scott J. Randomized trial of folic acid supplementation and serum homocysteine levels. <i>Arch Intern Med.</i> 2001 Mar 12; 161 (5): 695-700. PMID: 11231701.</p>	<p>It does not answer the question. About supplementation and homocysteine.</p>
<p>Wenger NK. Do diet, folic acid, and vitamins matter? What did we learn from the Women's Health Initiative, the Women's Health Study, the Women's Antioxidant and Folic Acid Cardiovascular Study, and other clinical trials? www.ncbi.nlm.nih.gov/pubmed/18090063 <i>Cardiol Rev.</i> 2007 Nov-Dec; 15 (6): 288-290. Review. PMID: 18090063.</p>	<p>Monograph.</p>

<p>Excluded Articles (July 21-09)</p>	<p>Reason for Exclusion</p>
<p>Andersson A, Jonasson T, Ohlin H, Lindgren A, Hultberg B. <u>Vitamin supplementation normalizes total plasma homocysteine concentration but not plasma homocysteine redox status in patients with acute coronary syndromes and hyperhomocysteinemia.</u> <i>Clin Chem Lab Med.</i> 2002 Jun; 40 (6): 554-558. PMID: 12211647.</p>	<p>About homocysteine.</p>
<p>Assanelli D, Bonanome A, Pezzini A, Albertini F, Maccalli P, Grassi M, Archetti S, Negrini R, Visioli F. <u>Folic acid and vitamin E supplementation effects on homocysteinemia, endothelial function and plasma antioxidant capacity in young myocardial-infarction patients.</u> <i>Pharmacol Res.</i> 2004 Jan; 49 (1): 79-84. Erratum in: <i>Pharmacol Res.</i> 2004 May; 49 (5): 501. Maccalli, Pietro [corrected to Maccalli, Paola]; Negrini, Roberto [corrected to Negrini, Riccardo]. PMID: 14597156.</p>	<p>About homocysteine</p>
<p>Chambers JC, Obeid OA, Refsum H, Ueland P, Hackett D, Hooper J, Turner RM, Thompson SG, Kooner JS. <u>Plasma homocysteine concentrations and risk of coronary heart disease in UK Indian Asian and European men.</u> <i>Lancet.</i> 2000 Feb 12; 355 (9203): 523-527. PMID: 10683001.</p>	<p>It does not address CVD or stroke risk.</p>
<p>Constans J, Blann AD, Resplandy F, Parrot F, Renard M, Seigneur M, Guérin V, Boisseau M, Conri C. <u>Three months supplementation of hyperhomocysteinemic patients with folic acid and vitamin B6 improves biological markers of endothelial dysfunction.</u> <i>Br J Haematol.</i> 1999 Dec; 107 (4): 776-778. PMID: 10606884.</p>	<p>Article prior June 2004.</p>

<p>Deicher R, Vierhapper H. <u>Homocysteine: A risk factor for cardiovascular disease in subclinical hypothyroidism?</u> <i>Thyroid</i>. 2002 Aug; 12 (8): 733-736. PMID: 12225643.</p>	<p>About homocysteine and hypothyroidism.</p>
<p>Galan P, de Bree A, Mennen L, Potier de Courcy G, Preziosi P, Bertrais S, Castetbon K, Hercberg S. <u>Background and rationale of the SU.FOL.OM3 study: Double-blind randomized placebo-controlled secondary prevention trial to test the impact of supplementation with folate, vitamin B₆ and B₁₂ and/or omega-3 fatty acids on the prevention of recurrent ischemic events in subjects with atherosclerosis in the coronary or cerebral arteries.</u> <i>J Nutr Health Aging</i>. 2003; 7 (6): 428-435. PMID: 14625623.</p>	<p>Background and rationale of the SU FOL OM3 study.</p>
<p>Guo H, Lee JD, Ueda T, Cheng J, Shan J, Wang J. <u>Hyperhomocysteinaemia and folic acid supplementation in patients with high risk of coronary artery disease.</u> <i>Indian J Med Res</i>. 2004 Jan; 119 (1): 33-37. PMID: 14997992.</p>	<p>Article prior June 2004.</p>
<p>Hernández-Díaz S, Martínez-Losa E, Fernández-Jarne E, Serrano-Martínez M, Martínez-González MA. <u>Dietary folate and the risk of non-fatal myocardial infarction.</u> <i>Epidemiology</i>. 2002 Nov; 13 (6): 700-706. PMID: 12410012.</p>	<p>Article prior June 2004.</p>
<p>Lee BJ, Huang MC, Chung LJ, Cheng CH, Lin KL, Su KH, Huang YC. <u>Folic acid and vitamin B₁₂ are more effective than vitamin B₆ in lowering fasting plasma homocysteine concentration in patients with coronary artery disease.</u> <i>Eur J Clin Nutr</i>. 2004 Mar; 58 (3): 481-487. PMID: 14985687.</p>	<p>It does not address CVD or stroke risk.</p>
<p>Lee BJ, Lin PT, Liaw YP, Chang SJ, Cheng CH, Huang YC. <u>Homocysteine and risk of coronary artery disease: Folate is the important determinant of plasma homocysteine concentration.</u> <i>Nutrition</i>. 2003 Jul-Aug; 19 (7-8): 577- 583. PMID: 12831941.</p>	<p>Article prior June 2004.</p>
<p>Lobo A, Naso A, Arheart K, Kruger WD, Abou-Ghazala T, Alsous F, Nahlawi M, Gupta A, Moustapha A, van Lente F, Jacobsen DW, Robinson K. <u>Reduction of homocysteine levels in coronary artery disease by low-dose folic acid combined with vitamins B₆ and B₁₂.</u> <i>Am J Cardiol</i>. 1999 Mar 15; 83 (6): 821-825. PMID: 10190392.</p>	<p>About homocysteine.</p>

<p>Mark L, Erdei F, Markizay J, K <u>Effect of treatment with folic acid and vitamin B₆ on lipid and homocysteine concentrations in patients with coronary artery disease.</u> <i>Nutrition</i>. 2002 May; 18 (5): 428-429. No abstract available. PMID: 11985950.</p>	<p>Article prior June 2004.</p>
<p>McCully KS <u>Homocysteine, vitamins and prevention of vascular disease.</u> <i>Mil Med</i>. 2004 Apr; 169 (4): 325-329. PMID: 15132238</p>	<p>About homocysteine.</p>
<p>Neal B, MacMahon S, Ohkubo T, Tonkin A, Wilcken D <u>Dose-dependent effects of folic acid on plasma homocysteine in a randomized trial conducted among 723 individuals with coronary heart disease.</u> PACIFIC Study Group. <i>Eur Heart J</i>. 2002 Oct; 23 (19): 1, 509-1, 515. PMID: 12395803.</p>	<p>About homocysteine.</p>
<p>Potena L, Grigioni F, Magnani G, Sorbello S, Sassi S, Poci MG, Carigi S, Bacchi-Reggiani L, Leone O, Magelli C, Branzi A. <u>Folate supplementation after heart transplantation: Effects on homocysteine plasma levels and allograft vascular disease.</u> <i>Clin Nutr</i>. 2002 Jun; 21 (3): 245-248. Erratum in: <i>Clin Nutr</i>. 2003 Feb; 22 (1): 107. Magnai G [corrected to Magnani G]. PMID: 12127934.</p>	<p>About homocysteine</p>
<p>Stanger O. <u>The potential role of homocysteine in percutaneous coronary interventions (PCI): Review of current evidence and plausibility of action.</u> <i>Cell Mol Biol (Noisy-le-grand)</i>. 2004 Dec; 50 (8): 953-988. Review. PMID: 15704259.</p>	<p>Not a systematic review.</p>
<p>Stanger O, Semmelrock HJ, Wonisch W, Bös U, Pabst E, Wascher TC. Effects of folate treatment and homocysteine lowering on resistance vessel reactivity in atherosclerotic subjects. <i>J Pharmacol Exp Ther</i>. 2002 Oct; 303 (1): 158-162. PMID: 12235246.</p>	<p>It does not address CVD of stroke risk</p>
<p>Thambyrajah J, Landray MJ, Jones HJ, McGlynn FJ, Wheeler DC, Townend JN. <u>A randomized double-blind placebo-controlled trial of the effect of homocysteine-lowering therapy with folic acid on endothelial function in patients with coronary artery disease.</u> <i>J Am Coll Cardiol</i>. 2001 Jun 1; 37 (7): 1, 858-1, 863. PMID: 11401123.</p>	<p>Article prior June 2004.</p>

<p>Tice JA, Ross E, Coxson PG, Rosenberg I, Weinstein MC, Hunink MG, Goldman PA, Williams L, Goldman L. <u>Cost-effectiveness of vitamin therapy to lower plasma homocysteine levels for the prevention of coronary heart disease: Effect of grain fortification and beyond.</u> <i>JAMA.</i> 2001 Aug 22-29; 286 (8): 936-943. PMID: 11509058.</p>	<p>Model to predict risk of CVD</p>
<p>Title LM, Cummings PM, Giddens K, Genest JJ Jr, Nassar BA. <u>Effect of folic acid and antioxidant vitamins on endothelial dysfunction in patients with coronary artery disease.</u> <i>J Am Coll Cardiol.</i> 2000 Sep; 36 (3): 758-765. PMID: 10987596.</p>	<p>Article prior June 2004.</p>
<p>Wald DS, Bishop L, Wald NJ, Law M, Hennessy E, Weir D, McPartlin J, Scott J. <u>Randomized trial of folic acid supplementation and serum homocysteine levels.</u> <i>Arch Intern Med.</i> 2001 Mar 12; 161 (5): 695-700. PMID: 11231701.</p>	<p>It does not address CVD or stroke risk</p>
<p>Weiss N, Hilge R, Hoffmann U. Vasa. <u>Mild hyperhomocysteinemia: Risk factor or just risk predictor for cardiovascular diseases?</u> 2004 Nov; 33 (4): 191-203. Review. PMID: 15623193.</p>	<p>Not a systematic review.</p>
<p>Woo KS, Chook P, Chan LL, Cheung AS, Fung WH, Qiao M, Lolin YI, Thomas GN, Sanderson JE, Metreweli C, Celermajer DS. <u>Long-term improvement in homocysteine levels and arterial endothelial function after one-year folic acid supplementation.</u> <i>Am J Med.</i> 2002 May; 112 (7): 535-539. PMID: 12015244.</p>	<p>Article prior June 2004.</p>
<p>Woo KS, Chook P, Lolin YI, Sanderson JE, Metreweli C, Celermajer DS. <u>Folic acid improves arterial endothelial function in adults with hyperhomocystinemia.</u> <i>J Am Coll Cardiol.</i> 1999 Dec; 34 (7): 2, 002-2, 006. PMID: 10588216.</p>	<p>Article prior June 2004.</p>

<p>Excluded Articles</p>	<p>Reason for Exclusion</p>
<p>Drogan D, Klipstein-Grobusch K, Dierkes J, Weikert C, Boeing H. <u>Dietary intake of folate equivalents and risk of myocardial infarction in the European Prospective Investigation into Cancer and Nutrition (EPIC) Potsdam study.</u> <i>Public Health Nutr.</i> 2006 Jun; 9 (4): 465-471. PMID: 16870018 International.</p>	<p>It does not answer the question.</p>

<p>Hodis HN, Mack WJ, Dustin L, Mahrer PR, Azen SP, Detrano R, Selhub J, Alaupovic P, Liu CR, Liu CH, Hwang J, Wilcox AG, Selzer RH; BVAIT Research Group. <u>High-dose B vitamin supplementation and progression of subclinical atherosclerosis: a randomized controlled trial.</u> <i>Stroke</i>. 2009 Mar; 40 (3): 730-736. Epub 2008 Dec 31. PMID: 19118243.</p>	<p>It does not answer the question.</p>
<p>Liem A, Reynierse-Buitenwerf GH, Zwinderman AH, Jukema JW, van Veldhuisen DJ. <u>Secondary prevention with folic acid: Effects on clinical outcomes.</u> <i>J Am Coll Cardiol</i>. 2003 Jun 18; 41 (12): 2, 105-2, 113. PMID: 12821232.</p>	<p>Articles included in the Bazzano meta-analysis article.</p>
<p>Liem AH, van Boven AJ, Veeger NJ, Withagen AJ, Robles de Medina RM, Tijssen JG, van Veldhuisen DJ; Folic Acid on Risk Diminishment After Acute Myocardial Infarction Study Group. <u>Efficacy of folic acid when added to statin therapy in patients with hypercholesterolemia following acute myocardial infarction: a randomised pilot trial.</u> <i>Int J Cardiol</i>. 2004 Feb; 93 (2-3): 175-179. PMID: 14975544.</p>	<p>Articles included in the Bazzano meta-analysis article.</p>
<p>Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, McQueen MJ, Probstfield J, Fodor G, Held C, Genest J Jr; Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators <u>Homocysteine lowering with folic acid and B vitamins in vascular disease.</u> <i>N Engl J Med</i>. 2006 Apr 13; 354 (15): 1, 567-1, 577. Epub 2006 Mar 12. Erratum in: <i>N Engl J Med</i>. 2006 Aug 17; 355 (7): 746. PMID: 16531613.</p>	<p>Articles included in the Bazzano meta-analysis article.</p>
<p>Shirodaria C, Antoniades C, Lee J, Jackson CE, Robson MD, Francis JM, Moat SJ, Ratnatunga C, Pillai R, Refsum H, Neubauer S, Channon KM. <u>Global improvement of vascular function and redox state with low-dose folic acid: Implications for folate therapy in patients with coronary artery disease.</u> <i>Circulation</i>. 2007 May 1; 115 (17): 2, 262-2, 270. Epub 2007 Apr 9. PMID: 17420345.</p>	<p>It does not answer the question.</p>
<p>Vrentzos GE, Papadakis JA, Malliaraki N, Zacharis EA, Mazokopakis E, Margioris A, Ganotakis ES, Kafatos A. <u>Diet, serum homocysteine levels and ischaemic heart disease in a Mediterranean population.</u> <i>Br J Nutr</i>. 2004 Jun; 91 (6): 1, 013-1, 019. PMID: 15182405 International.</p>	<p>It does not answer the question.</p>

CHAPTER 10. DIETARY BEHAVIORS AND NUTRIENT INTAKE –FOLIC ACID SUPPLEMENTATION AND RISK OF STROKE

WHAT EFFECT DOES FOLIC ACID SUPPLEMENTATION (WITH OR WITHOUT ADDITIONAL B VITAMIN SUPPLEMENTATION) HAVE ON RISK OF STROKE AMONG PERSONS WITH OR WITHOUT PRE-EXISTING VASCULAR DISEASE?

Conclusion statement

Evidence that folic acid supplementation might prevent stroke is limited due to inconsistency, with the most recent meta-analysis documenting no benefit.

Grade

Limited

Evidence summary overview

One randomized control trial (RCT) (Saposnick et al, 2009) and one meta-analysis (Wang et al, 2007) demonstrated a reduce risk of stroke with folic acid supplementation. The second meta-analysis (Bazzano et al, 2006) did not demonstrate a reduction in stroke. With the exception of two studies, the two meta-analyses included the same trials in their respective analyses. The reasons for the different findings between Wang et al (2007) and Bazzano et al (2006) may be small methodological differences and that there is a stronger effect with primary prevention vs. secondary prevention with stroke (Wang et al, 2007).

Evidence summary paragraphs

Meta-Analysis

Bazzano et al, 2006 (positive quality). This meta-analysis evaluated the effects of folic acid supplementation on risk of cardiovascular diseases (CVD) and all-cause mortality using a random-effects model. The 12 RCTs represented 16,958 men and women. The overall relative risk (RR) confidence intervals (CI) of outcomes for patients treated with folic acid supplementation compared with controls were 0.95 (0.88, 1.03) for CVD, 1.04 (0.92, 1.17) for coronary heart disease(CHD), 0.86 (0.71, 1.04) for stroke, and 0.96 (0.88, 1.04) for all-cause mortality. The relative risk was consistent among participants with pre-existing cardiovascular or renal disease. Folic acid supplementation has not been shown to reduce risk of cardiovascular diseases or all-cause mortality among participants with prior history of vascular disease. Studies included US, Canadian and European subjects.

Miller et al, 2010 (positive quality). This study aimed to explore the interaction between folic acid (FA) and baseline homocysteine levels on CVD through a meta-analysis of randomized controlled trials. The authors searched MEDLINE for trials of FA supplementation to prevent CVD events (January 1966 to July 2009). Articles included in the sample met the following criteria: 1) RCT study design; 2) Intervention included FA supplementation; 3) Intervention and control groups reported number of events for CVD, stroke and other health issues; and 4) Intervention lasted six months or more. Trials with children, pregnant women and patients with end-stage renal disease were excluded. Fourteen trials published from 2002 to 2009 were selected, and they included 38,941 randomized participants (trials ranged from 240 to 12,064

participants; mean age ranged between 52.2 to 68.9 years). Nine trials recruited patients after acute CVD events, four trials had patients with pre-existing CVD or those at high risk of CVD and one trial targeted patients at low risk of CVD. Overall, the findings suggest FA supplementation does not affect CVD or stroke (RR=1.02, 95% CI: 0.93 to 1.13, P=0.66; RR=0.95, 95% CI: 0.84 to 1.08, P=0.43). The authors concluded that FA supplementation should not be recommended as a way to prevent or treat stroke or CVD.

Wang et al, 2007 (positive quality). This meta-analysis collected data from eight randomized trials of folic acid that had stroke reported as one of the endpoints. Relative risk (RR) was used as a measure of the effect of folic acid supplementation on the risk of stroke with a random effect model. Folic acid supplementation significantly reduced the risk of stroke by 18% (RR=0.82, 95% CI: 0.68, 1.00; P=0.045). In the stratified analyses, a greater beneficial effect was seen in those trials with a treatment duration of more than 36 months (RR=0.71; 96% CI: 0.57, 0.87; P=0.001). When stratifying the trials by fortification status, the RR for trials in regions with fortified grain was 0.89 (95% CI: 0.55, 1.42; P=0.62); and for trials in regions without fortification was 0.75 (0.62, 0.91; P=0.003). When the trials were stratified by history of stroke, the RR for the trials in which there was a history of stroke was 1.04 (95% CI: 0.84, 1.29; P=0.71); the RR for trials with such history was 0.75 (95% CI: 0.62, 0.94; P=0.002). These findings indicate that folic acid supplementation can effectively reduce risk of stroke in primary prevention. Studies are from the US, Canada, China, Australia, New Zealand and various European countries.

Randomized Clinical Trial

Saposnik et al, 2009 (positive quality). This RCT studied men and women 55 years of age or older who had a history of stroke, transient ischemic attack (TIA), vascular disease (coronary, cerebrovascular or peripheral vascular) or diabetes, as well as additional risk factors for atherosclerosis, irrespective of their homocysteine levels. Participants are from countries with mandatory folate fortification of food (Canada and the United States) and countries without mandatory folate fortification (Brazil, western Europe and Slovakia). Stroke occurred in 258 (4.7%) individuals during a mean of five years of follow-up. The geometric mean homocysteine concentration decreased by 2.2 μ mol per L in the vitamin therapy group and increased by 0.80 μ mol per L in the placebo group. The incidence rate of stroke was 0.88 per 100 person-years in the vitamin therapy group and 1.15 per 100 person-years in the placebo group (HR, 0.75; 95% CI: 0.59, 0.97). Vitamin therapy also reduced the risk of non-fatal stroke (HR, 0.72; 95% CI: 0.54, 0.95), but did not have an impact on neurological deficit at 24 hours (P=0.45) or functional dependence at discharge or at seven days (OR, 0.95, 95% CI: 0.57, 1.56). The authors concluded that lowering homocysteine with folic acid and vitamins B₆ and B₁₂ did reduce the risk of overall occurrence of stroke but not its severity.

Overview table

Author, Year, Study Design, Class, Rating	Population/Sample description	Measurements of Intervention	Significant Outcomes
<p>Miller ER, Juraschek S et al, 2010</p> <p>Study Design: Meta-analysis or Systematic Review</p> <p>Class: M</p> <p>Rating: Positive Quality</p>	<p>Fourteen trials published from 2002 to 2009 were selected, and they included 38,941 randomized participants (trials ranged from 240 to 12,064 participants; mean age ranged between 52.2 and 68.9 years).</p> <p>Nine trials recruited patients after acute CVD events, four trials had patients with pre-existing CVD or those at high risk of CVD and one trial targeted patients at low risk of CVD.</p>	<p>Pool estimates and 95% CIs of net Δ in homocysteine and log-transformed risk ratio for each clinical outcome were calculated using inverse-variance weighted random-effects models.</p>	<p>Supplementation had no effect on CVD or stroke (RR=1.02, 95% CI: 0.93 to 1.13, P=0.66; RR=0.95, 95% CI: 0.84 to 1.08, P=0.43). The risk ratio was not altered dramatically by exclusion of each trial serially.</p> <p>There was moderate heterogeneity across trials ($I^2=38\%$). There was no evidence of publication-related bias (P=0.63).</p> <p>There were NS differences between countries with and without food fortification in baseline homocysteine, net homocysteine \downarrow or primary clinical effects.</p> <p>Supplementation had no effect on pooled risk ratios, and there was no evidence of heterogeneity or publication bias, for the following specific outcomes:</p> <p>CVD (P=0.42; $I^2=0\%$)</p> <p>CHD (P=0.42; $I^2=31\%$)</p> <p>Stroke (P=0.43; $I^2=25\%$)</p> <p>All-cause mortality (P=0.78; $I^2=0\%$).</p>

<p>Bazzano I, Reynolds K et al, 2006</p> <p>Study Design: Meta-analysis</p> <p>Class: M</p> <p>Rating: Positive Quality</p>	<p>12 RCTs, representing 16,958 participants, both men and women.</p> <p>The studies were conducted in:</p> <p>US (two)</p> <p>Australia and New Zealand (one)</p> <p>Canada (one)</p> <p>European countries (eight).</p>	<p>Clinical CVD events were reported as an end point.</p> <p>Folic acid supplementation was with either placebo or usual care.</p> <p>Dosage of folic acid supplementation in the intervention groups ranged from 0.5mg per day to 15mg per day, for a duration ranging from six months to five years.</p>	<p>Relative risks (RR) for folic acid supplemental patients vs. control were 0.86, 95% CI: 0.71, 1.04 for stroke.</p> <p>The RR was consistent among participants with pre-existing CVD or renal disease.</p>
<p>Wang X, Qin X et al, 2007</p> <p>Study Design: Meta-analysis</p> <p>Class: M</p> <p>Rating: Positive Quality</p>	<p>Eight RCTs, consisting of 16,841 individuals with pre-existing condition.</p> <p>The studies were conducted in:</p> <p>US and Canada (three)</p> <p>Australia and New Zealand (one)</p> <p>China (one)</p> <p>European countries (three).</p>	<p>Stroke is reported as one of the endpoints.</p> <p>Relative risk (RR) was used as a measure of the effect of folic acid supplementation on the risk of stroke with a random effect model.</p> <p>The dosage of folic acid in the intervention groups ranged from 0.5mg per day to 15mg per day.</p>	<p>Folic acid supplementation significantly ↓ the risk of stroke by 18% (RR=0.82, 95% CI: 0.68, 1.00; P=0.045).</p> <p>In the stratified analyses, a greater beneficial effect was seen in those trials with a treatment duration of more than 36 months (RR=0.71; CI: 0.57 to 0.87; P=0.001).</p> <p>When stratified the trials by fortification status, the RR for trials in regions with fortified grain was 0.89 (95% CI: 0.55, 1.42; P=0.62); and for trials in regions without fortification was 0.75 (0.62, 0.91; P=0.003).</p> <p>When stratified the trials by history of stroke, the RR for the trials in which there was a history of stroke was 1.04 (0.84, 1.29; P=0.71); the RR for trials with such history was 0.75 (0.62, 0.94; P=0.002).</p>

<p>Saposnik G, Ray JG et al, 2009</p> <p>Study Design: Randomized clinical trial</p> <p>Class: A</p> <p>Rating: Positive Quality</p>	<p>5,522 men and women, 55 years of age or older, were recruited from 145 participating centers within 13 countries, including:</p> <p>Canada (N=3568), the US (N=414); countries with mandatory folic acid fortification policy</p> <p>Brazil (N=265), Western Europe (N=426), and Slovakia (N=849); countries without mandatory folic acid fortification policy.</p>	<p>Measurements: Stroke events and homocysteine.</p> <p>Intervention: Daily combination of 2.5mg folic acid, 50mg vitamin B₆, and 1mg vitamin B₁₂, or matching placebo, for five years.</p>	<p>Stroke occurred in 258 (4.7%) individuals during a mean of five years of follow-up.</p> <p>The geometric mean homocysteine concentration ↓ by 2.2μmol per L in the vitamin therapy group, and ↑ by 0.80μmol per L in the placebo group.</p> <p>The incidence rate of stroke was 0.88 per 100 person-years in the vitamin therapy group and 1.15 per 100 person-years in the placebo group (HR, 0.75; 95% CI: 0.59,0.97).</p> <p>Vitamin therapy also ↓ the risk of nonfatal stroke (HR, 0.72 95% CI: 0.54-0.95), but did not impact on neurological deficit at 24 hours (P=0.45) or functional dependence at discharge or at seven days (OR, 0.95, 95% CI: 0.57-1.56).</p>
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Search plan and results

Inclusion criteria

- *Subjects/Population:* Human subjects
- *Age:* Children, men and women of all ages
- *Setting:* US and Canada only
- *Health status:* Healthy and those with elevated chronic disease risk (CHD/CVD, type 2 diabetes, metabolic syndrome and obesity)
- *Nutrition related problem/condition:* None

Search Criteria:

- *Study design preferences:* RCT or clinical controlled studies, large non-randomized observational studies, cohort, case-control studies, systematic reviews and meta-analysis
- *Size of study groups:* The sample size must equal 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 drop out rate:* Less than 20%; preference for smaller dropout rates
- *Year range:* June 2004 to present

- *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-reviewed journal.

Exclusion criteria

- *Subjects/population*:
 - Animal and in vitro studies
 - Malnourished or third-world populations or disease incidence not relative to US population (e.g., malaria)
- *Setting*: Hospitalized patients
- *Health status*: Medical treatment or therapy and diseased subjects (already diagnosed with disease related to study purpose)
- *Nutrition related problem/condition*: All conditions
- *Size of study groups*: Sample sizes less than 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 June 2004
- *Authorship*: Studies by same author similar in content
- *Languages*: Articles not in English
- *Other*: Abstracts or presentations and articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- Intake levels/consumption levels
- Fortification
- Supplementation
- Stroke
- Other terms: *NHANES*.

Electronic database used:

- PubMed:

("Folic Acid"[Mesh] OR "folate"[All Fields]) AND ("Food, Fortified"[Mesh] OR "Dietary Supplements"[Mesh]) AND "english and humans"[Filter] AND "stroke"[MeSH Terms] and risk
("Folic Acid"[Mesh] OR "folate"[All Fields]) AND "english and humans"[Filter] AND "stroke"[MeSH Terms] AND "published last 5 years"[Filter]

Date searched: 2/05/09; 2/19/09; 7/20/09

Summary of articles identified to review

- Total hits from all electronic database searches: 165
- Total articles identified to review from electronic databases: 54
- Articles identified via handsearch or other means: 1
- Number of Primary Articles Identified: 1
- Number of Review Articles Identified: 3
- Total Number of Articles Identified: 4

- Number of Articles Reviewed but Excluded: 51

Included articles (References)

Meta-analysis

1. Bazzano LA, Reynolds K, Holder KN, He J. Effect of folic acid supplementation on risk of cardiovascular diseases: A meta-analysis of randomized controlled trials. www.ncbi.nlm.nih.gov/pubmed/17164458. *JAMA*. 2006 Dec 13; 296(22): 2, 720-2, 726. Erratum in: *JAMA*. 2007 Mar 7; 297(9): 952. PMID: 17164458.
2. Miller ER 3rd, Juraschek S, Pastor-Barriuso R, Bazzano LA, Appel LJ, Guallar E. Meta-analysis of folic acid supplementation trials on risk of cardiovascular disease and risk interaction with baseline homocysteine levels. *Am J Cardiol*. 2010. Abstracted prior to publication.
3. Wang X, Qin X, Demirtas H, Li J, Mao G, Huo Y, Sun N, Liu L, Xu X. Efficacy of folic acid supplementation in stroke prevention: a meta-analysis. www.ncbi.nlm.nih.gov/pubmed/17544768. *Lancet*. 2007 Jun 2; 369(9, 576): 1, 876-1, 882. Review. PMID: 17544768.

Primary Research

4. Saposnik G, Ray JG, Sheridan P, McQueen M, Lonn E; Heart Outcomes Prevention Evaluation 2 Investigators. Homocysteine-lowering therapy and stroke risk, severity, and disability: additional findings from the HOPE 2 trial. *Stroke*. 2009 Apr; 40(4): 1, 365-1, 372. Epub 2009 Feb 19. PMID: 19228852.

Excluded articles

Article	Reason for Exclusion
Al-Delaimy WK, Rexrode KM, Hu FB, Albert CM, Stampfer MJ, Willett WC, Manson JE. Folate intake and risk of stroke among women. www.ncbi.nlm.nih.gov/pubmed/15105514 . <i>Stroke</i> . 2004 Jun; 35(6): 1, 259-1, 263. Epub 2004 Apr 22. PMID: 15105514.	Evaluates dietary intake.
Bazzano LA, He J, Ogden LG, Loria C, Vupputuri S, Myers L, Whelton PK. Dietary intake of folate and risk of stroke in US men and women: NHANES I Epidemiologic Follow-up Study. National Health and Nutrition Examination Survey. www.ncbi.nlm.nih.gov/pubmed/11988588 . <i>Stroke</i> . 2002 May; 33(5): 1, 183-1, 188. PMID: 11988588.	Evaluates dietary intake.
Biswas A, Ranjan R, Meena A, Akhter MS, Yadav BK, Munisamy M, Subbiah V, Behari M, Saxena R. <u>Homocystine levels, polymorphisms and the risk of ischemic stroke in young Asian Indians.</u> <i>J Stroke Cerebrovasc Dis</i> . 2009 Mar-Apr; 18(2): 103-110. PMID: 19251185.	International. It doesn't measure stroke or CVD risk.

<p>Ding EL, Mozaffarian D. Semin. <u>Optimal dietary habits for the prevention of stroke.</u> <i>Neurol.</i> 2006 Feb; 26(1): 11-23. Review. PMID: 16479440.</p>	<p>Does not answer the question; about dietary patterns and stroke.</p>
<p>Drogan D, Klipstein-Grobusch K, Dierkes J, Weikert C, Boeing H. <u>Dietary intake of folate equivalents and risk of myocardial infarction in the European Prospective Investigation into Cancer and Nutrition (EPIC): Potsdam study.</u> <i>Public Health Nutr.</i> 2006 Jun; 9(4): 465-471. PMID: 16870018.</p>	<p>Evaluates dietary intake.</p>
<p>Dusitanond P, Eikelboom JW, Hankey GJ, Thom J, Gilmore G, Loh K, Yi Q, Klijn CJ, Langton P, van Bockxmeer FM, Baker R, Jamrozik K. Homocysteine-lowering treatment with folic acid, cobalamin, and pyridoxine does not reduce blood markers of inflammation, endothelial dysfunction, or hypercoagulability in patients with previous transient ischemic attack or stroke: A randomized substudy of the VITATOPS trial. www.ncbi.nlm.nih.gov/pubmed/15569860. <i>Stroke.</i> 2005 Jan; 36(1):144-6. Epub 2004 Nov 29. PMID: 15569860.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>Furie KL, Kelly PJ. <u>Homocyst(e)ine and stroke.</u> <i>Semin Neurol.</i> 2006 Feb; 26(1): 24-32. Review. PMID: 16479441.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>Hankey GJ, Eikelboom JW, Loh K, Tang M, Pizzi J, Thom J, Yi Q. <u>Sustained homocysteine-lowering effect over time of folic acid-based multivitamin therapy in stroke patients despite increasing folate status in the population.</u> <i>Cerebrovasc Dis.</i> 2005; 19(2): 110-116. Epub 2004 Dec 17. PMID: 15608435.</p>	<p>Does not answer the question; about Vitatops a supplement and prevention of stroke.</p>
<p>He K, Merchant A, Rimm EB, Rosner BA, Stampfer MJ, Willett WC, Ascherio A. Folate, vitamin B₆, and B₁₂ intakes in relation to risk of stroke among men. www.ncbi.nlm.nih.gov/pubmed/14671243. <i>Stroke.</i> 2004 Jan;35(1):169-74. Epub 2003 Dec 11. PMID: 14671243.</p>	<p>Article prior June 2004.</p>
<p>Ho GY, Eikelboom JW, Hankey GJ, Wong CR, Tan SL, Chan JB, Chen CP. <u>Methylenetetrahydrofolate reductase polymorphisms and homocysteine-lowering effect of vitamin therapy in Singaporean stroke patients.</u> <i>Stroke.</i> 2006 Feb; 37(2): 456-460. Epub 2006 Jan 5. PMID: 16397167.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>Kalita J, Kumar G, Bansal V, Misra UK. <u>Relationship of homocysteine with other risk factors and outcome of ischemic stroke.</u> <i>Clin Neurol Neurosurg.</i> 2009 May; 111(4): 364-367. Epub 2009 Jan 30. PMID: 19185985.</p>	<p>Does not assess CVD or stroke risk.</p>

<p>Kelly PJ, Shih VE, Kistler JP, Barron M, Lee H, Mandell R, Furie KL. <u>Low vitamin B₆ but not homocyst(e)ine is associated with increased risk of stroke and transient ischemic attack in the era of folic acid grain fortification.</u> <i>Stroke</i>. 2003 Jun; 34(6): e51-e54. Epub 2003 May 8. PMID: 12738890.</p>	<p>Does not answer the question; about homocysteine and B₆.</p>
<p>Khan U, Crossley C, Kalra L, Rudd A, Wolfe CD, Collinson P, Markus HS. <u>Homocysteine and its relationship to stroke subtypes in a UK black population: the south London ethnicity and stroke study.</u> <i>Stroke</i>. 2008 Nov; 39(11): 2, 943-2, 949. Epub 2008 Aug 28. PMID: 18757289.</p>	<p>About homocysteine.</p>
<p>Larsson SC, Männistö S, Virtanen MJ, Kontto J, Albanes D, Virtamo J. Folate, vitamin B₆, vitamin B₁₂, and methionine intakes and risk of stroke subtypes in male smokers. www.ncbi.nlm.nih.gov/pubmed/18270369 <i>Am J Epidemiol</i>. 2008 Apr 15; 167(8): 954-61. Epub 2008 Feb 12. PMID: 18270369.</p>	<p>Evaluates dietary intake.</p>
<p>Lutsep HL, Campbell S, Chambless LE, Howard VJ, Toole JF. <u>Plasma total homocysteine levels in stroke patients screened for the vitamin intervention for stroke prevention clinical trial in the era of folate fortification.</u> <i>Neuroepidemiology</i>. 2006; 26(1): 45-51. Epub 2005 Oct 25. PMID: 16254453.</p>	<p>Does not answer the question; pre- and post-fortification comparison.</p>
<p>Mangoni AA, Ouldred E, Swif CG, Jackson SH, Draper RP, Sherwood RA, Lambert-Hamill M, Wierzbicki AS. <u>Vascular and blood pressure effects of folic acid in older patients with cardiovascular disease.</u> <i>J Am Geriatr Soc</i>. 2001 Jul; 49(7): 1, 003-1, 004. No abstract available. PMID: 11527499.</p>	<p>Article prior to June 2004.</p>
<p>Matsui T, Arai H, Yuzuriha T, Yao H, Miura M, Hashimoto S, Higuchi S, Matsushita S, Morikawa M, Kato A, Sasaki H. Elevated plasma homocysteine levels and risk of silent brain infarction in elderly people. www.ncbi.nlm.nih.gov/pubmed/11340219. <i>Stroke</i>. 2001 May; 32(5): 1, 116-1, 119. PMID: 11340219,</p>	<p>Does not answer the question. About homocysteine.</p>
<p>Maxwell CJ, Hogan DB, Eby EM. <u>Serum folate levels and subsequent adverse cerebrovascular outcomes in elderly persons.</u> <i>Dement Geriatr Cogn Disord</i>. 2002; 13(4): 225-234. PMID: 12006733.</p>	<p>Article prior to June 2004.</p>
<p>Morris MS, Jacques PF, Rosenberg IH, Selhub J, Bowman BA, Gunter EW, Wright JD, Johnson CL. <u>Serum total homocysteine concentration is related to self-reported heart attack or stroke history among men and women in the NHANES III.</u> <i>J Nutr</i>. 2000 Dec; 130(12): 3, 073-3, 0736. PMID: 11110872.</p>	<p>About homocysteine.</p>

<p>Ntaios GC, Savopoulos CG, Chatzinikolaou AC, Kaiafa GD, Hatzitolios A. Vitamins and stroke: The homocysteine hypothesis still in doubt. www.ncbi.nlm.nih.gov/pubmed/18195649. <i>Neurologist</i>. 2008 Jan; 14(1): 2-4. Review. PMID: 18195649.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>Peng H, Huang Q, Li Y, Sun S, Deng X, Liu H, Qiao X. J Tongji. <u>Study on the relationship between plasma homocysteine and acute cerebral vascular disease.</u> <i>Med Univ</i>. 2000; 20(4): 330-331. PMID: 12840927.</p>	<p>About homocysteine.</p>
<p>Potter K, Hankey GJ, Green DJ, Eikelboom J, Jamrozik K, Arnolda LF. <u>The effect of long-term homocysteine-lowering on carotid intima-media thickness and flow-mediated vasodilation in stroke patients: a randomized controlled trial and meta-analysis.</u> <i>BMC Cardiovasc Disord</i>. 2008 Sep 20; 8: 24. Review. PMID: 18803866.</p>	<p>Does not answer the question; doesn't address risk of CVD or stroke.</p>
<p>Potter K, Lenzo N, Eikelboom JW, Arnolda LF, Beer C, Hankey GJ. <u>Effect of long-term homocysteine reduction with B vitamins on arterial wall inflammation assessed by fluorodeoxyglucose positron emission tomography: A randomised double-blind, placebo-controlled trial.</u> <i>Cerebrovasc Dis</i>. 2009; 27(3): 259-265. Epub 2009 Feb 6. PMID: 19202330.</p>	<p>About homocysteine.</p>
<p>Sacher Y, Soroker N, Motin M, Treger I, Ring H, Sela BA. <u>Blood homocysteine levels in stroke patients undergoing rehabilitation.</u> <i>Med Sci Monit</i>. 2003 Jun; 9(6): CR201-CR207. PMID: 12824946.</p>	<p>About homocysteine.</p>
<p>Sato Y, Honda Y, Iwamoto J, Kanoko T, Satoh K. <u>Effect of folate and mecobalamin on hip fractures in patients with stroke: A randomized controlled trial.</u> <i>JAMA</i>. 2005 Mar 2; 293(9): 1, 082-1, 088. Erratum in: <i>JAMA</i>. 2006 Jul 26; 296(4): 396. PMID: 15741530.</p>	<p>Does not answer the question; about hip fractures and low folic acid</p>
<p>Sato Y, Kaji M, Kondo I, Yoshida H, Satoh K, Metoki N. <u>Hyperhomocysteinemia in Japanese patients with convalescent stage ischemic stroke: Effect of combined therapy with folic acid and mecobalamine.</u> <i>J Neurol Sci</i>. 2002 Oct 15; 202(1-2): 65-68. PMID: 12220694.</p>	<p>International; Does not measure stroke or CVD risk.</p>
<p>Schwammenthal Y, Tanne D. <u>Homocysteine, B-vitamin supplementation, and stroke prevention: From observational to interventional trials.</u> <i>Lancet Neurol</i>. 2004 Aug; 3(8): 493-495. Review. PMID: 15261610 [PubMed - indexed for MEDLINE].</p>	<p>Does not answer the question; about homocysteine.</p>
<p>Sirachainan N, Tapanapruksakul P, Visudtibhan A, Chuansumrit A, Cheeramakara C, Atamasirikul K, Chotsuppakarn S, Areekul S. <u>Homocysteine, MTHFR C677 T, vitamin B₁₂, and folate levels in Thai children with ischemic stroke: A case-control study.</u> <i>J Pediatr Hematol Oncol</i>. 2006 Dec; 28(12): 803-808. PMID: 17164649.</p>	<p>Does not assess CVD or stroke risk.</p>

<p>Spada RS, Stella G, Calabrese S, Bosco P, Anello G, Guéant-Rodriguez RM, Romano A, Benamghar L, Fontaine T, Guéant JL. <u>Association of vitamin B₁₂, folate and homocysteine with functional and pathological characteristics of the elderly in a mountainous village in Sicily.</u> <i>Clin Chem Lab Med.</i> 2007; 45(2): 136-142. PMID: 17311497.</p>	<p>About homocysteine.</p>
<p>Spence JD. <u>Homocysteine-lowering therapy: A role in stroke prevention?</u> <i>Lancet Neurol.</i> 2007 Sep; 6(9): 830-838. Review. PMID: 17706567.</p>	<p>Does not answer the question. About Vitamin B₁₂.</p>
<p>Spence JD, Bang H, Chambless LE, Stampfer MJ. <u>Vitamin Intervention For Stroke Prevention trial: An efficacy analysis.</u> <i>Stroke.</i> 2005 Nov; 36(11): 2, 404-2, 409. Epub 2005 Oct 20. PMID: 16239629.</p>	<p>Does not answer the question; about vitamin B₁₂.</p>
<p>Spence JD, Howard VJ, Chambless LE, Malinow MR, Pettigrew LC, Stampfer M, Toole JF. <u>Vitamin Intervention for Stroke Prevention (VISP) trial: Rationale and design.</u> <i>Neuroepidemiology.</i> 2001 Feb; 20(1): 16-25. PMID: 11174041.</p>	<p>Article prior June 2004.</p>
<p>Ullegaddi R, Powers HJ, Gariballa SE. <u>Antioxidant supplementation with or without B-group vitamins after acute ischemic stroke: A randomized controlled trial.</u> <i>JPEN J Parenter Enteral Nutr.</i> 2006 Mar-Apr; 30(2): 108-114. PMID: 16517955.</p>	<p>Does not answer the question; about antioxidants.</p>
<p>Vanuzzo D, Pilotto L, Lombardi R, Lazzarini G, Carluccio M, Diviaco S, Quadrifoglio F, Danek G, Gregori D, Fioretti P, Cattaneo M, De Caterina R. <u>Both vitamin B₆ and total homocysteine plasma levels predict long-term atherothrombotic events in healthy subjects.</u> <i>Eur Heart J.</i> 2007 Feb; 28(4): 484-491. Epub 2007 Jan 31. PMID: 17267459.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>Virtanen JK, Voutilainen S, Happonen P, Alfthan G, Kaikkonen J, Mursu J, Rissanen TH, Kaplan GA, Korhonen MJ, Sivenius J, Salonen JT. <u>Serum homocysteine, folate and risk of stroke: Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study.</u> <i>Eur J Cardiovasc Prev Rehabil.</i> 2005 Aug; 12(4): 369-375. PMID: 16079645.</p>	<p>Evaluates dietary intake.</p>
<p>Viswanathan A, Raj S, Greenberg SM, Stampfer M, Campbell S, Hyman BT, Irizarry MC. <u>Plasma Abeta, homocysteine, and cognition: The Vitamin Intervention for Stroke Prevention (VISP) trial.</u> <i>Neurology.</i> 2009 Jan 20; 72(3): 268-272. PMID: 19153374.</p>	<p>About homocysteine.</p>
<p>Wang H, Fan D, Zhang H, Fu Y, Zhang J, Shen Y. <u>Serum level of homocysteine is correlated to carotid artery atherosclerosis in Chinese with ischemic stroke.</u> <i>Neurol Res.</i> 2006 Jan; 28(1): 25-30. PMID: 16464359.</p>	<p>International, about homocysteine.</p>

Weikert C, Dierkes J, Hoffmann K, Berger K, Drogan D, Klipstein-Grobusch K, Spranger J, Möhlig M, Luley C, Boeing H. <u>B vitamin plasma levels and the risk of ischemic stroke and transient ischemic attack in a German cohort.</u> <i>Stroke</i> . 2007 Nov; 38(11): 2, 912-2, 918. Epub 2007 Sep 20. PMID: 17885260.	Does not assess CVD or stroke risk.
Weng LC, Yeh WT, Bai CH, Chen HJ, Chuang SY, Chang HY, Lin BF, Chen KJ, Pan WH. www.ncbi.nlm.nih.gov/pubmed/18988909 . <i>Stroke</i> . 2008 Dec; 39(12): 3, 152-3, 158. Epub 2008 Nov 6. PMID: 18988909.	Evaluates dietary intake.
Woo KS, Qiao M, Chook P, Poon PY, Chan AK, Lau JT, Fung KP, Woo JL. <u>Homocysteine, endothelial dysfunction, and coronary artery disease: emerging strategy for secondary prevention.</u> <i>J Card Surg</i> . 2002 Sep-Oct; 17(5): 432-435. PMID: 12630544.	International; about homocysteine.
Yang LK, Wong KC, Wu MY, Liao SL, Kuo CS, Huang RF. <u>Correlations between folate, B₁₂, homocysteine levels, and radiological markers of neuropathology in elderly post-stroke patients.</u> <i>J Am Coll Nutr</i> . 2007 Jun; 26(3): 272-278. PMID: 17634173.	Evaluates dietary intake.
Yilmaz N, Yilmaz M, Pençe S, Ozaslan J, Koçoglu H, Yilmaz G. <u>Determination of serum B₁₂ vitamin and folic acid levels in patient with stroke.</u> <i>Acta Medica (Hradec Kralove)</i> . 2001; 44(1): 37-39. PMID: 11367891.	Article prior June 2004

Meta-analyses Articles	Reason for Exclusion
Bønaa KH, Njølstad I, Ueland PM, Schirmer H, Tverdal A, Steigen T, Wang H, Nordrehaug JE, Arnesen E, Rasmussen K; NORVIT Trial Investigators. <u>Homocysteine lowering and cardiovascular events after acute myocardial infarction.</u> <i>N Engl J Med</i> . 2006 Apr 13; 354(15): 1, 578-1, 588. Epub 2006 Mar 12. PMID: 16531614.	Article included in the Bazzano (2006) meta-analysis.
Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, McQueen MJ, Probstfield J, Fodor G, Held C, Genest J Jr; Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. <i>N Engl J Med</i> . 2006 Apr 13; 354 (15): 1, 567-1, 577. Epub 2006 Mar 12. Erratum in: <i>N Engl J Med</i> . 2006 Aug 17; 355 (7): 746. PMID: 16531613.	Article included in the Bazzano (2006) meta-analysis.

<p>Toole JF, Malinow MR, Chambless LE, Spence JD, Pettigrew LC, Howard VJ, Sides EG, Wang CH, Stampfer M. <u>Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial.</u> <i>JAMA</i>. 2004 Feb 4; 291 (5): 565-575. PMID: 14762035.</p>	<p>Article included in the Bazzano (2006) meta-analysis.</p>
<p>VITATOPS Trial Study Group. <u>The VITATOPS (Vitamins to Prevent Stroke) Trial: rationale and design of an international, large, simple, randomised trial of homocysteine-lowering multivitamin therapy in patients with recent transient ischaemic attack or stroke.</u> <i>Cerebrovasc Dis</i>. 2002; 13 (2): 120-126. Review. PMID: 11867886.</p>	<p>Article included in the Bazzano (2006) meta-analysis.</p>
<p>Ullegaddi R, Powers HJ, Gariballa SE. <u>B-group vitamin supplementation mitigates oxidative damage after acute ischaemic stroke.</u> <i>Clin Sci (Lond)</i>. 2004 Nov; 107 (5): 477-484. PMID: 15279619.</p>	<p>Article included in the Bazzano (2006) meta-analysis.</p>