2010 Dietary Guidelines Advisory Committee:

Systematic Reviews of the Carbohydrates 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 Carbohydrates 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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CHAPTER 1. OVERVIEW AND NEEDS FOR FUTURE RESEARCH

OVERVIEW

The Committee first reviewed the 2005 Dietary Guidelines Advisory Committee (DGAC) report to inform their review process in 2010. Various topics in this section were also considered by the 2005 DGAC, including:

- Whole grains
- Vegetables and fruits
- Glycemic index and load
- Added sugars
- Liquids vs. solids.

Non-caloric sweeteners was a new question to be considered by a DGAC. For each of the Nutrition Evidence Library (NEL) systematic reviews, the following general criteria applied. All study designs were originally included in the searches, but cross-sectional studies were later excluded from the review if there was sufficient evidence from studies with stronger study designs. The Committee excluded studies that only included participants diagnosed with chronic disease, hyperlipidemia, hypertension (HTN) and related health conditions. Many systematic reviews and meta-analyses of primary research articles were considered by the Committee, and care was taken not to review the same study twice in the NEL evidence-based review.

For the topics considered by the 2005 DGAC, the Conclusions expressed in the 2010 DGAC report are informed by the evidence compiled for the 2005 DGAC report, but are based primarily on the NEL evidence gathered and reviewed since 2004. As discussed in the associated review, for some questions, the search was extended back further to capture a larger body of evidence. The Committee only considered studies that directly assessed the relationship between the intake of food groups and health outcomes; studies examining the intake of food groups as a part of a larger dietary pattern were not considered in the review.

NEEDS FOR FUTURE RESEARCH

1. Develop and validate carbohydrate assessment methods. Explore and validate new and emerging biomarkers to elucidate alternative mechanisms and explanations for observed effects of carbohydrates on health.
   - Rationale: Studies of carbohydrates and health outcomes on a macronutrient level are often inconsistent or ambiguous due to inaccurate measures and varying food categorizations and definitions. The science cannot progress without further advances in both methodology and theory.
2. Develop definitions for whole grain foods and criteria for whole grain foods that can be universally accepted.
   - Rationale: At present, there is no consistent way that whole grain foods are defined and determined. Without clear definitions for whole grain foods, it is difficult to compare research studies examining the effectiveness of various whole grains on biomarkers of interest in cardiovascular disease(CVD), diabetes and obesity. Clear definitions would also help consumers identify foods

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that can help them meet the Dietary Guidelines recommendation.

3. Conduct intervention and research studies with strong designs that include sufficient sample sizes over time and specific measures of vegetable and fruit intake, including specific types of vegetables and fruits, overall dietary patterns, exercise, sex and other confounding factors to evaluate the impact of consuming vegetables and fruits on health.
   - Rationale: Rigorous methods of assessing dietary intake are needed along with rigorous measures of outcomes. Strong designs that control for confounding variables will provide deeper insight into the effect vegetables and fruits have on health. Plausible mechanisms for these effects also need to be studied in depth. Traditional markers, such as blood lipids, while useful for risk factor assessment, appear to have limited explanatory value.
4. Conduct long-term, randomized controlled trials (RCTs) to resolve whether use of nonnutritive sweeteners can actually aid weight loss or prevention of weight gain.
   - Rationale: Currently available data are insufficient to recommend non-nutritive sweeteners as an aid to weight loss, except on a theoretical basis for calorie reduction.
5. Develop standardized assessment tools to determine accurate intake of added sugars.
   - Rationale: This is challenging because carbohydrate methods are also limited, as total carbohydrate is measured “by difference.” Unless efforts are made to define and measure carbohydrates and carbohydrate fractions with potential health benefits, it will be difficult to determine if different carbohydrate types have different health effects.
6. Develop innovative methods to evaluate “food form” as a variable in food intake studies for the field to progress.
   - Rationale: Unless macronutrients are carefully controlled, it is not possible to answer the question on how food form affects energy intake. These questions will remain unless RCTs are conducted that measure differences in exposure to different carbohydrates (glucose, fructose, sucrose) and different forms (liquid, solid, whole food).
7. Develop methods for use in epidemiologic studies to measure accurately or quantify intake of liquids, either caloric or non-caloric.
   - Rationale: There has been an increase in the number of beverages available, and it would be valuable to know how these beverages are contributing to satiety, energy intake and body weight. Drinks can include a wide range of macronutrients and artificial sweeteners are difficult to assess with food frequency instruments. The type of drinks consumed now includes sport drinks, designer coffees and teas, smoothies and juices and carbonated beverages with different sugars or artificial sweeteners.
8. Determine whether the effects of vegetables and fruits in the overall dietary pattern are due to displacement of other foods in the diet or to the action of vegetables and fruits, per se, on specific health outcomes.
   - Rationale: The mechanism(s) of action for the effects of vegetables and fruits have not been determined and, therefore, may vary for different health outcomes. The observed effects could be a simple displacement of these foods with other foods that cause poorer outcomes, or vegetables and fruits may contribute specific benefits or a combination of the above may explain the observations made thus far in the literature. Only further research can provide

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more definitive answers.

9. Identify whether a progressive, inverse relationship of fruits and vegetable consumption exists with the prevention of chronic disease(s) or whether there is a threshold effect that may vary depending on factors such as disease, sex or dietary pattern.
   - Rationale: The evidence suggests that there may be a threshold effect of vegetables and fruits, at least within the American dietary pattern, but further research is needed to verify this hypothesis and to test whether the threshold varies among a variety of dietary patterns or among the specific variety of vegetables and fruits consumed
   - Rationale: Studies of carbohydrates and health outcomes on a macronutrient level are often inconsistent or ambiguous due to inaccurate measures and varying food categorizations and definitions. The science cannot progress without further advances in both methodology and theory.

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CHAPTER 2. GLYCEMIC INDEX/LOAD – BODY WEIGHT

WHAT IS THE RELATIONSHIP BETWEEN GLYCEMIC INDEX OR GLYCEMIC LOAD AND BODY WEIGHT?

Conclusion statement

Strong and consistent evidence shows that glycemic index and/or glycemic load are not associated with body weight and do not lead to greater weight loss or better weight maintenance.

Grade

Strong

Evidence summary overview

Current evidence shows that the glycemic index (GI) and glycemic load (GL) are not associated with body weight and do not lead to greater weight loss or better weight maintenance. Evidence from randomized controlled trials (RCTs) shows no difference between high-GI and low-GI diets on weight loss in studies longer than eight weeks. Evidence from fewer RCTs show the same for high glycemic load (GL) vs. low GL. The Committee reviewed 22 studies published since 2005. Of these, 13 were RCTs, two were prospective cohort studies and seven were cross-sectional studies.

Seven RCTs compared high vs. low glycemic index (GI) or high vs. low glycemic load (GL) in a reducing diet protocol. Of these, two studies (Abete, 2008; de Rougemont, 2007) showed a significant weight loss difference of 2.3kg and 0.8kg after eight and five weeks with a greater drop in the low-GI diet. The other five RCTs (Phillipou, 2009; Pittas, 2005; Raatz, 2005; Sichieri, 2007; Sloth, 20004) showed no difference in weight loss in much longer studies lasting from 16 to 76 weeks. Three RCTs (Ebbeling, 2007; Maki, 2007; Pereira, 2004) compared low-GL diets vs. low-fat diets. They did not show any differences in weight loss between the diets. One RCT (Pal, 2008) compared the effect of a high-GI vs. low-GI breakfast and found no difference in weight after three weeks. One RCT (McMillan-Price, 2006) compared four diets, two of which were high carbohydrate (CHO) and two were high protein (PRO) with either high or low GI. No difference in weight loss was found with any of the diets over 12 weeks. In summary, the RCTs overwhelmingly report no difference between low and high-GI diets in achieving weight loss during reducing diet programs or maintenance diet programs. The data on GL are less numerous but report similar results.

Two prospective cohort studies also examined this issue (Deienlein, 2008; Hare-Bruun, 2006). The first was a gestational diabetes study that found glycemic load (GL) not to be associated with gestational weight gain or weight gain ratio. The second followed normal weight participants for six years and showed no significant (NS) association between GL and change in weight in either men or women. It showed no association between glycemic index (GI) and change in weight in men, but did show an association of GI with lower weight gain in women. These studies suggest that in men there is no relation between either GI or GL and weight, and in women there is no relation of GL and weight, but a possible relation of GI and weight.

Seven cross-sectional studies also have been carried out, comprising a total of 21,231 participants, both children and adults. Of these, six (Hui, 2006; Lau, 2006; Liese, 2005;

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Mendez, 2009; Milton, 2007; Nielsen, 2005) showed no association between glycemic index (GI) or glycemic load (GL) and weight or body mass index (BMI). One study (Murakami, 2007) did show a positive correlation between GI and GL with BMI in young, lean Japanese women. These cross-sectional studies support the conclusion that GI or GL and weight are not associated.

Evidence summary paragraphs

Abete, 2008 (neutral quality), a randomized trial conducted in Spain, investigated the effects of two dietary energy-restricted approaches with similar macronutrient content, but different food distribution modifying the glycemic index (GI) on body weight and other metabolic markers. Participants were 32 obese (mean BMI = 32.5±4.3kg/m^2) adults (mean age = 36±7 years, 56% male) who were randomly assigned to higher- or lower-GI energy-restricted diets, both with 53% of energy as carbohydrate (CHO), 17% as protein (PRO) and 30% as fats. Participants were individually instructed to follow the prescribed dietary regime for eight consecutive weeks by a trained dietitian within a strict dietary framework, which was repeated on a three-day rotation basis. Subjects were asked to maintain the same habitual physical activity during the intervention. Body weight and BMI were significantly reduced in both groups, being greater in the lower-GI group. Percent change (SD) in body weight (kg) between baseline and eight-week follow-up for the higher- vs. lower-GI diets were -5.3 (2.6) and -7.5 (2.9), respectively (P-value for difference in percent change between groups = 0.033). Percent change (SD) in BMI (kg/m^2) between baseline and eight-week follow-up for the higher- vs. lower-GI diets were -5.4 (2.5) and -7.6 (3.0), respectively (P-value for difference in percent change between groups = 0.030). Both energy-restricted diets resulted in significant weight loss, but the diet with lower GI (84% of CHO from pasta and legumes) resulted in a greater weight loss.

Aston, 2008 (neutral quality), an RCT conducted in the United Kingdom, explored the effects of lower and higher glycemic index (GI) foods, independently of changes to other dietary factors on body weight and other outcomes in 19 overweight and obese female subjects (mean BMI=33.1±4.9kg/m^2, mean age = 51.9±7.6). This study included a randomized cross-over intervention with two consecutive 12-week periods. Subjects were provided with lower or higher GI versions of key 'staple' CHO-rich foods, according to intervention period, to incorporate into habitual diet. Provided foods included breads, breakfast cereals and rice, plus pasta on the lower GI diet and potatoes during the higher GI period. These 'low' and 'high' GI foods had a mean difference of 28.5 units. Subjects were instructed to maintain their habitual diets for the duration of the study, but to substitute the supplied foods into their diets on at least three occasions per day in the quantity they would normally consume. All subjects reduced dietary GI on the lower GI diet compared with the higher GI diet, with a mean difference of 8.4 units (P<0.001). Glycemic load was NS reduced on the low GI diet due to a small increase in CHO intake. Weight increased during both intervention periods, although weight gain did not differ between treatments. Mean (SD) change in body weight in the low- and high-GI treatments were 1.1 (1.5) kg and 1.4 (1.7) kg, respectively (P=0.7). The authors noted that participants were not attempting to lose weight during the trial, and the modest weight gain during both periods could be a function of receiving ‘free’ food.

de Rougemont, 2007 (positive quality), a randomized trial conducted in France, examined the effects of low and high glycemic index (GI) interventions on body weight, BMI and other parameters in overweight adults (53% male, BMI: mean±SEM =

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27.3±0.2kg/m2). Participants were randomized to a five-week intervention that consisted of ad libitum diets in which usual starch intake was replaced by either low- or high-GI starch. The subjects received individual guidance by a trained clinical dietitian during the pre-inclusion period, on day one and at the end of week three (day 21). Part of the starches were provided for both groups throughout the study. Subjects were asked to consume the same amount of starch as usual and change only the type of starch. They were also asked not to modify their usual dietary habits. The difference in mean GI between the low- and high-GI groups was significant after five weeks of treatment (P<0.0001). There was NS difference in glycemic load (GL) between the two groups after five weeks of intervention. After the five-week intervention, body weight and BMI were significantly decreased in the low-GI group [-1.1 (SEM, 0.3) kg, P=0.004 and -0.4 (SEM 0.1) kg/m^2, P=0.005, respectively], while NS changes were reported in the high-GI group [-0.2 (SEM, 0.2) kg, P=0.41 and -0.1 (SEM, 0.1) kg/m^2, P=0.39, respectively]. Differences between groups for body weight and BMI were significant (P=0.04 and P=0.03, respectively). The authors concluded that low-GI diets may be beneficial on body weight regulation.

Deierlein, 2008 (positive quality), a prospective cohort study in the US, examined whether total gestational weight gain or weight gain ratio (observed weight gain/expected weight gain) was associated with glycemic load (GL) in pregnant women from the third cohort of the Pregnancy, Infection, and Nutrition Study. Participants were 1,231 women carrying a singleton fetus (75% white, 64% were 25 to 34 years at conception). Using self-reported body weight prior to pregnancy to calculate BMI, 14.3% were underweight, 53.0% were normal weight, 10.2% were overweight and 22.5% were obese. Dietary intake was assessed at 26 to 29 weeks of gestation with a 100-item food-frequency questionnaire (FFQ) modified to include local foods. Body weight was measured near the time of delivery. Weight gain during pregnancy was inadequate in 13.6% of women, adequate in 22.2% and excessive in 64.2%. Glycemic load was not associated with total gestational weight gain or weight gain ratio.

Ebbeling, 2007 (positive quality), an RCT in the US, examined the impact of low-glycemic load (GL) (40% CHO and 35% fat) vs. low-fat (55% CHO and 20% fat) diets on weight loss among obese young adults (aged 18 to 35 years, 79% female, N=73). The interventions included a six-month intensive intervention period and 12-month follow-up period. There were 23 group workshops, one private counseling session and five motivational phone calls. Participants in the low-GL diet group were counseled to consume low-glycemic foods and limit high-glycemic foods. Participants in the low-fat diet group were counseled to consume low-fat grains, fruits and legumes and to limit intake of added fats, sweets and high-fat snacks. Dietary intake was assessed with telephone-administered 24-hour recalls and body weight was measured throughout the study period. A significant decrease in GL was observed in the low-GL diet group, and a significant decrease in total and saturated fat intake were observed for the low-fat diet group. Weight loss did not differ between diet groups for the full cohort of 73 participants (P=0.99). For those with a low insulin concentration at 30 minutes after a 75g dose of oral glucose, both diets produced similar results. However, for those with a high insulin concentration at 30 minutes, the low-GL diet was more effective for weight loss. For those with high insulin, the low-GL group lost weight more rapidly during the six months of intensive intervention (-1.0 vs. -0.4kg per month; P<0.001) and achieved greater overall weight loss at 18 months (–5.8 vs. –1.2kg; P=0.004) compared with the low-fat group. In addition, there was no weight regain after six months for participants

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with high insulin who were assigned the low-GL diet. The authors concluded that variability in dietary weight loss trials may be partially explained by differences in hormonal response.

Hare-Bruun, 2006 (positive quality), a prospective cohort study in Denmark, investigated the relation between glycemic index (GI) and glycemic load (GL) on subsequent six-year changes in body weight in a subsample of 376 men (N=185) and women (N=191) from the Danish arm of the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study. Participants completed a baseline health exam in 1982, a health exam and diet survey in 1987 to 1988 and a follow-up health exam in 1993 to 1994. Dietary intake was assessed with a diet history interview by a dietitian. No significant associations between GL and change in body weight were observed for men or women. No significant association between GI and change in body weight was observed for men. Among women, GI was positively associated with changes in body weight in adjusted analyses (P<0.04). In six years, values per 10-unit increase in baseline GI increased by 2% (95% CI: 0.1, 4%) for body weight. In sedentary women, values per 10-unit increase in baseline GI rose by 6% (95% CI: 2, 9%; P=0.001) for body weight. The authors concluded that there may be sex differences in the associations between GI and body weight. In addition, physical activity may protect against diet-induced weight gain in women.

Hui, 2006 (neutral quality), a cross-sectional study in Hong Kong, investigated whether meal glycemic load (GL) was associated with childhood overweight. Participants were 316 children (6.7 0.3 years) identified by study methodology as overweight (N=121), middle-weight (N=130) and low-weight (N=65). Children were recruited in 2000 when they attended one of 12 Student Health Service Centers of the Department of Health. Weight and height were measured at the health centers. Three-day dietary records were completed prior to a home interview. Meal GL was the sum of the GLs of all food eaten in each meal (breakfast, lunch and dinner). Using adjusted logistic regression, meal GL was not NS associated with childhood overweight after adjusting for parental obesity, birth weight, sleeping duration, mean energy intake and paternal smoking. The authors concluded that meal GL was not an independent factor associated with childhood overweight in children aged six to seven years.

Lau, 2006 (neutral-quality), a cross-sectional study in Denmark, examined the associations between glycemic index (GI), glycemic load (GL) and BMI in 6,334 adults [mean (SD) age: 46.1 (7.8) years and BMI: 26.2 (4.6) kg/m^2] from the Inter99 study. A secondary purpose was to examine the effect of low energy reporters (LERs) on these relationships. Data was collected in 1999 and 2000 from participants of the Inter99 study who were eligible and agreed to participate. Dietary intake over the previous month was estimated with 198-item FFQ. Height and weight were measured. 24.7% of the study population were classified as LERs. In the univariate analyses of the entire population, GL was inversely associated with BMI (P<0.001). No association was observed for GI. After full adjustment including adjustment for energy intake, both GI and GL were positively associated with BMI (P=0.017 and P<0.001, respectively). When LERs were excluded, GL was positively associated with BMI in all analyses and GI was positively associated with BMI in the multiple analyses. The authors concluded that both GI and GL were positively associated with BMI when energy adjustment or LERs were considered.

Liese, 2005 (neutral quality), a cross-sectional study at four centers in the US, Canada and Germany, studied the association between glycemic index (GI) and glycemic load

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(GL) with BMI in 979 participants [54.9% female, mean (SD) age: 54.8 (8.5) years and BMI: 28.4 (5.6) kg/m^2] from the Insulin Resistance Atherosclerosis Study (1992 to 1994). Usual intake of diet was assessed by interview using a one-year, semi-quantitative, 114-item FFQ designed to include regional and ethnic food choices. Height and weight were measured. No association of GI with BMI was observed by linear regression analysis. Adjustment for relevant confounders including energy intake did not impact the results. Additional adjustment for fiber intake also had no impact on results. A significant, positive relationship between GL and BMI was observed. This association was present both in the crude models and after multivariate adjustment. Adjusting for total energy intake from non-CHO sources entirely explained the association. After additional adjustment for fiber intake, no association with BMI was observed. The authors concluded that GI was not associated with BMI. Although GL was positively associated with BMI, this association was explained entirely by confounding due to correlated energy intake.

Maki, 2007 (positive quality), an RCT in the US, examined the effects of an ad libitum reduced-glycemic load (GL) diet on body weight in 86 overweight and obese adults (67% female, mean age of 50 years, mean BMI approximately 32kg/m^2). Participants were randomly assigned to a reduced-GL diet or a low-fat, portion-controlled diet. The two-arm parallel design trial included a 12-week weight-loss phase followed by a weight-loss maintenance phase during weeks 24 to 36. The reduced GL diet group lost significantly more weight than the control group at week 12 (-4.9 and -2.5kg, respectively; P=0.002), but the two groups did not differ significantly at week 36 (-4.5 and -2.6kg, respectively; P=0.085). At week 12, 24 subjects (55%) in the reduced GL group and nine subjects (21%) in the control group had achieved a loss of 5% or more of body weight (P=0.002), but the two groups did not differ significantly at week 36 (45% and 29%, respectively; P=0.114). The authors concluded that a reduced GL diet is a reasonable alternative to a low-fat, portion-controlled diet for weight management.

McMillan-Price, 2006 (positive quality), a randomized trial in Australia, compared the effects of low-glycemic index (GI) and high-PRO diets on weight loss. Participants were 129 young adults (76% female, 18 to 40 years at baseline) with a BMI of 25kg/m^2 or more. Participants were stratified according to weight and sex and randomized to one of four diets for 12 weeks. Diets one and two were high CHO (55% of energy intake), with high- and low-GI, respectively; diets three and four were high PRO (25% of energy intake), with high- and low-GI, respectively. Glycemic load (GL) was highest in diet one and lowest in diet four. Analysis of food diaries indicated that all four groups achieved their intended CHO and PRO distributions and there was NS difference in energy intake between groups (P=0.41). The four groups lost a similar percentage of body weight (mean±SE percentage: diet one, −4.2%±0.6%; diet two, −5.5%±0.5%; diet three, −6.2%±0.4%; and diet four, −4.8%±0.7%; P=0.09). The findings were similar among those with high fasting insulin or triglyceride (TG) levels. There was a significant difference in the proportion of individuals who lost 5% or more of their initial body weight: 31% of subjects on diet one, 56% on diet two, 66% on diet three and 33% on diet 4 (P=0.01). The authors concluded that both high-PRO and low-GI patterns promote weight loss.

Mendez, 2009 (neutral quality), a cross-sectional study in Spain, examined the associations between glycemic index (GI) and glycemic load (GL) and BMI in a Mediterranean population. Participants were 7,670 adults (52% female, 35 to 74 years

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of age) who completed population-based cross-sectional surveys in 2000 and 2005. The same standard methods were used for both surveys. A self-administered, validated 165-item FFQ was used to estimate dietary intake. Height and weight were measured. Glycemic index was not associated with BMI in any model. To take into account interactions with under-reporting (interaction P<0.001 for both sexes), associations between BMI and GL were stratified by this variable. Among plausible reporters, multivariate-adjusted associations between BMI and dietary GL were null before adjusting for energy (P>0.05 for both sexes). After adjusting for energy, GL was associated with significant (P<0.05) declines in BMI. The adjusted mean difference in BMI between the highest and lowest GL tertile was -0.71kg/m^2 (P<0.05) for women and -0.43kg/m^2 (P<0.10) for men. Among under-reporters, there was a positive relation between BMI and GL (P<0.002 for men, P=0.178 for women) in models excluding energy intakes. After adjusting for energy intakes, these associations were substantially attenuated, and associations with dietary GL became null or inverse. The authors concluded that their study does not support the hypothesis that high GI or GL is positively related to obesity; in contrast, in a Mediterranean food culture, a diet characterized by a higher GL may be associated with a lower BMI.

Milton, 2007 (neutral quality), a cross-sectional study in the United Kingdom, examined if low-dietary glycemic index (GI) was associated with lower body weight or BMI in 1,152 adults aged 65 years and older who were part of the National Diet and Nutrition Survey. A total of 50.5% of participants were males with mean (SD) age of 75.9 (7.0) years and BMI of 26.3 (3.6) kg/m^2. A total of 49.5% of participants were females with mean (SD) age of 77.6 (8.0) years and BMI of 26.6 (4.8) kg/m^2. Participants completed two four-day weighed dietary records. Body weight and height were measured by study personnel in the home of the participant. No significant relationships were observed for GI and body weight or BMI. The authors concluded that the study does not support advising the consumption of a low-GI diet to prevent weight gain in the elderly.

Murakami, 2007 (neutral quality), a cross-sectional study in Japan, examined the association between dietary glycemic index (GI) and glycemic load (GL) with BMI in Japanese women. Participants were freshman students (N=3,931) in dietetic course from 53 institutions in Japan who completed validated, self-administered, diet history questionnaires. Body weight and height were self-reported. Dietary GI and GL were independently positively correlated with BMI (20.8 and 21.2kg/m^2; P=0.03, and 20.5 and 21.5kg/m^2; P=0.0005, respectively) after controlling for potential confounders. The authors concluded that GI and GL were positively correlated with BMI in this study of relatively lean Japanese women aged 18 to 20 years.

Nielsen, 2005 (neutral quality), a cross-sectional study in Denmark, examined the associations between dietary glycemic index (GI) and glycemic load (GL) with BMI in 849 Danish children aged 10 (54% girls) and 16 (50% girls) years who were part of the European Youth Heart Study. Dietary intake were obtained through a 24-hour recall supported by a qualitative food record. Body weight and height were measured. Associations between energy-adjusted dietary GI or GL and BMI were NS among each group of age and gender.

Pal, 2008 (neutral quality), a randomized trial in Australia, investigated whether altering the glycemic index (GI) of one meal (breakfast) for 21 days in obese individuals would have a favorable effect on body weight and other outcomes. Participants were 21 overweight or obese adults (five men, 16 women) aged 25 to 65 years. A

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randomized cross-over trial with two three-week interventions separated by a three-week washout period was used. Breakfast meals of either low GI or high GI were provided to participants. Subjects consumed breakfast at 8:30 a.m. and usual lunch at 12:30 p.m. Subjects were instructed to maintain their habitual intakes for the other meals (ad libitum). Both breakfast meals provided the same energy, PRO, fat and CHO values within 6%. Total daily energy intake was not different between the groups (P=0.45). Body weight was similar at the end of the low and high-GI breakfast interventions (mean±SEM: 84.34±4.88kg vs. 84.25±4.43kg, respectively; P=0.614). This study found that modifying GI in a single meal (i.e., breakfast) alone did not impact body weight in overweight and obese adults.

Pereira, 2004 (positive quality), a randomized trial in the US, examined whether dietary glycemic load (GL) would influence rate of weight loss and other parameters during an energy-restricted diet program. Participants were 39 overweight or obese young adults aged 18 to 40 years who received an energy-restricted diet, either low-GL or low-fat. During a nine-day run-in period, all subjects were given a standard weight-maintaining diet and then were admitted to a metabolic unit for three days to obtain baseline measurements. At discharge, participants began diets, providing 60% of predicted energy requirements. After a 10% reduction in body weight during a six- to 10-week period, subjects were readmitted for five days to obtain final measurements of study end points. All food was prepared in a metabolic kitchen. Subjects were required to eat only the food provided and to consume one meal (lunch) onsite Monday through Friday. All other food was provided as take-home meals. Dietitians provided behavioral support daily. Weight loss and percent weight loss for the low-GL and low-fat diets were similar. Individual rates of weight loss were NS greater in the low-GL compared with the low-fat group [mean (SE): 1.09 (0.05) and 0.99 (0.05) kg per week, respectively; P=0.19].

Philippou, 2009 (neutral quality), a randomized trial in the United Kingdom, examined the effect of manipulating glycemic index (GI) on body weight maintenance following weight loss in 43 overweight adults. This study represents the second phase of a weight-loss study. The first phase included a weight-loss program. Participants who lost at least 5% of their initial body weight (median = 6.1%) were randomized to a four-month weight maintenance phase with a high- or low-glycemic diet. Participants in the high-glycemic group were asked to include at least one high-glycemic food with each of their meals and snacks. Similarly, participants in the low-glycemic group were asked to include at least one low-glycemic food with each of their meals and snacks. Subjects were encouraged to eat until satisfied and to follow healthy eating guidelines. Dietary composition differed only in GI (63.7±9.4 vs. 49.7±5.7, for high- and low-glycemic diets, respectively; P<0.001) and GL (136.8±56.3 vs. 89.7±27.5, for high- and low-glycemic diets, respectively; P<0.001). There was no difference in body weight change over four months between the high- and low-glycemic index groups (0.3±1.9kgvs. -0.7±2.9kg, respectively, P=0.3). The authors concluded that manipulating GI does not appear to significantly affect weight maintenance.

Pittas, 2006 (positive quality), a randomized trial in the US, examined whether two calorie-restricted diets that differ in glycemic load (GL) would have differential effects on weight loss. Participants were 32 overweight adults (78% female, predominantly white, mean age of 34.6 years, mean BMI of 27.5kg/m^2). After a seven-week baseline period, when usual energy requirements for weight stability were measured, subjects were randomized for 24 weeks to either a high-GL diet or a low-GL diet. Both diets

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provided 30% calorie restriction compared with individual baseline weight maintenance energy requirements. All food was provided during the six months by the research center. Subjects were expected to consume only this food; however, they were to report additional foods or drinks if they were eaten. Subjects attended regular behavioral group meetings and individual sessions with a dietitian. At three months and six months, both groups achieved statistically significant (P<0.001) weight loss compared with their baseline weight. Adjusted for baseline weight, weight loss was 7.2kg in the high-GL group vs. 7.7kg in the low-GL group at six months (P=0.69). Healthy overweight individuals lost similar weight during calorie-restricted diets of varying GL.

Raatz, 2005 (neutral quality), a randomized trial in the US, examined whether a hypocaloric diet with reduced glycemic load (GL) and glycemic index (GI) would result in greater sustained weight loss in 29 obese men and women. This study included a three-arm parallel-design randomized 12-week controlled feeding trial with a 24-week follow-up phase. Participants were randomized to one of three energy-restricted diets that varied in macronutrient content, GI and GL: high-GI diet, low-GI diet and high-fat diet. During weeks one to 12 (feeding phase), subjects consumed individualized energy-restricted diets to promote a weight loss of 0.70kg per week. All meals were prepared in a metabolic kitchen. Subjects were required to consume all food provided and no foods other than those provided. During weeks 13 to 24 (free-living phase), diet assignment was maintained, but subjects prepared their own meals. Subjects were given intensive dietary instruction and had nutritional counseling every two weeks. Each diet group lost weight during the 12-week feeding phase (P<0.001), but the amount lost did not differ among the groups (mean±SEM: -9.3±1.3kg for the high-GI diet, -9.9±1.4kg for the low-GI diet, and -8.4±1.5kg for the high-fat diet). Weight loss achieved during the first 12 weeks were maintained in all three groups at week 36 and these values did not differ among the groups. The authors concluded that energy restriction over a 36-week period promotes weight loss in obese adults, irrespective of diet composition. A reduced GI and GL diet did not enhance weight loss relative to the other diets.

Sichieri, 2007 (neutral quality), a randomized trial in Brazil, investigated the long-term effect of a low glycemic index (GI) diet compared with that of a high-GI diet on weight change in 203 women aged 25 to 45 years with a BMI between 23 and 29.9kg/m^2. This study consisted of an 18-month randomized trial with a six-week run-in period. The run-in period, consisted of two weeks of a low-GI diet followed by four weeks of a high-GI diet. Those who completed the run-in period (203 of 414 recruited) were randomized to a low-GI diet or a high-GI diet. Dietary counseling was based on a small energy restriction (100 to 300kcal), and skipping the diet one day a week was permitted. Subjects were instructed to eat three meals and three snacks according to a six-day menu plan. Nutritional counseling was provided monthly. Both diets were designed with 26% to 28% of energy as fat. For each meal, the low-GI diets were designed to maintain an average difference of 40 units compared with the high-GI diet. Sixty percent of participants completed the study. The difference in GI between the diets was approximately 35 to 40 units (40 compared with 79) during all 18 months of follow-up. The low-GI group had a slightly greater weight loss in the first two months of follow-up (-0.72 compared with -0.31kg), but after 12 months of follow-up, both groups began to regain weight. After 18 months, the weight change was NS different (P=0.93) between groups (-0.41 vs. -0.26kg for low- and high-GI diets, respectively). The authors concluded that their results do not support the hypothesis that a low-GI diet

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improves weight loss success.

Sloth, 2004 (positive quality), a randomized trial in Denmark, investigated the effects of a 10-week low-fat, high-CHO diet with either low-glycemic index (GI) or high-GI on body weight. Participants were 45 healthy, overweight women between 20 and 40 years of age. The 10-week parallel, randomized intervention trial consisted of two matched groups. Energy requirements were calculated and subjects were categorized and assigned to test food intakes of different levels. Groups received either low-GI or high-GI foods in replacement of their usual CHO-rich foods. Subjects were also instructed to eat a diet with 20% to 30% of energy from fat, and a list with other CHO-rich foods was given to participants so they could monitor the GI of the foods they ate during the study. Participants could eat ad libitum of their own diet in addition to the test foods. There was a significant decrease in energy intake over time, but there were NS differences between groups. Self-reported data from the food diaries indicated that subjects ate 95% of the amounts of test foods they were requested to eat. Body weight significantly decreased over time for both groups, but the differences were NS between the groups [mean (SEM): -1.9 (0.5) kg and -1.3 (0.3) kg for the low- and high-GI diets, respectively). The authors concluded that the study does not support the hypothesis that low-fat, low-GI diets are more beneficial than high-GI diets with regard to body weight regulation as evaluated over 10 weeks.

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Overview table

Author, Year, Study Design, Class, Rating	Population/Subjects	Methodology	Significant Outcomes
Abete I, Parra D et al, 2008 Study Design: Randomized controlled trial Class: A Neutral Quality	N=32 (14 female, 18 male). Mean (SD) age: 36 (seven) years. Mean (SD) BMI: 32.5 (4.3) kg/m^2. Location: Spain.	Eight-week randomized trial of two energy-restricted diets with higher or lower GI with obese participants. Subjects randomly assigned to high- or lower-GI energy-restricted diets, both with 53% of energy as CHO, 17% as PRO and 30% as fats. Participants individually instructed to follow prescribed dietary regime for eight consecutive weeks by a trained dietitian within a strict dietary framework; repeated on a three-day rotation basis. Subjects asked to maintain same habitual physical activity during intervention. Low-GI diet: 84% of CHO from pasta and legumes; GI of 40 to 45 units. High-GI diet: 84% of CHO from rice and potatoes; GI of 60 to 65 units. Weight loss monitored weekly by a dietitian; additional values obtained at baseline (day zero) and at endpoint (day 56). Three-day weighted food records for information about baseline intake and adherence to prescribed diet.	Body weight and BMI were significantly ↓ in both groups (P<0.05), being greater in the lower-GI group. Percent Δ (SD) [eight-week follow-up vs. baseline] for the high and low-GI diet interventions: Weight (kg): -5.3 (2.6) and -7.5 (2.9) higher vs. lower GI diet, respectively (P-value for difference in %Δ between groups = 0.033) BMI (kg/m^2): -5.4 (2.5) and -7.6 (3.0) higher vs. lower GI diet, respectively (P-value for difference in %Δ between groups = 0.030).

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Aston LM, Stokes CS et al, 2008 Study Design: Randomized controlled trial Class: A Neutral Quality	N=19 women. Mean (SD) age: 51.9 (7.6) years (range 34 to 65). Mean (SD) BMI: 33.1 (4.9) kg/m^2. Location: United Kingdom.	Randomized cross-over intervention with two consecutive 12-week periods. Subjects provided with lower or higher GI versions of key 'staple' CHO-rich foods, according to intervention period, to incorporate into habitual diet. Provided foods included breads, breakfast cereals and rice, plus pasta on the lower GI diet and potatoes during the higher GI period. 'Low' and 'high' GI foods had mean difference of 28.5 units. Subjects instructed to maintain their habitual diets for duration of study, but to substitute supplied foods into their diets on at least three occasions per day in the quantity they would normally consume. Subjects kept four-day diet diaries at baseline and during final week of each intervention period	No difference in body weight between intervention periods. Weight ↑ during both intervention periods, although weight gain did not differ between treatments. Mean (SD) Δ in body weight in the low- and high-GI treatments were 1.1 (1.5)kg and 1.4 (1.7)kg, respectively (P=0.7). All subjects ↓ dietary GI on lower GI diet compared with higher GI diet, with mean difference of 8.4 units (P<0.001). GL was NS ↓ on the low-GI diet, due to a small ↑ in CHO intake.

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de Rougemont A, Normand S et al, 2007 Study Design: Randomized Controlled Trial Class: A Positive Quality	N=38 (20 males, 18 females). Mean (SEM) age: 36.3 (2.0) years for low-GI group and 40.4 (2.2) years for high-GI group. Mean (SEM) BMI: 27.3 (0.2)kg/m^2. Location: France.	Five-week randomized, parallel two-arm trial. Five-week intervention consisted of ad libitum diets in which usual starch intake was replaced by either low- or high-GI starch. Subjects received individual guidance by a trained clinical dietitian during the pre-inclusion period, on day one and at end of week three (day 21). Part of the starches were provided for both groups throughout the study. Subjects asked to consume same amount of starch as usual and Δ only the type of starch; Also asked not to modify their usual dietary habits. Low-GI diet: Included foods with GI <50 (relative to glucose). High-GI diet: Included foods with GI >70. Subjects instructed to record amount of food/beverages eaten each day using a five-day food diary during the pre-inclusion period (day 1 to day 7) and in weeks three (day 16 to day 20) and five (day 31 to day 35).	After the five-week intervention, body weight and BMI significantly ↓ in the low-GI group (-1.1 (SEM 0.3) kg, P=0.004 and -0.4 (SEM 0.1) kg/m^2, P=0.005, respectively), while NS Δ were reported in the high-GI group (-0.2 (SEM 0.2) kg, P=0.41 and -0.1 (SEM 0.1) kg/m^2, P=0.39, respectively). Differences between groups for body weight and BMI were significant (P=0.04 and P=0.03, respectively). NS differences in GI and GL between groups at baseline. After the five-week intervention, all subjects in the low-GI group reached the defined low-GI target with a significant ↓ in mean GI after five weeks of diet. In the high-GI group, the defined high-GI target was not reached. Difference in mean GI between the low- and high-GI groups was significant after five weeks of treatment (P<0.0001). GL ↓ in the low-GI group [-2•1 (SEM 0•6), P=0.002], but did not Δ in the high-GI group. NS difference in GL between the two groups after five weeks of intervention.

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Deierlein AL, Siega-Riz AM et al, 2008 Study Design: Prospective cohort Class: B Positive Quality	N=1,231 women carrying a singleton fetus from the third cohort of the Pregnancy, Infection, and Nutrition Study. Age at conception: 16 to 24 years (18.6%), 25 to 29 years (28.8%), 30 to 34 years (35.6%), 35 to 47 years (17.0%). Pregravid BMI: 14.3% underweight, 53.0% normal weight, 10.2% overweight, 22.5% obese. Ethnicity: White (74.5%), black (16.2%), other (9.3%). Location: United States.	Participants recruited between January 1, 2001 through June 30, 2005. Dietary intake assessed at 26 to 29 weeks of gestation with a 100-item FFQ modified to include local foods. Body weight measured near the time of delivery and pre-pregnancy weight self-reported. Gestational weight gain: Difference between pregravid weight (self-reported) and weight measured near the time of delivery. Weight gain ratio: Observed total weight gain over expected total weight gain up until the last prenatal visit using weight gain recommendations from the 1990 Institute of Medicine report.	Weight gain during pregnancy was inadequate in 13.6% of women, adequate in 22.2% and excessive in 64.2%. GL was not associated with total gestational weight gain or weight gain ratio.

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Ebbeling CB, Leidig MM et al, 2007 Study Design: Randomized controlled trial Class: A Positive Quality	N=73 (15 males, 58 females). Age: 18 to 35 years. Obese. Location: United States.	RCT with a six-month intensive intervention period and 12-month follow-up period. N=23 group workshops, one private counseling session and five motivational phone calls. Low-GL diet: Participants counseled to consume low-glycemic foods and limit high-glycemic foods. Target macronutrient composition: 40% of energy from CHO, 35% from fat and 25% from PRO. Low-fat diet: Participants counseled to consume low-fat grains, fruits and legumes and to limit intake of added fats, sweets and high-fat snacks. Target macronutrient composition: 55% of energy from CHO, 20% from fat and 25% from PRO. Diets prescribed using ad-libitum approach. Participants advised to acknowledge hunger and satiety cues. Physical activity recommendations based on public health guidelines. Three telephone-administered 24-hour recall interviews (two weekdays and one weekend day) conducted at baseline and six, 12 and 18 months to assess diet. Body weight measured at baseline and weeks one, two, four, five, six, 10, 14, 17, 21 and 26; then every four weeks through week 74.	Weight loss did not differ between diet groups for the full cohort of 73 participants (P=0.99). For those with a low insulin concentration at 30 minutes after a 75g dose of oral glucose, both diets produced similar results. However, for those with a high insulin concentration at 30 minutes, the low-GL diet was more effective for weight loss. For those with high insulin, the low-GL group lost weight more rapidly during the six months of intensive intervention (-1.0 vs. –0.4kg per month; P<0.001) and achieved greater overall weight loss at 18 months (-5.8 vs. -1.2kg; P=0.004) compared with the low-fat group. In addition, there was no weight regain after six months for participants with high insulin who were assigned the low-GL diet. Low-GL diet: GI and CHO intake ↓, resulting in a significant ↓ in GL [mean (SE), -19.8 [2.5] g per 1,000kcal; P<0.001]. Low-fat diet: Total fat intake ↓ [mean (SE), -10.8% (1.3%) of energy; P<0.001] and saturated fat intake ↓ [mean (SE), -4.5% (0.6%) of energy; P<0.001].

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Hare-Bruun H, Flint A et al, 2006 Study Design: Prospective Cohort Study Class: B Positive Quality	N=376 men (N=185) and women (N=191) from the Danish arm of the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study. Age: 30 to 60 years at baseline. Location: Denmark.	Participants completed baseline health exam in 1982, health exam and diet survey in 1987 to 1988 and follow-up health exam in 1993 to 1994. Body weight measured by study personnel. Dietary intake assessed with a diet history interview by a dietitian. Average daily intake was based on intakes during the previous month.	NS associations between GL and Δ in body weight observed for men or women. NS association between GI and Δ in body weight observed for men. Among women, GI was positively associated with Δ in body weight in adjusted analyses (P<0.04). In six years, values per 10-unit ↑ in baseline GI ↑ by 2% (95% CI: 0.1, 4%) for body weight. In sedentary women, values per 10-unit ↑ in baseline GI ↑ by 6% (95% CI: 2, 9%; P=0.001) for body weight.
Hui LL and Nelson EA, 2006 Study Design: Case Control Study Class: C Neutral Quality	N=316 children. Age: Mean (SD) 6.7 (0.3) years. Overweight (N=121), middle weight (N=130), low weight (N=65). Location: Hong Kong.	Children recruited in 2000 when they attended one of 12 Student Health Service Centers of the Department of Health. Weight and height measured at the health centers. Three-day dietary records completed prior to home interview. Meal GL: The sum of the GLs of all food eaten in each meal (breakfast, lunch and dinner). Using data from a local cross-sectional growth survey, three weight groups were identified for study purposes: Overweight group (≥92nd percentile for BMI) Middle-weight group (45th to 55th percentile for BMI) Low-weight group (≤8th percentile for BMI).	Using adjusted logistic regression, meal GL was NS associated with childhood overweight after adjusting for parental obesity, birth weight, sleeping duration, mean energy intake and paternal smoking. Adjusted ORs for overweight by meal GL for the highest vs. lowest tertile was 1.08 (95% CI: 0.52, 2.26; P=0.83).

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Lau C, Toft U et al, 2006 Study Design: Cross-Sectional Study Class: D Neutral Quality	N=6,334 men and women from the Danish population-based Inter99 study. Mean (SD) age: 46.1 (7.8) years. Mean (SD) BMI: 26.2 (4.6) kg/m^2. Location: Denmark.	Data collected in 1999 and 2000 from participants of the Inter99 study who were eligible and agreed to participate. Dietary intake over the previous month estimated with 198-item FFQ. Height and weight measured.	24.7% of study population were classified as low energy reporters (LERs) In the univariate analyses of entire population, GL was inversely associated with BMI (P<0.001). No association observed for GI. After full adjustment including adjustment for energy intake, both GI and GL were positively associated with BMI (P=0.017 and P<0.001, respectively). When LERs were excluded, GL was positively associated with BMI in all analyses and GI positively associated with BMI in the multiple analyses.
Liese A, Schulz M et al, 2005 Study Design: Cross-sectional study Class: D Neutral Quality	N=979 adults (54.9% female) from the Insulin Resistance Atherosclerosis Study. Mean (SD) age: 54.8 (8.5) years. Mean (SD) BMI: 28.4 (5.6) kg/m^2. Ethnicity: 39.8% non-Hispanic white, 34.2% Hispanic and 26.0% African American. Location: United States, Germany, Canada.	Cross-sectional study of participants from the Insulin Resistance Atherosclerosis Study (1992 to 1994). Usual intake of diet assessed by interview using a one-year, semi-quantitative, 114-item FFQ designed to include regional and ethnic food choices. Height and weight were measured.	No association of GI with BMI was observed by linear regression analysis. Adjustment for relevant confounders including energy intake did not impact the results. Additional adjustment for fiber intake also had no impact on results. A significant, positive relationship between GL and BMI was observed. Association present, both in the crude models and after multivariate adjustment. Adjusting for total energy intake from non-CHO sources entirely explained the association. After additional adjustment for fiber intake, no association with BMI observed.

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Maki KC, Rains TM et al, 2007 Study Design: Randomized Controlled Trial Class: A Positive Quality	N=86 adults (67% female). Mean age: 50 years. Mean BMI: ~32kg/m^2; 67% obese. 52% non-Hispanic white, 35% African American, 8% Hispanic, 5% other. Location: United States.	Two-arm (reduced-GL diet or low-fat, portion-controlled diet) parallel design randomized trial. 12-week weight-loss phase followed by weight-loss maintenance phase during weeks 24 to 36. Reduced GL group instructed to eat three meals a day until satisfied, maintaining a low-CHO intake during weeks zero to two and adding low-GI foods thereafter. Control subjects instructed to ↓ fat intake and ↓ portion sizes to produce a target energy deficit of 500 to 800kcal per day.	Reduced GL diet group lost significantly more weight than control group at week 12 (-4.9 and -2.5kg, respectively; P=0.002), but the two groups did not differ significantly at week 36 (-4.5 and -2.6kg, respectively; P=0.085). At week 12, 24 subjects (55%) in the reduced GL group and nine subjects (21%) in the control group had achieved a loss of ≥5% of body weight (P=0.002), but the two groups did not differ significantly at week 36 (45% and 29%, respectively; P=0.114).

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McMillan-Price J, Petocz P et al, 2006 Study Design: Randomized Controlled Trial Class: A Positive Quality	N=129 (31 males, 98 females). Age: 18 to 40 years at baseline. BMI: ≥25kg/m^2 at baseline. Location: Australia.	Participants stratified according to weight and sex and randomized to one of four diets for 12 weeks. Participants were given diet plans that were devised to aid weight loss and had similar daily caloric (1,400kcal for women; 1,900kcal for men), dairy, fat (30% total energy intake), type of fat consumed (saturated, unsaturated) and fiber (30g a day) intake. Participants given instructions regarding appropriate food choices within their plan. Participants met weekly with dietitians; Key CHO, PRO and some prepared foods were provided. Diet 1: High CHO (55% total energy intake), high-GL, average PRO (15% total energy). Diet 2: High CHO (55% total energy intake), low-GL, average PRO (15% total energy). Diet 3: High PRO (25% total energy intake based on lean red meats), high-GL based on whole grains, reduced CHO (45% total energy). Diet 4: High PRO (25% total energy intake), low-GL, reduced CHO (45% total energy). GL highest in diet one and lowest in diet four. Body weight measured weekly.	The four groups lost a similar percentage of body weight (mean±SE %: diet one, -4.2%±0.6%; diet two, -5.5%±0.5%; diet three, -6.2%±0.4%; and diet four, -4.8%±0.7%; P=0.09). Findings were similar among those with high fasting insulin levels [6μIU or more per ml (110pmol or more per L), N=37] or high fasting TG levels [133mg or more per dL (1.5mmol or more per L), N=38]. Significant difference in the proportion of individuals who lost ≥5% of initial body weight: 31% of subjects on diet one, 56% on diet two, 66% on diet three and 33% on diet four (P=0.01). Analysis of food diaries indicated that all four groups achieved their intended CHO and PRO distributions and there was NS difference in energy intake (P=0.41).

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Mendez MA, Covas MI et al, 2009 Study Design: Cross-Sectional Study Class: D Neutral Quality	N=7,670 adults (52% female). Age: 35 to 74 years. Location: Spain.	Analysis of two population-based cross-sectional surveys collected in 2000 and 2005. Same standard methods were used for both surveys. Self-administered, validated 165-item FFQ used to estimate dietary intake. Height and weight measured.	GI not associated with BMI in any model. To take into account interactions with under-reporting (interaction P<0.001 for both sexes), associations between BMI and GL were stratified by this variable. Among plausible reporters, multivariate-adjusted associations between BMI and dietary GL were null before adjusting for energy (P>0.05 for both sexes). After adjusting for energy, GL was associated with significant (P<0.05) ↓ in BMI. Adjusted mean difference in BMI between the highest and lowest GL tertile was 0.71kg/m^2 (P<0.05) for women and -0.43kg/m^2 (P<0.10) for men. Among under-reporters, there was a positive relation between BMI and GL (P<0.002 for men, P=0.178 for women) in models excluding energy intakes. After adjusting for energy intakes, these associations were substantially attenuated and associations with dietary GL became null or inverse.

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Milton JE, Briche B et al, 2007 Study Design: Cross-Sectional Study Class: D Neutral Quality	N=1.152 (50.5% male). Mean (SD) age: Males, 75.9 (7.0) years; females,- 77.6 (8.0) years. Mean (SD) BMI: Males,- 26.3 (3.6) kg/m^2; females, 26.6 (4.8) kg/m^2. Location: United Kingdom.	Participants were part of the National Diet and Nutrition Survey, a cross-sectional survey that collected data on dietary habits and nutritional status. Two four-day weighed dietary records were completed. Height and weight measured by study personnel in participant's home.	NS relationships were observed for GI and body weight or BMI.
Murakami K, Sasaki S et al, 2007 Study Design: Cross-Sectional Study Class: D Neutral Quality	N=3,931 females. Mean (SD) age: 18.1 (0.3) years. Mean (SD) BMI: 21.0 (2.8) kg/m^2. Location: Japan.	Freshman students in dietetic course from 53 institutions in Japan. Dietary intake assessed by validated, self-administered, diet history questionnaire. Body weight and height self-reported.	Dietary GI and GL were independently positively correlated with BMI after controlling for potential confounders. Lowest vs. highest quintile for GI: 20.8 and 21.2kg/m^2; P=0.03. Lowest vs. highest quintile for GL: 20.5 and 21.5kg/m^2; P=0.0005.
Nielsen BM, Bjornsbo KS et al, 2005 Study Design: Cross-Sectional Study Class: D Neutral Quality	N=849 children aged 10 and 16 years from the European Youth Heart Study: 10-year-old girls (N=262, median BMI=16.7kg/m^2) 10-year-old boys (N=223, median BMI=16.7kg/m^2) 16-year-old girls (N=183, median BMI=20.6kg/m^2) 16-year-old boys (N=181, median BMI=20.5kg/m^2). Location: Denmark.	Dietary intake obtained through a 24-hour recall supported by a qualitative food record. Body weight and height measured.	Associations between energy-adjusted dietary GI or GL and BMI were NS among each group of age and gender.

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Pal S, Lim S et al, 2008 Study Design: Randomized Controlled Trial Class: A Neutral Quality	N=21 adults (five men, 16 women). Age: 25 to 65 years. Overweight or obese. Location: Australia.	Randomized cross-over trial with two three-week interventions separated by a three-week washout period. Interventions: Breakfast meals of either low-GI or high-GI were provided to participants. Subjects consumed a low- or high-GI breakfast at 8:30 a.m. and usual lunch at 12:30 p.m. Subjects instructed to maintain their habitual intakes for the other meals (ad libitum). Both breakfast meals provided the same energy, PRO, fat and CHO values within 6%. Dietary intake monitored through the completion of three-day food diaries at the beginning (three days before baseline) and end of each intervention period (days 19 to 21). Anthropometric measures measured before and after each intervention period.	Total daily energy intake was not different between the groups (P=0.45). Body weight was similar at the end of the low- and high-GI breakfast interventions (mean±SEM: 84.34±4.88kg vs. 84.25±4.43kg, respectively; P=0.614).

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Pereira MA, Swain J et al 2004 Study Design: Randomized Controlled Trial Class: A Positive Quality	N=39 adults. Gender: 77.3% and 76.5% female for low-glycemic and low-fat diet groups, respectively. Age: Mean (SD)=28.8 (6.3) and 32.6 (4.3) years for the low-glycemic and low-fat diet groups, respectively. Ethnicity: 59.1% white, 18.2% black, 4.5% other for low-glycemic group and 47% white, 29.4% black, 6.0% other for low-fat group. Location: United States.	Randomized trial, two-arm (low-GL or low-fat diet) parallel design. During nine-day run-in period, all subjects given a standard weight-maintaining diet and then were admitted to a metabolic unit for three days to obtain baseline measurements. At discharge, participants began diets, providing 60% of predicted energy requirements. After a 10% ↓ in body weight during a six- to 10-week period, subjects were readmitted for five days to obtain final measurements of study end points. All food prepared in a metabolic kitchen. Subjects required to eat only the food provided and consume one meal (lunch) onsite Monday through Friday. All other food provided as take-home meals. Dietitians provided behavioral support daily. Low-fat diet was low in fat, high in CHO and GL and satisfied recommendations for whole grains, fruits and vegetables and saturated fat and cholesterol. Low-glycemic diet designed to be as low in GL as possible, while providing enough CHO to prevent ketosis. GL was reduced by modifications of both the amount and type of CHO.	Weight loss for the low-GL and low-fat diets were similar. Mean (SE): 9.6 (0.3) and 9.5 (0.3) kg, respectively; P=0.75. Weight loss % for the low-GL and low-fat diets were also similar. Mean (SE): 10.5% (0.3) and 10.5% (0.3), respectively; P=0.93. Individual rates of weight loss were NS greater in the low-GL compared with the low-fat group. Mean (SE): 1.09 (0.05) and 0.99 (0.05) kg per week, respectively; P=0.19.

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Philippou E, Neary NM et al, 2008 Study Design: Randomized Controlled Trial Class: A Neutral Quality	N=43 adults. Age: 18 to 65 years. BMI: 27 to 45kg/m^2. Location: United Kingdom.	Study represents the second phase of a weight-loss study. First phase included weight-loss program. Participants who lost ≥5% of their body weight (median = 6.1%) were randomized to a four-month weight maintenance phase with a high- or low-glycemic diet for this phase of the study. Intervention: Participants asked to include at least one high glycemic or low glycemic food with each of their meals and snacks. Subjects encouraged to eat until satisfied and to follow healthy eating guidelines. Participants seen monthly for a dietetic assessment (semi-quantitative three-day diaries) and anthropometric measurements.	No difference in body weight Δ over four months between the high- and low-GI groups (0.3±1.9kg vs. -0.7±2.9kg, respectively, P=0.3). Dietary composition differed only in GI (63.7±9.4 vs. 49.7±5.7, for high- and low-glycemic diets, respectively; P<0.001) and GL (136.8±56.3 vs. 89.7±27.5, for high- and low-glycemic diets, respectively; P<0.001).

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Pittas AG, Roberts SB et al, 2006 Study Design: Randomized Controlled Trial Class: A Positive Quality	N=32 adults (78% female). Mean age: 34.6 years. Predominantly white (more than 80%). Mean BMI: 27.5 kg/m^2. Location: United States.	Randomized six-month two-arm parallel trial. After seven-week baseline period, when usual energy requirements for weight stability were measured, subjects randomized for 24 weeks to either a high-GL diet or a low-GL diet. Both diets provided 30% calorie restriction compared with individual baseline weight maintenance energy requirements. All food provided during the six months by the research center. Subjects expected to consume only this food; however, they were to report additional foods or drinks if eaten. Subjects attended regular behavioral group meetings and individual sessions with a dietitian. High-GL diet: 60% CHO, 20% PRO, 20% fat, with mean estimated daily GI of 86 and a mean estimated daily GL of 116 g per 1,000kcal. Low-GL diet: 40% CHO, 30% PRO, 30% fat, with a mean estimated daily GI of 53 and a mean estimated daily GL of 45 g per 1,000 kcal.	At three months and six months, both groups achieved statistically significant (P<0.001) weight loss, compared with their baseline weight. Adjusted for baseline weight, weight loss was 7.2kg in the high-GL group vs. 7.7kg in the low-GL group at six months, P=0.69.

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Raatz SK, Torkelson CJ et al, 2005 Study Design: Randomized Controlled Trial Class: A Neutral Quality	N=29 adults. Obese. Location: United States.	Three-arm parallel-design randomized 12-week controlled feeding trial with a 24-week follow-up phase. During weeks one to 12 (feeding phase), subjects consumed individualized energy-restricted diets to promote a weight loss of 0.70kg per week. All meals prepared in a metabolic kitchen. Subjects required to consume all food provided and no foods other than those provided. During weeks 13 to 24 (free-living phase), diet assignment maintained, but subjects prepared their own meals. Subjects given intensive dietary instruction and nutritional counseling every two weeks. The three hypocaloric diet arms varied in macronutrient content, GI and GL. High-GI diet: High-GL and GI [60% CHO, 15% PRO, 25% fat, GI = 63, GL = 272]. Low-GI diet: Low-GL and GI [60% CHO, 15% PRO, 25% fat, GI = 33, GL = 178]. High-fat diet: Low-GL and high-GI [45% CHO, 15% PRO, 40% fat, GI = 59, GL = 182]. Anthropomorphic measurements obtained at baseline and weeks four, eight, 12, 24 and 36. Five-day food records completed at week 24 and 36 during the free-living phase.	Each diet group lost weight during the 12-week feeding phase (P<0.001), but amount lost did not differ among the groups (mean±SEM: -9.3±1.3kg for high-GI diet, 9.9±1.4kg for low-GI diet and 8.4±1.5kg for the high-fat diet). Weight loss achieved during the first 12 weeks were maintained in all three groups at week 36 and these values did not differ among the groups. Glycemic indices of the diets differed at week 24 (P=0.014), with low-GI diet group consuming a lower GI diet. By week 36, diets did not differ in GI.

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Sichieri R, Moura AS et al, 2007 Study Design: Prospective Cohort Study Class: A Neutral Quality	N=203 women. Mean (SD) age: 37.2 (5.4) years and 37.5 (5.6) years for low- and high-GI groups, respectively. Mean (SD) BMI: 26.9 (1.8) kg/$m^2$and 26.7 (2.1) kg/m^2 for low- and high-GI groups, respectively. Ethnicity: Percent white, black and mulatto: 54.5%, 19.8% and 25.7% for low-GI group and 52.0%, 15.0% and 33.0% for high-GI group. Location: Brazil.	18-month randomized trial with a six-week run-in period. The initial phase, a six-week run-in period, consisted of two weeks of a low-GI diet followed by four weeks of a high-GI diet. Those who completed the run-in period (203 of 414 recruited) were randomized to a low-GI diet or a high-GI diet. Dietary counseling based on a small energy restriction (100 to 300kcal) and skipping the diet one day a week permitted. Subjects instructed to eat three meals and three snacks according to a six-day menu plan. Nutritional counseling provided monthly. Both diets designed with 26-28% of energy as fat. For each meal, low-GI diets were designed to maintain an average difference of 40 units compared with high-GI diet. FFQs completed at the beginning of the run-in period and after 3, 6, 12 and 18 months of follow-up. Weight measured monthly.	60% of participants completed the study. Difference in GI between the diets was ~35 to 40 units (40 compared with 79) during all 18 months of follow-up. Low-GI group had a slightly ↑ weight loss in the first two months of follow-up (-0.72 compared with -0.31kg), but after 12 months of follow-up both groups began to regain weight. After 18 months, weight Δ was NS different (P=0.93) between groups (-0.41 vs. -0.26kg for low- and high-GI diets, respectively).

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Sloth B, Krog-Mikkelsen I et al 2004 Study Design: Randomized Controlled Trial Class: A Positive Quality	N=45 women. Age: 20 to 40 years old. BMI: 27.6±0.2kg/m^2. Location: Denmark.	10-week parallel, randomized intervention trial with two matched groups. Energy requirements calculated and subjects categorized and assigned to test food intakes of different levels. Groups received either low-GI or high-GI foods in replacement of their usual CHO-rich foods. Subjects also instructed to eat a diet with 20% to 30% of energy from fat and a list with other CHO-rich foods given so they could monitor the GI of foods they ate during the study. Subjects instructed to have a ↓ sugar intake. Subjects could eat ad libitum of their own diet in addition to the test foods. They received individual guidance by trained clinical dietitians on the first day of the study period and at group meetings at weeks three, five, seven and nine. Subjects completed a seven-day weighed dietary record just before entering the study and in weeks five and 10 of the intervention. Height and weight measured.	Body weight significantly ↓ over time for both groups, but the differences were NS between the groups [mean (SEM): -1.9 (0.5) kg and -1.3 (0.3) kg for the low- and high-GI diets, respectively). Significant ↓ in energy intake over time, but NS differences between groups. Self-reported data from food diaries indicated that subjects ate 95% of the amounts of test foods they were requested to eat.

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Search plan and results

Inclusion criteria

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

Exclusion criteria

- Reviews (narrative and systematic reviews), meta-analyses
- Medical treatment or therapy, including medical treatment of diabetes
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed: ("Glycemic Index[Mesh] OR "glycemic load") AND "Body Weights and Measures"[Mesh]] OR "body composition"[mh])

Date searched: 03/18/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 232
- Total articles identified to review from electronic databases: 45
- Articles identified via handsearch or other means: 3
- Number of Primary Articles Identified: 22
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 22
- Number of Articles Reviewed but Excluded: 26

Included articles (References)

1. Abete I, Parra D, Martinez JA. Energy-restricted diets based on a distinct food selection affecting the glycemic index induce different weight loss and oxidative response. *Clin Nutr.* 2008 Aug; 27(4): 545-551. Epub 2008 Mar 4. PMID: 18308431.
2. Aston LM, Stokes CS, Jebb SA. No effect of a diet with a reduced glycaemic index on satiety, energy intake and body weight in overweight and obese women. *Int J Obes (Lond).* 2008 Jan; 32(1): 160-165. Epub 2007 Oct 9. PMID: 17923862.
3. de Rougemont A, Normand S, Nazare JA, Skilton MR, Sothier M, Vinoy S, Laville M. Beneficial effects of a 5-week low-glycaemic index regimen on weight control and cardiovascular risk factors in overweight non-diabetic subjects. *Br J Nutr.* 2007 Dec; 98(6): 1, 288-1, 298. Epub 2007 Jul 9. PMID: 17617942.

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4. Deierlein AL, Siega-Riz AM, Herring A. Dietary energy density but not glycemic load is associated with gestational weight gain. *Am J Clin Nutr.* 2008 Sep; 88(3): 693-699. PMID: 18779285.
5. Ebbeling CB, Leidig MM, Feldman HA, Lovesky MM, Ludwig DS. Effects of a low-glycemic load vs low-fat diet in obese young adults: A randomized trial. *JAMA.* 2007 May 16; 297(19): 2, 092-2, 102. Erratum in: *JAMA.* 2007 Aug 8; 298(6): 627. PMID: 17507345.
6. Hare-Bruun H, Flint A, Heitmann BL. Glycemic index and glycemic load in relation to changes in body weight, body fat distribution, and body composition in adult Danes. *Am J Clin Nutr.* 2006 Oct; 84(4): 871-879; quiz, 952-953. PMID: 17023715.
7. Hui LL, Nelson EA. Meal glycaemic load of normal-weight and overweight Hong Kong children. *Eur J Clin Nutr.* 2006 Feb; 60(2): 220-227. PMID: 16278694.
8. Lau C, Toft U, Tetens I, Richelsen B, Jørgensen T, Borch-Johnsen K, Glümer C. Association between dietary glycemic index, glycemic load, and body mass index in the Inter99 study: Is underreporting a problem? *Am J Clin Nutr.* 2006 Sep; 84(3): 641-645. PMID: 16960180.
9. Liese AD, Schulz M, Fang F, Wolever TM, D'Agostino RB Jr, Sparks KC, Mayer-Davis EJ. Dietary glycemic index and glycemic load, carbohydrate and fiber intake, and measures of insulin sensitivity, secretion, and adiposity in the Insulin Resistance Atherosclerosis Study. *Diabetes Care.* 2005 Dec; 28(12): 2, 832-2, 838. PMID: 16306541.
10. Maki KC, Rains TM, Kaden VN, Raneri KR, Davidson MH. Effects of a reduced-glycemic-load diet on body weight, body composition, and cardiovascular disease risk markers in overweight and obese adults. *Am J Clin Nutr.* 2007 Mar; 85(3): 724-734. PMID: 17344493.
11. McMillan-Price J, Petocz P, Atkinson F, O'neill K, Samman S, Steinbeck K, Caterson I, Brand-Miller J. Comparison of 4 diets of varying glycemic load on weight loss and cardiovascular risk reduction in overweight and obese young adults: a randomized controlled trial. *Arch Intern Med.* 2006 Jul 24; 166(14): 1, 466-1, 475. PMID: 16864756.
12. Mendez MA, Covas MI, Marrugat J, Vila J, Schröder H. Glycemic load, glycemic index, and body mass index in Spanish adults. *Am J Clin Nutr.* 2009 Jan; 89(1): 316-322. Epub 2008 Dec 3. PMID: 19056597.
13. Milton JE, Briche B, Brown IJ, Hickson M, Robertson CE, Frost GS. Relationship of glycaemic index with cardiovascular risk factors: Analysis of the National Diet and Nutrition Survey for people aged 65 and older. *Public Health Nutr.* 2007 Nov; 10(11): 1, 321-1, 335. Epub 2007 Apr 24. PMID: 17456246.
14. Murakami K, Sasaki S, Okubo H, Takahashi Y, Hosoi Y, Itabashi M. Dietary fiber intake, dietary glycemic index and load, and body mass index: A cross-sectional study of 3, 931 Japanese women aged 18-20 years. *Eur J Clin Nutr.* 2007 Aug; 61(8): 986-995. Epub 2007 Jan 24. PMID: 17251928.
15. Nielsen BM, Bjørnsbo KS, Tetens I, Heitmann BL. Dietary glycaemic index and glycaemic load in Danish children in relation to body fatness. *Br J Nutr.* 2005 Dec; 94(6): 992-997. PMID: 16351778.
16. Pal S, Lim S, Egger G. The effect of a low glycaemic index breakfast on blood glucose, insulin, lipid profiles, blood pressure, body weight, body composition and satiety in obese and overweight individuals: a pilot study. *J Am Coll Nutr.* 2008 Jun; 27(3): 387-393. PMID: 18838526.

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17. Pereira MA, Swain J, Goldfine AB, Rifai N, Ludwig DS. Effects of a low-glycemic load diet on resting energy expenditure and heart disease risk factors during weight loss. *JAMA.* 2004 Nov 24; 292(20): 2, 482-2, 490. PMID: 15562127.
18. Philippou E, Neary NM, Chaudhri O, Brynes AE, Dornhorst A, Leeds AR, Hickson M, Frost GS. The effect of dietary glycemic index on weight maintenance in overweight subjects: A pilot study. *Obesity (Silver Spring).* 2009 Feb; 17(2): 396-401. Epub 2008 Dec 4.
19. Pittas AG, Roberts SB, Das SK, Gilhooly CH, Saltzman E, Golden J, Stark PC, Greenberg AS. The effects of the dietary glycemic load on type 2 diabetes risk factors during weight loss. *Obesity (Silver Spring).* 2006 Dec; 14(12): 2, 200-2, 209. PMID: 17189547.
20. Raatz SK, Torkelson CJ, Redmon JB, Reck KP, Kwong CA, Swanson JE, Liu C, Thomas W, Bantle JP. Reduced glycemic index and glycemic load diets do not increase the effects of energy restriction on weight loss and insulin sensitivity in obese men and women. *J Nutr.* 2005 Oct; 135(10): 2, 387-2, 391. PMID: 16177201.
21. Sichieri R, Moura AS, Genelhu V, Hu F, Willett WC. An 18-month randomized trial of a low-glycemic-index diet and weight change in Brazilian women. *Am J Clin Nutr.* 2007 Sep; 86(3): 707-713. PMID: 17823436.
22. Sloth B, Krog-Mikkelsen I, Flint A, Tetens I, Björck I, Vinoy S, Elmståhl H, Astrup A, Lang V, Raben A. No difference in body weight decrease between a low-glycemic-index and a high-glycemic-index diet but reduced LDL cholesterol after 10-week ad libitum intake of the low-glycemic-index diet. *Am J Clin Nutr.* 2004 Aug; 80(2): 337-347. PMID: 15277154.

Excluded articles

Article	Reason for Exclusion
Arumugam V, Lee JS, Nowak JK, Pohle RJ, Nyrop JE, Leddy JJ, Pelkman CL. A high-glycemic meal pattern elicited increased subjective appetite sensations in overweight and obese women. *Appetite.* 2008 Mar-May; 50(2-3): 215-222. Epub 2007 Jul 25. PMID: 17714828.	Does not include body weight in analyses.
Aston LM. Glycaemic index and metabolic disease risk. *Proc Nutr Soc.* 2006 Feb; 65(1): 125-134. Review. PMID: 16441952.	Study design is narrative review.
Astrup A. How to maintain a healthy body weight. *Int J Vitam Nutr Res.* 2006 Jul; 76(4): 208-215. Review. PMID: 17243084.	Study design is narrative review.
Barclay AW, Petocz P, McMillan-Price J, Flood VM, Prvan T, Mitchell P, Brand-Miller JC. Glycemic index, glycemic load, and chronic disease risk: A meta-analysis of observational studies. *Am J Clin Nutr.* 2008 Mar; 87(3): 627-637. Review. PMID: 18326601.	Does not include body weight in analyses.

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Bornet FR, Jardy-Gennetier AE, Jacquet N, Stowell J. Glycaemic response to foods: impact on satiety and long-term weight regulation. *Appetite.* 2007 Nov; 49(3): 535-553. Epub 2007 May 3. Review. PMID: 17610996.	Study design is systematic review.
Buyken AE, Trauner K, Günther AL, Kroke A, Remer T. Breakfast glycemic index affects subsequent daily energy intake in free-living healthy children. *Am J Clin Nutr.* 2007 Oct; 86(4): 980-987. PMID: 17921374.	Does not include body weight in analyses.
Carels RA, Darby LA, Douglass OM, Cacciapaglia HM, Rydin S. Education on the glycemic index of foods fails to improve treatment outcomes in a behavioral weight loss program. *Eat Behav.* 2005 Feb; 6(2): 145-150. PMID: 15598601.	Does not answer question; examined behavioral weight loss program.
Davis MS, Miller CK, Mitchell DC. More favorable dietary patterns are associated with lower glycemic load in older adults. *J Am Diet Assoc.* 2004 Dec; 104(12): 1, 828-1, 835. PMID: 15565077.	Does not include body weight in analyses.
Díaz EO, Galgani JE, Aguirre CA, Atwater IJ, Burrows R. Effect of glycemic index on whole-body substrate oxidation in obese women. *Int J Obes (Lond).* 2005 Jan; 29(1): 108-114. Erratum in: *Int J Obes Relat Metab Disord.* 2005 Jul; 29(7): 879. PMID: 15505637.	Does not include body weight in analyses.
Fajcsak Z, Gabor A, Kovacs V, Martos E. The effects of six-week low glycemic load diet based on low glycemic index foods in overweight/obese children: Pilot study. *J Am Coll Nutr.* 2008 Feb; 27(1): 12-21. PMID: 18460477.	Sample size less than inclusion criteria.
Gibson LJ, Peto J, Warren JM, dos Santos Silva I. Lack of evidence on diets for obesity for children: A systematic review. *Int J Epidemiol.* 2006 Dec; 35(6): 1, 544-1, 552. Epub 2006 Sep 19. Review. PMID: 16984930.	Study design is systematic review.
Hare-Bruun H, Nielsen BM, Grau K, Oxlund AL, Heitmann BL. Should glycemic index and glycemic load be considered in dietary recommendations? *Nutr Rev.* 2008 Oct; 66(10): 569-590. Review. PMID: 18826453.	Study design is narrative review.

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Henry CJ, Lightowler HJ, Dodwell LM, Wynne JM. Glycaemic index and glycaemic load values of cereal products and weight-management meals available in the UK. *Br J Nutr.* 2007 Jul; 98(1): 147-153. Epub 2007 Mar 30. PMID: 17397560.	Does not answer question: examined product availability in the UK.
Henry CJ, Lightowler HJ, Strik CM. Effects of long-term intervention with low- and high-glycaemic-index breakfasts on food intake in children aged 8 to 11 years. *Br J Nutr.* 2007 Sep; 98(3): 636-640. Epub 2007 Apr 23. PMID: 17451613.	Does not include body weight in analyses.
Jiménez-Cruz A, Gutiérrez-González AN, Bacardi-Gascon M. Low glycemic index lunch on satiety in overweight and obese people with type 2 diabetes. *Nutr Hosp.* 2005 Sep-Oct; 20(5): 348-350. PMID: 16229403.	Participants diagnosed with type 2 diabetes.
Kim K, Yun SH, Choi BY, Kim MK. Cross-sectional relationship between dietary carbohydrate, glycaemic index, glycaemic load and risk of the metabolic syndrome in a Korean population. *Br J Nutr.* 2008 Sep; 100(3): 576-584. Epub 2008 Mar 10. PMID: 18328117.	Does not answer question; examined relationship between glycemic index and glycemic load and risk of metabolic syndrome.
Krishnan S, Rosenberg L, Singer M, Hu FB, Djoussé L, Cupples LA, Palmer JR. Glycemic index, glycemic load, and cereal fiber intake and risk of type 2 diabetes in US black women. *Arch Intern Med.* 2007 Nov 26;167(21):2304-9. PMID: 18039988 [PubMed - indexed for MEDLINE]	Does not answer question; examined relationship between glycemic index and glycemic load and risk of type 2 diabetes.
Lajous M, Boutron-Ruault MC, Fabre A, Clavel-Chapelon F, Romieu I. Carbohydrate intake, glycemic index, glycemic load, and risk of postmenopausal breast cancer in a prospective study of French women. *Am J Clin Nutr.* 2008 May; 87(5): 1, 384-1, 391. PMID: 18469262.	Does not answer question; examined relationship between glycemic index and glycemic load and breast cancer.
Liu S. Lowering dietary glycemic load for weight control and cardiovascular health: A matter of quality. *Arch Intern Med.* 2006 Jul 24; 166(14): 1, 438-1, 439. PMID: 16864751.	Publication is editorial.
Livesey G, Taylor R, Hulshof T, Howlett J. Glycemic response and health--a systematic review and meta-analysis: Relations between dietary glycemic properties and health outcomes. *Am J Clin Nutr.* 2008 Jan; 87(1): 258S-268S. Review. PMID: 18175766.	Study design is systematic review/meta-analysis.

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Newby PK. Are dietary intakes and eating behaviors related to childhood obesity? A comprehensive review of the evidence. *J Law Med Ethics.* 2007 Spring; 35(1): 35-60. Review. PMID: 17341216.	Study design is narrative review.
Schulz M, Liese AD, Fang F, Gilliard TS, Karter AJ. Is the association between dietary glycemic index and type 2 diabetes modified by waist circumference? *Diabetes Care.* 2006 May; 29(5): 1, 102-1, 104. PMID: 16644644.	Does not answer question; examined relationship between glycemic index and type 2 diabetes.
Smith MA, Foster JK. The impact of a high versus a low glycaemic index breakfast cereal meal on verbal episodic memory in healthy adolescents. *Nutr Neurosci.* 2008 Oct; 11(5): 219-227. PMID: 18782482.	Does not answer question; examined relationship between glycemic index and memory.
Thomas DE, Elliott EJ, Baur L. Low glycaemic index or low glycaemic load diets for overweight and obesity. *Cochrane Database Syst Rev.* 2007 Jul 18; (3): CD005105. Review. PMID: 17636786.	Study design is systematic review.
Ukleja A, Kunachowicz H, Pachocka L. The use of glycaemic index in the prevention of cardiovascular diseases. *Rocz Panstw Zakl Hig.* 2007; 58(1): 145-151. Review. PMID: 17711103.	Study design is narrative review.
Wylie-Rosett J, Segal-Isaacson CJ, Segal-Isaacson A. Carbohydrates and increases in obesity: Does the type of carbohydrate make a difference? *Obes Res.* 2004 Nov; 12 Suppl 2: 124S-129S. Review. PMID: 15601960.	Study design is narrative review.

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CHAPTER 3. GLYCEMIC INDEX/LOAD – CANCER

WHAT IS THE RELATIONSHIP BETWEEN GLYCEMIC INDEX OR GLYCEMIC LOAD AND CANCER?

Conclusion statement

Abundant, strong epidemiological evidence demonstrates that there is no association between glycemic index or load and cancer.

Grade

Strong

Evidence summary overview

The epidemiological evidence for an association between glycemic index (GI) or glycemic load (GL) and cancer is overwhelmingly negative. Twenty-eight reports have been published since 2005. Of these, 20 are prospective longitudinal observation studies, one is a cross-sectional observation study, five are case-control studies and two are case-cohort studies.

Of the 20 prospective longitudinal observational studies, 18 studied the association between GI and cancer. One showed a very weak positive association between GI and total cancer risk (George, 2009), while thirteen studies found no association between GI and specific types of cancer including pancreatic (Heinen, 2008; Johnson, 2005; Nothlings, 2007; Patel, 2007; Silvera, 2005), breast (Giles, 2006; Lajous, 2008; Sieri, 2007; Silvera, 2005), endometrial (Cust, 2007; Larsson and Friberg, 2007) stomach (Larsson, 2006) and ovarian (Silvera, 2007) cancers. Varying results were found for colorectal cancer with no association reported in three studies (Larsson, 2007; McCarl, 2006; Michaud, 2005) and an inverse association reported by Strayer et al (2007).

Of the 20 prospective longitudinal observational studies, all studied the association between GL and cancer. Two showed a positive association for total cancer (George, 2009) and ovarian cancer (Silvera, 2007). However, most studies reported no association between GL and cancer, including pancreatic (Heinen, 2008; Johnson, 2005; Nothlings, 2007; Patel, 2007; Silvera, 2005), breast (Giles, 2006; Lajous, 2008; Sieri, 2007; Silvera, 2005), endometrial (Cust, 2007; Larsson and Friberg, 2007), and stomach (Larsson, 2006) cancers. Similar to glycemic index, there were mixed results regarding the relationship between GL and colorectal cancer, with five studies finding no association (Kabat, 2008; Larsson, 2007; McCarl, 2006; Michaud, 2005; Strayer, 2007) and one study reporting an inverse association (Howarth, 2008).

The two case-cohort studies reported no association of either GI or GL with pancreatic (Kabat, 2008) or colorectal (Weijenberg, 2008) cancers. Similarly, one cross-sectional observational study showed no association between either GI or GL and colorectal adenomas (Flood, 2006a).

The five available case-control reports reported mixed results. Of these, three found GI to be significantly associated with prostate (Augustin, 2004), gastric (Bertuccio, 2009) and thyroid (Randi, 2008) cancers, and two found no association with breast cancer (Lajous, 2005; McCann, 2007). Similarly, three found glycemic load to be significantly associated with cancer of the breast (Lajous, 2005), prostate (Bertuccio, 2009) or thyroid (Randi, 2008) and found no association for breast (McCann, 2007) and

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prostate (Augustin, 2004) cancers.

Evidence summary paragraphs

Augustin, 2004 (neutral quality), a case-control study conducted in Italy, investigated the association of dietary glycemic index (GI) and glycemic load (GL) with prostate cancer risk in 1,204 male cases and 1,352 male controls (aged 46 to 74 years). Compared to the lowest quintile of GI, odds ratios (OR) for developing prostate cancer were 1.23, 1.24, 1.47 and 1.57 for subsequent levels of GI, and the corresponding values for GL were 0.91, 1.00, 1.20, 1.41. The authors concluded that direct relations between dietary GI and GL and prostate risk were found. Correcting for potential confounding factors did not substantially modify these associations.

Bertuccio, 2009 (positive quality), a case-control study conducted in Italy, assessed the relationship between glycemic load (GL), glycemic index (GI) and gastric cancer in patients admitted to major teaching and general hospitals in Italy. 230 patients had incident, histologically confirmed gastric cancer and 547 patients served as matched controls (mean age for both groups of 63 years, range 22 to 80 years). The OR in the highest vs. lowest quintile were 1.9 (95% CI: 1.0 to 3.3) for GI and 2.5 (95% CI: 1.3 to 4.9) for GL. The OR rose across strata of high GL and low fruit and vegetable intake to reach 5.0 (95% CI: 2.2 to 11.5) for those reporting high GL and low fruit and vegetable intake, compared with participants reporting low GL and high fruit and vegetable intake. The authors concluded that GL may have an independent role in gastric cancer formation and they noted lack of information on *H. pylori* infection and hospital dietary habits differing from the general population as possible limitations.

Cust, 2007 (positive quality), the European Prospective Investigation into Cancer and Nutrition cohort study (prospective cohort study), examined the association of endometrial cancer risk with dietary total carbohydrates, glycemic index (GI) and glycemic load (GL) in 288,428 women recruited between 1992 and 2000 throughout 10 western European countries. During a mean 6.4 years and 1,842,995 person-years of follow-up, 710 incident endometrial cancer cases were diagnosed. Data suggest no association of overall GI, total starch and total fiber with endometrial cancer risk; however, multivariable RR were 1.61 (95% CI: 1.06 to 2.45) per 100g per day of total carbohydrates, 1.40 (95% CI: 0.99 to 1.99) per 50g per day of total dietary GL, and 1.36 (95% CI: 1.05 to 1.76) per 50g per day of total sugars. These associations were stronger among women who had never used post-menopausal hormone therapy.

Flood, 2006 (positive quality), a multi-center cross-sectional study conducted in the US, determined if glycemic index (GI) or load (GL) was associated with risk of distal adenomas in 44,572 participants from the Prostate, Lung, Colorectal and Ovarian screening trial. A total of 3,696 participants were diagnosed with at least one distal adenoma. There were no significant (NS) associations between GI and risk of distal adenomas for men or women; after multivariate adjustment, there was a significant inverse association between GL and risk of distal adenomas in men, but not in women.

George, 2009 (positive quality), a prospective cohort study conducted in the US, investigated whether glycemic index (GI) and glycemic load (GL) were related to increased risk of developing a primary cancer in 262,642 male and 183,535 female participants from the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study (average age approximately 60 years). The RR for total cancer for high vs. low GI were 1.03 for women (P=0.217) and 1.04 for men (P=0.012), and for high vs. low GL, were 0.90 for men (P=0.024) and

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0.93 for women (P=0.01), suggesting that GI and GL are not strong predictors of cancer incidence.

Giles, 2006 (neutral quality), a prospective cohort study conducted in Australia, investigated associations between dietary carbohydrates (CHO), dietary fiber, glycemic index (GI) and glycemic load (GL), and risk of invasive breast cancer in female participants (aged 40 to 69 years at baseline) of the Melbourne Collaborative Cohort Study. During an average of 9.1 years follow-up, 324 breast cancers were diagnosed in 12,273 post-menopausal women. Although an increase of one standard deviation (SD) in CHO intake was marginally associated with risk of breast cancer (RR=1.31, 95% CI: 0.98, 1.75), there were NS associations with fiber, GI, GL or CHO foods.

Heinen, 2008 (neutral quality), a prospective cohort study in the Netherlands, examined pancreatic cancer risk in a subcohort of the Netherlands Cohort Study. After 13.3 years of follow-up, the final subcohort included 4,438 subjects (2,191 men, 2,247 women) and 408 exocrine pancreatic cancer cases (217 men, 191 women) (subcohort aged 55 to 69 years at baseline). Dietary glycemic load, glycemic index or intake of CHO and mono- and disaccharides were not associated with pancreatic cancer risk.

Howarth, 2008 (neutral quality), a prospective cohort study conducted in the US, determined the risk of colorectal cancer associated with glycemic load (GL), CHO and sucrose, and ascertained whether this risk was modified by sex and ethnicity in 191,004 men and women participating in the Multiethnic Cohort Study. Over eight years of follow-up, 2,379 incident cases of colorectal adenocarcinoma occurred in 1,293 men and 1,086 women. In multivariate models, relative risks (RR) for colorectal cancer decreased significantly with increasing GL in women (RR for the highest vs. lowest quintile = 0.75, 95% CI: 0.57, 0.97; P=0.02) but not in men (RR=1.15, 95% CI: 0.89, 1.48; P=0.19); results for CHO and sucrose were similar. The inverse association was found in women of all ethnic groups. The authors concluded that GL and CHO intake appeared to be protective against colorectal cancer in women after adjustment for potential confounders.

Johnson, 2005 (neutral quality), a prospective cohort study conducted in the US, examined the hypothesis that high dietary glycemic index (GI) and glycemic load (GL) were associated with increased risk of pancreatic cancer in 33,551 women from the Iowa Women's Health Study (aged 55 to 69 at baseline). Participants were followed from 1986 until 2002. Incidence of pancreatic cancer was higher in subjects aged 65 to 69 vs. aged 55 to 64, diabetic vs. non-diabetic, current smokers vs. non-smokers, and multivitamin non-users vs. users, but there was no increased hazard of pancreatic cancer associated with high dietary GI or GL. The authors did not find evidence to support the hypothesis that high dietary GI or GL increases the risk of pancreatic cancer.

Kabat, 2008 (neutral quality), using data from the Observational Study and Clinical Trial cohorts of the Women's Health Initiative (prospective cohort study) in the US, examined the association of intake of CHO, glycemic index (GI), glycemic load (GL) and related dietary factors in relation to colorectal cancer and subsites within the colorectum in 158,800 post-menopausal women (aged 50 to 79 at baseline). Over an average of 7.8 years of follow-up, 1,476 incident cases of colorectal cancer were identified. When data were analyzed separately as well as combined, total

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carbohydrate intake, GI and GL, plus intake of sugars and fiber showed no association with colorectal cancer and there were no trends over increasing quintiles. This study provides no evidence that a diet characterized by high GI or GL, or by a high intake of CHO or sugars, increases the risk of colorectal cancer in generally healthy post-menopausal women.

Lajous, 2005 (neutral quality), a case-control study conducted in Mexico, compared dietary glycemic load (GL) and overall glycemic index (GI) with breast cancer risk in 475 women with biopsy-confirmed breast cancer and 1,391 controls. The multivariate adjusted OR for all women comparing the highest and lowest tertiles of dietary GL was 1.62 (95% CI: 1.13 to 2.32, P=0.02), and the association was stronger in post-menopausal women [multivariate adjusted OR was 2.18 (95% CI: 1.34 to 3.55; P=0.005)]. Glycemic index was NS associated with risk of breast cancer. The authors concluded that high intake of rapidly absorbed CHO may play a role in the risk of breast cancer in Mexican women.

Lajous, 2008 (neutral quality), a prospective cohort study in France, evaluated CHO intake, glycemic index (GI), glycemic load (GL) and fiber intake and the subsequent risk of overall and hormone receptor-defined breast cancer among 62,739 post-menopausal women (aged 42 to 72 years at baseline) participating in the E3N French Study, the French component of the European Prospective Investigation into Cancer and Nutrition. During nine years of follow-up, 1,812 cases of pathology-confirmed breast cancer were documented. Dietary carbohydrate intakes, GI and GL were not associated with overall breast cancer risk. However, among overweight women, there was an association between GI and breast cancer (RR=1.35, 95% CI: 1.00, 1.82, P=0.04); this association was absent for women with body mass index (BMI) <25kg/m^2. The authors concluded that rapidly absorbed CHO may be associated with post-menopausal breast cancer risk among overweight women and women with large waist circumference. In addition, carbohydrate intake may be associated with estrogen receptor-negative breast cancer.

Larsson, Giovannucci et al, 2007 (neutral quality), a prospective cohort study in Sweden, examined the associations between CHO intake, glycemic index (GI) and glycemic load (GL) and the risk of colorectal cancer in 61,433 women participating in the Swedish Mammography Cohort Study who completed a baseline questionnaire in 1987 to 1990. Over 963,426 person-years of follow-up (mean = 15.7 years), there were 870 cases of colorectal cancer, but CHO intake, GI and GL had NS association with colorectal, colon or rectal cancer, regardless of BMI and alcohol consumption. The authors concluded that this study does not support the hypothesis that high carbohydrate intake, high GI and high GL increase the risk of colorectal cancer.

Larsson, Friberg et al, 2007 (neutral quality), a prospective cohort study in Sweden, examined the associations between CHO intake, glycemic index (GI) and glycemic load (GL) and the risk of endometrial cancer in 61,226 women participating in the Swedish Mammography Cohort Study. Over 952,629 person-years of follow-up, 608 cases of endometrial cancer developed, but there was no overall association between carbohydrate intake, GI or GL and incidence of endometrial cancer. However, carbohydrate intake and GL were positively related to endometrial cancer risk among overweight women (BMI higher than 25kg/m^2) with low physical activity in a subanalysis of these data; multivariate RRs comparing extreme quartiles were 1.90 (95% CI: 0.84 to 4.31) for CHO intake and 2.99 (95% CI: 1.17 to 7.67) for GL. The authors concluded that they found no overall associations between CHO intake, GI

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or GL and the incidence of endometrial cancer. However, among overweight women with low physical activity, we observed a NS 1.9-fold increase in risk of endometrial cancer for those who had a high CHO intake and a statistically significant three-fold increase in risk for those who had a high GL.

Larsson, 2006 (neutral quality), a prospective cohort study in Sweden, examined the associations between dietary glycemic load (GL), overall glycemic index (GI) and CHO intake in relation to the incidence of stomach cancer among 61,433 women in the Swedish Mammography Cohort. Diet was assessed at baseline (1987 to 1990) with a 67-item food-frequency questionnaire (FFQ) and again in 1997 with a 96-item FFQ. Stomach cancer incidence was obtained by linkage to national and regional Swedish Cancer registers with follow up through 2004. During 903,586 person-years of follow-up, there were 156 incident cases of stomach cancer. There was no association between CHO intake, GI or GL and incidence of stomach cancer using any of the dietary intake data. The multivariate hazard ratios (HR) for the highest vs. the lowest quintile were 0.76 (95% CI: 0.46, 1.25) for GL, 0.77 (95% CI: 0.46, 1.30) for overall GI and 0.85 (95% CI: 0.50, 1.43) for CHO intake. The study did not provide evidence of a positive association between GI, GL or CHO intake among middle-aged and elderly women and they noted lack of information on *H. pylori* infection.

McCann, 2007 (positive quality), a case-control study in the US, examined the associations between glycemic index (GI) and glycemic load (GL) and the risk of breast cancer in 1,166 women with incident, primary, histologically confirmed breast cancer and 2,105 matched controls in the Western New York Exposure and Breast Cancer Study (WEB). Participants were predominantly white (90%), and approximately 40% were pre-menopausal. In pre-menopausal women, breast cancer was not related to GI or GL. There was a NS trend toward a decrease in the risk of breast cancer for post-menopausal women in the highest vs. lowest quartile of GI (OR: 0.80; 95% CI: 0.61, 1.03) and GL (OR: 0.74; 95% CI: 0.53, 1.03). The authors concluded that they observed little association between breast cancer and GI or GL.

McCarl, 2006 (neutral quality), a prospective cohort study in the US, examined the associations between glycemic index (GI) and glycemic load (GL) and the risk of colorectal cancer in 35,197 women from the Iowa Women's Health Study (99% Caucasian, aged 55 to 69 years at baseline). Over 15 years of follow-up, 757 cases of colon cancer and 209 cases of rectal cancer (954 CRC cases) were observed. Overall, GI and GL were NS associated with incident colorectal cancer. However, when stratified by BMI, among obese women, colorectal cancer incidence was increased in the highest vs. lowest quintiles of GI (RR=1.66; 95% CI: 1.13 to 2.43; P=0.02) and GL (RR=1.79; 95% CI: 1.19 to 2.70; P<0.01). Similar results were observed for colon and rectal cancer. No significant associations between GI and GL and colorectal cancer risk were observed for non-obese women (BMI <30kg/m^2). The authors concluded that high GI or GL are not major colorectal cancer risk factors among older women in general, but may increase risk among women who are categorized as obese.

Michaud, 2005 (positive quality), a prospective cohort studies in the US, examined the associations between glycemic index (GI) and glycemic load (GL) and the risk of colorectal cancer in 47,422 male participants from the Health Professionals Follow-Up Study and 83,927 women from the Nurses' Health Study. During 20 years of follow-up, 1,809 incidence colorectal cancer cases were available for analyses. A slight increase in colorectal cancer risk for dietary GL was observed in men, but not women. The associations were slightly stronger among men with higher BMI, but there were still no

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associations observed after stratifying by BMI, physical activity or hormone use among women. The authors concluded that the glycemic response to diet may not play a major role in colorectal cancer.

Nöthlings, 2007 (neutral quality), a prospective cohort study in the US, examined the associations between dietary glycemic load (GL), dietary CHO, sucrose, fructose, total sugars and added sugars and pancreatic cancer risk among 162,150 men (N=72,966) and women (N=89,184) participating in the Multiethnic Cohort Study. Between 1993 and 1996 and 2002, 434 incident pancreatic cancer cases occurred in the cohort. Glycemic load was not associated with pancreatic cancer risk in the overall cohort (P=0.65). Non-significantly higher risks of pancreatic cancer were seen in the overweight and obese group (BMI ≥25kg/m^2) than in the normal weight group (BMI ≤25kg/m^2) in the top quartiles of GL. The authors concluded that dietary GL may not add important information about the quality of CHO in the diet of their cohort participants.

Patel, 2007 (positive quality), a prospective cohort study in the US, examined the association between glycemic load (GL), glycemic index (GI), CHO intake and pancreatic cancer risk among 124,907 men and women in the American Cancer Society Cancer Prevention Study II (CPS-II) Nutrition Cohort. During nine years of follow-up, 401 incident pancreatic cancer cases were identified. No association between GL or GI and risk of pancreatic cancer was observed. No factors examined (including being overweight or sedentary) modified the association between these dietary measures and pancreatic cancer risk. The authors concluded that their data do not support the hypothesis that GL or GI are associated with a substantial increase in pancreatic cancer risk.

Randi, 2008 (neutral quality), a case-control study in Italy, examined the association between glycemic index (GI) and glycemic load (GL) and risk of thyroid cancer. Cases (N=399, median age 44 years, 73% women) had histologically confirmed and incident cases of thyroid cancer. Controls (N=617, median age 46 years, 69% women) were patients admitted to the same network of hospitals as cases for acute non-neoplastic diseases unrelated to known or potential risk factors for thyroid carcinoma, and unrelated to long-term diet modification. Compared with the lowest tertile, the multivariate ORs in subsequent tertiles were 1.68 and 1.73 for GI (P=0.0047) and 1.76 and 2.17 for GL (P<0.0001). The authors concluded that GI and GL are associated with thyroid cancer risk.

Sieri, 2007 (neutral quality), a prospective cohort study in Italy, examined the association between glycemic index (GI) and glycemic load (GL) and risk of breast cancer in 8,926 women from the Hormones and Diet in the Etiology of Breast Tumors Study (ORDET Study). After a mean follow-up of 11.5 years, 289 breast cancers were identified. The adjusted RR of breast cancer in the highest vs. lowest quintiles of GI and GL was 1.57 (95% CI: 1.04, 2.36; P=0.040) and 2.53 (95% CI: 1.54, 4.16; P=0.001), respectively. When categorized by baseline menopausal status and BMI, the increased risk of dietary GL was confined to those who were pre-menopausal (RR=3.89; 95% CI: 1.81, 8.34) and who had normal BMI (i.e., <25kg/m^2) (RR=5.79; 95% CI: 2.60, 12.90; P=0.001 for both). The authors concluded that high dietary GL and, to a lesser extent, high dietary GI were significantly associated with a greater risk of breast cancer, particularly for pre-menopausal women and those with BMI <25kg/m^2.

Silvera, 2005 (positive quality), a prospective cohort study in Canada, examined the

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association between glycemic index (GI) and glycemic load (GL) and risk of breast cancer in 49,111 women from the Canadian National Breast Screening Study (NBSS). During a mean follow-up of 16.6 years, 1,450 incident breast cancer cases were observed. Dietary GL was not associated with risk of breast cancer. Overall GI was not associated with risk of breast cancer in the total study population. However, there was evidence of effect modification of the association between GI and breast cancer risk by menopausal status (P=0.01), the hazard ratio (HR) for the highest vs. the lowest quintile level of GI being 0.78 (95% CI: 0.52, 1.16; P=0.12) in pre-menopausal women and 1.87 (95% CI: 1.18, 2.97; P=0.01) in post-menopausal women. The associations between GI and GL were not modified by BMI or by vigorous physical activity among pre- or post-menopausal women. The associations between GI and GL and risk in post-menopausal women were not modified by BMI, vigorous physical activity or ever use of hormone replacement therapy (HRT), although the associations were slightly stronger among those who reported no vigorous physical activity (P=0.02), among those who reported ever using HRT (P=0.02) and among normal weight women (BMI <25kg/m^2; P=0.03). The authors concluded that dietary GL was not associated with risk of breast cancer. However, a relatively high overall GI might be associated with increased risk among women who are post-menopausal, possibly more so among subgroups defined by participation in vigorous physical activity, ever used HRT and those with BMI >25kg/m^2.

Silvera, 2005 (neutral quality), a prospective cohort study in Canada, examined the association between glycemic index (GI) and glycemic load (GL) and risk of endometrial cancer in 34,391 women from the Canadian National Breast Screening Study (NBSS). During a mean of 16.4 years of follow-up, 426 incident cases of endometrial cancer were observed. Adjusted hazard ratios (HR) for the highest vs. the lowest quartile of overall GI and GL were 1.47 (95% CI: 0.90, 2.41; P=0.14) and 1.36 (95% CI: 1.01, 1.84; P=0.21), respectively. When quartiles of GI and GL and risk of endometrial cancer were stratified by categories of BMI (<25, 25 to 29, 30kg/m^2 or more), participation in vigorous physical activity(none vs. some), menopausal status and use of HRT (never vs. ever), NS trends were observed. However, the authors concluded that dietary GL and overall GI may be associated with risk of endometrial cancer overall. They also stated that a relatively high dietary GL might be associated with increased risk among obese women and pre-menopausal women. Finally, they concluded that GL may be positively associated with endometrial cancer risk among post-menopausal women who have used HRT.

Silvera, 2005 (positive quality), a prospective cohort study in Canada, examined the association between glycemic index (GI) and glycemic load (GL) and risk of pancreatic cancer in 49,111 women from the Canadian National Breast Screening Study (NBSS). During a mean 16.5 years of follow-up, 112 incident pancreatic cancer cases were observed. No association between overall GI or GL and pancreatic cancer risk was observed. In multivariate adjusted models, the hazard ratio (HR) for the highest vs. lowest quartile levels of overall GI and GL were 1.43 (95% CI: 0.56, 3.65; P=0.58) and 0.80 (95% CI: 0.45, 1.41; P=0.41), respectively. The authors concluded that overall GI and GL were not associated with pancreatic cancer risk.

Silvera, 2007 (positive quality), a prospective cohort study in Canada, examined the association between glycemic index (GI) and glycemic load (GL) and risk of ovarian cancer in 48,776 women from the Canadian National Breast Screening Study (NBSS). During a mean 16.4 years of follow-up, 264 incident cases of ovarian cancer were

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observed. Glycemic index was not associated with risk of ovarian cancer in the total cohort. Glycemic load was positively associated with a 72% increase in risk of ovarian cancer (HR=1.72, 95% CI: 1.13, 2.62; P=0.01). The magnitude of the association was slightly greater among post-menopausal (HR=1.89, 95% CI: 0.98, 3.65, P=0.03) than among pre-menopausal women (HR=1.64, 95% CI: 0.95, 2.88; P=0.07); however, there was no statistical evidence of effect modification by baseline menopausal status (P for interaction = 0.54). The authors concluded that high GL may be associated with increased risk of ovarian cancer.

Strayer, 2007 (positive quality), a prospective cohort study in the US, examined the association between glycemic index (GI) and glycemic load (GL) and risk of colorectal cancer in 41,133 women from the Breast Cancer Detection Demonstration Project (BCDDP). During an average of 8.5 years of follow-up, 490 incident cases of colorectal cancer were observed. Reduction in colorectal cancer risk was observed for diets high in GI (RR for Q5 vs. Q1 = 0.75, 95% CI: 0.56, 1.00, P=0.03). There was NS association for GL (RR = 0.91, 95% CI: 0.70, 1.20; P=0.32). The authors concluded that the BCDDP cohort did not support the hypothesis that diets high in GI or GL increase the risk of colorectal cancer.

Weijenberg, 2008 (neutral quality), a case-cohort study in the Netherlands, examined the association between glycemic index (GI) and glycemic load (GL) and risk of colorectal cancer in participants in the Netherlands Cohort Study on Diet and Cancer. After 11.3 years of follow-up, 1,225 colon and 418 rectal cancer cases were identified. A case-cohort approach was used for data analysis. Case subjects were enumerated from the entire cohort, whereas the person-years at risk were estimated from a random sample of 5,000 subjects, taken from the cohort at baseline in 1987. The RR for colorectal cancer comparing the highest to the lowest quintile levels of GL and GI were 0.83 (95% CI: 0.64, 1.08; P=0.37) and 0.81 (95% CI: 0.61, 1.08, P=0.27) for men and 1.00 (95% CI: 0.73, 1.36, P=0.81) and 1.20 (95% CI: 0.85, 1.67; P=0.53) for women. In men, GI was associated with a reduced risk of distal colon cancer (P=0.03). The authors concluded that a diet with a high GL or GI was not associated with an increased risk of colorectal cancer in men or women in the Netherlands Cohort Study on Diet and Cancer.

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Overview table

Author, Year, Study Design, Class, Rating	Population/Subjects	Methodology	Significant Outcomes
Augustin et al 2004 Study Design: Case-Control Study Class: C Neutral Quality	N=1,204 male cases and 1,352 male controls. Median age: 66 years cases, 63 years controls.	Cases and controls recruited between 1991 and 2002 in network of major teaching and general hospitals in four Italian areas. Cases were men admitted for incident, histologically confirmed prostate cancer. Controls were men admitted for acute, non-malignant conditions unrelated to long-term modifications of diet. Interviewer-administered 78-item FFQ utilized to assess usual diet for the two years preceding diagnosis for cases or hospital admission for controls.	Compared to the lowest quintile of GI, OR for developing prostate cancer were 1.23, 1.24, 1.47 and 1.57 for subsequent levels of GI and the corresponding values for GL were 0.91, 1.00, 1.20,1.41.

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Bertuccio et al 2009 Study Design: Case-Control Study Class: C Positive Quality	Total N: 787 (429 males, 348 females). Study group: 230 (143 males, 87 females) Control group: 547 (286 males, 261 women). Median age: 63 years for both study group and control group. Location: Italy.	230 patients had incident, histologically confirmed gastric cancer between 1997 and 2007 and 547 patients who had non-neoplastic conditions served as matched controls. Researchers assessed subjects' usual diet from the two years prior to hospital admission and diagnosis using a valid FFQ.	OR in the highest vs. lowest quintile were 1.9 (95% CI: 1.0 to 3.3) for GI and 2.5 (95% CI: 1.3 to 4.9) for GL. OR rose across strata of high GL and low fruit and vegetable intake to reach 5.0 (95% CI: 2.2 to 11.5) for those reporting high GL and low fruit and vegetable intake, compared with participants reporting low GL and high fruit and vegetable intake.
Cust et al 2007 Study Design: Prospective cohort study Class: B Positive Quality	N=288,428 women from the European Prospective Investigation into Cancer and Nutrition cohort study. Age: 54.1±8.7 years endometrial cancer cases; 49.9±11.6 years non-cases. Location: Europe.	Participants enrolled between 1992 and 2000 in 23 centers throughout 10 western European countries . During a mean 6.4 years and 1,842,995 person-years of follow-up, 710 incident endometrial cancer cases were diagnosed. Cancer diagnosis microscopically verified for 89.3% of cases and by clinical examination for 8.5%; the remaining 2.2% verified by self-report, tomography scan, surgery, autopsy or death certificate. Overall GI or GL: Usual diet during the previous 12 months was assessed with country-specific, validated dietary assessment instruments.	Data suggest no association of overall GI, total starch and total fiber with endometrial cancer risk; however, multivariable RR were 1.61 (95% CI: 1.06 to 2.45) per 100g per day of total CHOs, 1.40 (95% CI: 0.99 to 1.99) per 50g per day of total dietary GL, and 1.36 (95% CI: 1.05 to 1.76) per 50g per day of total sugars. Associations were stronger among women who had never used post-menopausal hormone therapy.

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Flood et al. 2006 Study Design: Cross-sectional Study Class: D Positive Quality	N=44,572 participants from the Prostate, Lung, Colorectal and Ovarian Screening Trial. N=24,017 men and 20,555 women. Age: 55 to 74 years. Location: United States.	Participants completed a flexible sigmoidoscopy exam. N=34,817 had no lesions and 3,696 had at least one distal adenoma. 137-item FFQ used to assess usual dietary intake for each participant over the 12 months before enrollment. FFQ provided information for ascertainment of portion size for all food items except fruit and vegetables.	GI was NS associated with risk for distal adenomas in men or women. Among men, GL had significant inverse association with distal adenomas (OR for quintile five compared with quintile one in multivariate-adjusted models for men: 0.79; 95% CI: 0.68, 0.93; P=0.003). Among women, GL was NS associated with risk for distal adenomas (OR for women: 0.98; 95% CI: 0.81, 1.19; P=0.70).
George et al 2009 Study Design: Prospective Cohort Study Class: B Positive Quality	N=262,642 male and 183,535 female participants from the NIH-AARP Diet and Health Study. Age: 50 to 71 years at baseline. Location: United States.	Participants followed from 1995 to 2003. Cancer cases identified through probabilistic linkage with 11 state cancer registry databases. Dietary intake assessed at baseline using a self-administered 124-item FFQ.	15,215 cancer cases identified in women; 33,203 cases identified in men. RR for total cancer for high vs. low GI were 1.03 for women (P=0.217) and 1.04 for men (P=0.012), and for high vs. low GL, were 0.90 for women (P=0.024) and 0.93 for women (P=0.01), suggesting that GI and GL are not strong predictors of cancer incidence.

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Giles et al 2006 Study Design: Prospective Cohort Study Class: B Neutral Quality	N=12,273 post-menopausal women in the Melbourne Collaborative Cohort Study (MCCS). Age: 40 to 69 years at baseline. Location: Australia.	Participants recruited in 1990 to 1994 and followed until 2002. Breast cancers ascertained by the Victorian Cancer Registry. Dietary intake assessed at baseline using 121-item, self-administered FFQ, specifically developed for the MCCS.	During an average of 9.1 years follow-up, 324 breast cancers were diagnosed. Although an ↑ of one SD in CHO intake was marginally associated with risk of breast cancer (RR=1.31, 95% CI: 0.98, 1.75), there were NS associations with fiber, GI, GL or CHO foods.
Heinen et al 2008 Study Design: Prospective Cohort Study Class: B Neutral Quality	Subcohort of the Netherlands Cohort Study. Final N: 4,438 subjects (2,191 men, 2,247 women) and 408 exocrine pancreatic cancer cases (217 men, 191 women). Age: 55 to 69 years at baseline. Location: Netherlands.	Baseline questionnaire completed in 1986 and participants followed to 1999. Pancreatic cancer occurrence by annual record linkage to the Netherlands Cancer Registry and the Netherlands Pathology Registry. 150-item validated FFQ completed at baseline and used to calculate CHO and mono- and disaccharide intake and GI and GL of the diet.	13.3 years of follow-up, 408 pancreatic cancer cases were detected (66% microscopically confirmed). Dietary GL, GI or intake of CHO and mono- and disaccharides were not associated with pancreatic cancer risk.

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Howarth et al 2008 Study Design: Prospective Cohort Study Class: B Neutral Quality	Total N=191,004 men (N=85,898) and women (N=105,106) participating in the Multiethnic Cohort Study. Age: 45 to 75 years at baseline. From five ethnic groups: African American, White, Latino, Native Hawaiian or Japanese American. Location: United States.	Baseline measurements conducted between 1993 and 1996 and participants followed through 2002. Incident colorectal cancer cases identified by record linkage to the Hawaii Tumor Registry, the Cancer Surveillance Program for Los Angeles County and the California State Cancer Registry; all registries are members of the Surveillance, Epidemiology and End Results Program (SEER) of the National Cancer Institute. Quantitative FFQ data with over 180 food items used to assess usual dietary intake over preceding year. Quantitative FFQ was developed specifically for study population and based on 3-day measured food records from each ethnic group	Over eight years of follow-up, 2,379 incident cases of colorectal adenocarcinoma occurred in 1,293 men and 1,086 women. In multivariate models, RR for colorectal cancer ↓ significantly with ↑ GL in women (RR for the highest vs. lowest quintile = 0.75, 95% CI: 0.57, 0.97; P=0.02), but not in men (RR=1.15, 95% CI: 0.89, 1.48; P=0.19). Inverse association with GL found in women of all ethnic groups (P for interaction = 0.58). In men, interaction found between ethnicity and GL (P<0.01) in that white men had positive association with ↑ GL (RR=1.69, 95% CI: 0.98, 2.92, P=00.01), but men of other ethnic groups did not. Note: GI not included in analyses.
Johnson et al 2005 Study Design: Prospective Cohort Study Class: B Neutral Quality	N=33,551 women from the Iowa Women's Health Study. Age: 55 to 69 years at baseline. Location: United States.	Baseline data collected in 1986 and followed to 2002. Incidence of pancreatic cancer as measured by Iowa death records, the National Death Index and the Iowa Cancer Registry. Dietary intake assessed using a 126-item FFQ.	Incidence of pancreatic cancer was higher in subjects aged 65 to 69 vs. aged 55 to 64, diabetic vs. non-diabetic, current smokers vs. non-smokers and multivitamin non-users vs. users, but there was no ↑ hazard of pancreatic cancer associated with ↑ dietary GI or GL.

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Kabat et al 2008 Study Design: Prospective Cohort Study Class: B Neutral Quality	N=158,800 post-menopausal women from the Observational Study and Clinical Trial cohorts of the Women's Health Initiative. Age: 50 to 79 years at baseline, average 63 years. Location: United States.	Participants recruited between 1993 and 1998. Colorectal cancer diagnosis obtained using mail or telephone questionnaires; self-reports verified by trained physician adjudicators; all cancer diagnoses confirmed by blinded review. Dietary intake in past three months assessed using self-administered FFQ with 122 food items, 19 “adjustment” questions and three summary questions.	Over an average of 7.8 years of follow-up 1,476 incident cases of colorectal cancer were identified. Total CHO intake, GI, GL and intake of sugars and fiber showed no association with colorectal cancer.
Lajous et al 2005 Study Design: Population-based Case Control Study Class: C Neutral Quality	N=475 women with breast cancer and 1,391 controls. Age: <40 years: 16% of cases, 25% of controls 40 to 49 years: 24% of cases, 27% of controls 50 to 59 years: 27% of cases, 22% of controls ≥60 years: 33% of cases, 26% of controls. Location: Mexico.	Participants recruited between 1990 and 1995. Breast cancer confirmed by biopsy. Diet assessed with validated, semi-quantitative FFQ adapted to Mexican population.	Multivariate adjusted OR for all women comparing the highest and lowest tertiles of dietary GL was 1.62 (95% CI: 1.13 to 2.32, P=0.02); the association was stronger in post-menopausal women, where the multivariate adjusted OR comparing the extreme quartiles was 2.18 (95% CI: 1.34 to 3.55; P=0.005). Overall, GI was NS associated with risk of breast cancer.

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Lajous et al 2008 Study Design: Prospective Cohort Study Class: B Neutral Quality	N=62,739 post-menopausal women participating in the E3N French Study (French component of the European Prospective Investigation into Cancer and Nutrition). Age: Mean 53±7 years (range 42 to 72 years). Location: France.	Diet history questionnaires completed in 1993. Follow-up questionnaires sent in 1994, 1997, 2000 and 2002. Incidental cases of breast cancer were initially identified by self-report . Physicians contacted to obtain pathology reports and information on estrogen receptor and progesterone receptor status. Deaths in cohort were identified by reports from family members, postal service and MGEN health insurance database. Dietary intake during past year assessed using 208-item FFQ.	During nine years of follow-up, 1,812 cases of pathology-confirmed breast cancer documented. Dietary CHO intakes, GI and GL not associated with overall post-menopausal breast cancer risk. However, among overweight women (BMI >25kg/m^2), there was an association between GI and breast cancer (RR=1.35, 95% CI: 1.00, 1.82, P=0.04); this association was absent for women with BMI <25kg/m^2. For women in the highest category of WC, the RR (Q1-Q4) was 1.28 (95% CI: 0.98, 1.67; P for trend = 0.10) for CHO, 1.35 (95% CI: 1.04, 1.75; P for trend = 0.01) for GI and 1.37 (95% CI: 1.05, 1.77; P for trend = 0.003) for GL. They also reported a direct association between CHO intake, GL and estrogen receptor-negative breast cancer risk.

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Larsson et al 2006 Study Design: Prospective Cohort Study Class: B Neutral Quality	N=61,433 women participating in the Swedish Mammography Cohort Study. Diet was assessed at baseline (1987–1990) and again in 1997.	Follow-up through 2004. Stomach cancer incidence obtained by linkage to national and regional Swedish Cancer registers Subjects completed a 67-item FFQ at baseline and a 96-item FFQ in 1997.	During 903,586 person-years of follow-up, there were 156 incident cases of stomach cancer. No association between CHO intake, GI or GL and incidence of stomach cancer using any of the dietary intake data. Multivariate HR for highest vs. lowest quintile were 0.76 (95% CI: 0.46, 1.25) for GL, 0.77 (95% CI: 0.46, 1.30) for overall GI and 0.85 (95% CI: 0.50, 1.43) for CHO intake. Associations did not vary according to BMI.

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Larsson et al 2007 Am J Epidemiol Study Design: Prospective Cohort Study Class: B Neutral Quality	N=61,433 women participating in the Swedish Mammography Cohort Study. Age: 40 to 76 years. Location: Sweden.	Baseline questionnaire in 1987 to 1990. Follow-up through 2005. Incidence of colorectal cancers ascertained by computerized record linkage of the study population with the national and regional Swedish Cancer registers. Subjects completed a 67-item FFQ at baseline. N=36,616 women completed a 96-item FFQ in 1997.	Analysis with first FFQ (1987 to 1990): 1) Over 963,426 person-years of follow-up (mean = 15.7 years), there were 870 cases of colorectal adenocarcinoma 2) CHO intake, GI and GL had NS association with risk of colorectal, colon or rectal cancer regardless of BMI and alcohol intake. Analysis with second FFQ (1997): 1) Over 266,022 person-years of follow-up (mean 7.3 years), there were 297 incident colorectal cancer cases 2) No association between CHO intake or GL and risk of colorectal cancer 3) GI positively associated with colorectal cancer risk (multivariate HR comparing highest and lowest quintile was 1.95; 95% CI: 1.19, 3.20; P=0.01) even after adjustment for confounders, but was attenuated when first three years of follow-up excluded (HR=1.58; 95% CI: 1.17, 3.16).

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Larsson et al 2007 Int J Cancer Study Design: Prospective Cohort Study Class: B Neutral Quality	N=61,226 women participating in the Swedish Mammography Cohort Study. Age: 40 to 76 years. Location: Sweden.	Baseline questionnaire in 1987 to 1990. Follow-up through 2005. Incidence of endometrial cancers ascertained by computerized record linkage of the study population with the national and regional Swedish Cancer registers. Subjects completed a 67-item FFQ at baseline. N=36,369 women completed 96-item FFQ in 1997. Analysis with first FFQ (1987 to 1990): Over 952,629 person-years of follow-up (mean 15.6 years), there were 608 cases of endometrial cancer, but no overall association between CHO intake, GI or GL and incidence of endometrial cancer.	Analysis with second FFQ (1997): 1) Over 262,993 person-years of follow-up, 214 incidence endometrial cancer cases available 2) No overall association between CHO intake, GI or GL and endometrial cancer risk 3) CHO intake and GL were positively related to endometrial cancer risk among overweight women (BMI >25kg/m^2) with ↓ physical activity; multivariate RRs comparing extreme quartiles were 1.90 (95% CI: 0.84 to 4.31) for CHO intake and 2.99 (95% CI: 1.17 to 7.67) for GL.
McCann SE, McCann WE et al, 2007 Study Design: Case Control Study Class: C Positive Quality	N=1,166 cases and 2,105 matched controls in the Western New York Exposure and Breast Cancer Study (WEB). Age: 35 to 79 years. Predominantly white (90%). 40% pre-menopausal (30% of cases pre-menopausal). Location: United States.	Data collected between 1996 and 2001. Cases were incident, primary, histologically confirmed breast cancer. Participants were randomly selected from either New York State Department of Motor Vehicles drivers' license list (participants under 65 years) or from the Health Care Finance Administration rolls (participants age ≥65 years). Diet 12 to 24 months before diagnosis assessed with FFQ in cases or an interview in controls.	In pre-menopausal women, breast cancer was not related to GI or GL. NS trend toward a ↓ in risk of breast cancer for post-menopausal women in the highest vs. lowest quartile of GI (OR: 0.80; 95% CI: 0.61, 1.03) and GL (OR: 0.74; 95% CI: 0.53, 1.03).

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McCarl M, Harnack L et al, 2006 Study Design: Prospective Cohort Study Class: B Neutral Quality	N=35,197 women from the Iowa Women's Health Study. Age: 55 to 69 years at baseline (mean of 61.7 years). 99% Caucasian. Location: United States.	Baseline assessments in 1986 and followed through 2000. Colorectal cancer incidence and deaths ascertained by computer linkage with the State Health Registry of Iowa, which includes a Surveillance, Epidemiology, and End Results cancer registry. Dietary intake over previous year assessed with validated 127-item FFQ at baseline.	Over 15 years of follow-up, 757 cases of colon cancer and 209 cases of rectal cancer (954 CRC cases) were observed. When adjusted for age and energy, no association between either GI or GL and incident colorectal cancer. Adjustment for other risk factors or adding other dietary variables to the model did not appreciably Δ results. Separate analyses based on colon and rectal subsites were similarly unremarkable. Analyses stratified by BMI (<25, 25 to 30, >30kg/m^2) showed that GI and GL positively associated with colorectal cancer in highest BMI category (P for interaction = 0.04 for GI; 0.05 for GL). GL, but not GI, positively associated with colon cancer in highest BMI category (P<0.01), whereas GL and GI were both positively associated with rectal cancer in highest BMI category (P=0.04 and 0.02, respectively). NS relations between GI or GL and CRC among subjects whose baseline BMI was <30 kg/m^2 were observed.

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Michaud DS, Fuchs CS et al, 2005 Study Design: Prospective Cohort Study Class: B Positive Quality	N=131,349 participants from the Health Professionals Follow-Up Study (47,422 men aged 40 to 75 years) and the Nurses' Health Study (83,927 women aged 30 to 55 years). Location: United States.	Health Professionals Follow-up Study: Initiated in 1986 and followed through January 2000. Nurses' Health Study: Initiated in 1976 and followed through May 2000. Colorectal cancer, colon cancer, rectal cancer: Participants asked to report specified cancers that were diagnosed in the two-year period between each follow-up questionnaire. Confirmation attempted with medical record review or additional questioning of the participant. Nurses' Health Study: Diet assessed with a 61-item FFQ in 1980; a 116-item FFQ assessed intake in 1984, 1986 and every four years thereafter. Health Professionals Follow-Up Study: Diet assessed with a 131-item FFQ in 1986 and every four years thereafter.	During 20 years of follow-up, 1,809 incidence colorectal cancer cases were available for analysis. Among women, no associations were observed for dietary CHO, GL or GI and risk of colorectal cancer. No associations identified after stratifying by BMI or physical activity. Among men, a small ↑ in risk was observed with high GL (multivariate RR, 1.32; 95% CI, 0.98 to 1.79; highest vs. lowest quintile) and associations were slightly stronger among men with ↑ BMI (≥25kg/m^2).

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Nothlings U, Murphy SP et al, 2007 Study Design: Prospective Cohort Study Class: B Neutral Quality	N=162,150 men (N=72,966) and women (N=89,184) participating in the Multiethnic Cohort Study. Age: 45 to 75 years at baseline. Ethnic groups: African American, White, Latino, Native Hawaiian or Japanese American. Location: United States.	Baseline measurements conducted between 1993 and 1996 and participants followed through 2002. Incident exocrine pancreatic cancer cases identified by record linkage to Hawaii Tumor Registry, Cancer Surveillance Program of Los Angeles County and California State Cancer Registry. Dietary intake assessed with quantitative FFQ especially designed and validated for use in this multiethnic population.	During follow-up, 434 incident pancreatic cancer cases occurred in cohort. GL not associated with pancreatic cancer risk in the overall cohort (P=0.65). Higher (but NS higher) risks of pancreatic cancer were seen in the overweight and obese group (BMI ≥25kg/m^2) than in normal-weight group (BMI ≤25kg/m^2) in the top quartiles of GL. Note: GI not included in analyses.
Patel AV, McCullough ML et al, 2007 Study Design: Prospective Cohort Study Class: B Positive Quality	N=124,907 men and women from the American Cancer Society Cancer Prevention Study II (CPSII) Nutrition Cohort. Mean age at study entry: 62.7 years (±6.35 SD). Location: United States.	Baseline in 1992 and follow-up through August 2001. 78% of pancreatic cancer cases identified initially as interval deaths for which pancreatic cancer was listed as cause of death on death certificate; additional cases identified by self-report with verification by medical records or linkage with state registries. Dietary intake over past year assessed at baseline using a semi-quantitative 68-item FFQ.	During nine years of follow-up, 401 incident pancreatic cancer cases were identified. No association between GL or GI and risk of pancreatic cancer observed. Hazard rate ratio (RR) was 1.01 (95% CI: 0.75, 1.37, P=0.80) for GL and 0.92 (95% CI: 0.68, 1.24) for GI among men and women in the highest quintile vs. the lowest quintile. NS association between these measures and pancreatic cancer risk observed among individuals who were overweight or more sedentary.

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Randi G, Ferraroni M et al, 2008 Study Design: Case Control Study Class: C Neutral Quality	N=399 cases (291 women, 108 men, aged 16 to 72 years, median age 44 years). N=617 controls (427 women, 190 men, aged 16 to 74 years, median age 46 years). Location: Italy.	Study conducted from 1986 to 1992 in major teaching and university hospitals in three areas of Northern Italy. Cases: Histologically confirmed and incident cases of thyroid cancer. Controls: Patients admitted to same network of hospitals as cases for acute non-neoplastic diseases unrelated to known or potential risk factors for thyroid carcinoma and unrelated to long-term diet modification. Dietary intake assessed by trained interviewer. Weekly frequency of consumption of 29 food items during the two years before the onset of symptoms that led to the diagnosis were recorded.	Multivariate ORs of thyroid cancer according to GI: Compared with the lowest tertile, the ORs in subsequent tertiles were 1.68 and 1.73 for GI (P=0.0047). Multivariate ORs of thyroid cancer according to GL: Compared with the lowest tertile, the ORs in subsequent tertiles were 1.76 and 2.17 for GL (P<0.0001).
Sieri S, Pala V et al, 2007 Study Design: Prospective Cohort Study Class: B Neutral Quality	N=8,926 women from the Hormones and Diet in the Etiology of Breast Tumors Study (ORDET Study). Age: 34 to 70 years at baseline. Location: Italy.	Baseline enrollment between 1987 and 1992 and follow-up to December 2001. Breast cancer cases from cancer registry (Varese Cancer Registry). Dietary intake over previous year assessed with 107-item semi-quantitative FFQ at baseline.	After a mean follow-up of 11.5 years, 289 breast cancers identified. Adjusted RR of breast cancer in highest vs. lowest quintiles of GI and GL was 1.57 (95% CI: 1.04, 2.36; P=0.040) and 2.53 (95% CI: 1.54, 4.16; P=0.001), respectively. When categorized by baseline menopausal status and BMI, the ↑ risk of dietary GL was confined to those who were pre-menopausal (RR=3.89; 95% CI: 1.81, 8.34) and who had normal BMI (i.e., <25kg/m^2) (RR=5.79; 95% CI: 2.60, 12.90) (P=0.001 for both).

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Silvera SA, Jain M et al, 2005 Study Design: Prospective Cohort Study Class: B Positive Quality	N=49,111 women from the Canadian National Breast Screening Study (NBSS). Age: 40 to 59 years at baseline. Location: Canada.	Baseline between 1980 and 1985 and follow-up ending between 1998 and 2000. Linkages to national mortality and cancer databases yielded data on deaths and breast cancer incidence. Dietary intake assessed with self-administered 86-item FFQ.	During a mean follow-up of 16.6 years, 1,450 incident breast cancer cases observed. GI and GL not associated with breast cancer risk in the total cohort. There was evidence of effect modification of the association between GI and breast cancer risk by menopausal status (P=0.01), the HR for the highest vs. the lowest quintile level of GI being 0.78 (95% CI: 0.52, 1.16; P=0.12) in pre-menopausal women and 1.87 (95% CI: 1.18, 2.97; P=0.01) in post-menopausal women. Associations between GI and GL were not modified by BMI or by vigorous physical activity among pre- or post-menopausal women. Associations between GI and GL and risk in post-menopausal women were not modified by BMI, vigorous physical activity or ever use of HRT, although associations were slightly stronger among those who reported no vigorous physical activity (P=0.02), among those who reported ever using HRT (P=0.02) and among normal weight women (BMI <25kg/m^2; P=0.03).

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Silvera SA, Jain M et al, 2007 Study Design: Prospective Cohort Study Class: B Positive Quality	N=48,776 women from the Canadian National Breast Screening Study (NBSS). Age: 40 to 59 years at baseline. Location: Canada.	Baseline between 1980 and 1985 and follow-up ending between 1998 and 2000. Linkages to Canadian Cancer Database and National Mortality Database yielded data on deaths and ovarian cancer incidence. Dietary intake assessed with self-administered 86-item FFQ.	During a mean 16.4 years of follow-up, 264 incident cases of ovarian cancer observed. GI not associated with risk of ovarian cancer in total cohort. GL positively associated with a 72% ↑ in risk of ovarian cancer (HR=1.72, 95% CI: 1.13, 2.62; P=0.01). Magnitude of association was slightly greater among post-menopausal (HR=1.89, 95% CI: 0.98, 3.65, P=0.03) than among pre-menopausal women (HR=1.64, 95% CI: 0.95, 2.88; P=0.07); however, no statistical evidence of effect modification by baseline menopausal status (P for interaction = 0.54).
Silvera SA, Rohan TE et al, 2005 (endometrial) Study Design: Prospective Cohort Study Class: B Neutral Quality	N=34,391 women from the Canadian National Breast Screening Study (NBSS). Age: 40 to 59 years at baseline. Location: Canada.	Baseline between 1980 and 1985 and follow-up ending between 1998 and 2000. Linkages to national mortality and cancer databases yielded data on deaths and endometrial cancer incidence. Dietary intake assessed with self-administered 86-item FFQ.	During a mean of 16.4 years of follow-up, 426 incident cases of endometrial cancer observed. Adjusted HR for the highest vs. the lowest quartile of overall GI and GL were 1.47 (95% CI; 0.90, 2.41; P=0.14) and 1.36 (95% CI: 1.01, 1.84; P=0.21), respectively. When quartiles of GI and GL and risk of endometrial cancer were stratified by categories of BMI (<25, 25 to 29, ≥30kg/m^2), participation in vigorous physical activity (none vs. some), menopausal status and use of HRT (never vs. ever), NS trends were observed.

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Silvera SA, Rohan TE et al, 2005 (pancreatic) Study Design: Prospective Cohort Study Class: B Positive Quality	N=49,111 women from the Canadian National Breast Screening Study (NBSS). Age: 40 to 59 years at baseline. Location: Canada.	Baseline between 1980 and 1985 and follow-up ending between 1998 and 2000. Linkages to Canadian Cancer Database and National Mortality Database yielded data on deaths and pancreatic cancer incidence. Dietary intake assessed with self-administered 86-item FFQ.	During a mean 16.5 years of follow-up, 112 incident pancreatic cancer cases observed. No association between overall GI and GL and pancreatic cancer risk. In multivariate adjusted models, the HR for the highest vs. lowest quartile levels of overall GI and GL were 1.43 (95% CI: 0.56, 3.65; P=0.58) and 0.80 (95% CI: 0.45, 1.41; P=0.41), respectively.
Strayer L, Jacobs DR Jr et al, 2007 Study Design: Prospective Cohort Study Class: B Positive Quality	N=41,133 women from the Breast Cancer Detection Demonstration Project (BCDDP). Mean age: 61.9 years. Location: United States.	Dietary assessment completed between 1987 and 1989. Follow-up continued through 1995 and 1998. Colorectal cancer cases identified from self-reports on questionnaires in 1992 to 1995 and 1995 to 1998 (79% confirmed by pathology), statewide cancer registries and the National Death Index (through 1997). 62-item validated FFQ used to assess usual dietary intake over the previous year.	During an average of 8.5 years of follow-up, 490 incident cases of colorectal cancer observed. ↓ in colorectal cancer risk observed for diets high in GI (RR for Q5 vs. Q1 = 0.75, 95% CI: 0.56, 1.00, P=0.03). NS association for GL (RR=0.91, 95% CI: 0.70, 1.20; P=0.32).

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Weijenberg MP, Mullie PF et al, 2008 Study Design: Prospective Cohort Study Class: B Neutral Quality	N=120,852 men and women from the Netherlands Cohort Study. Age: 55 to 69 years at baseline (53% women). Location: Netherlands.	Case-cohort approach used for data analysis. Case subjects enumerated from entire cohort, whereas person-years at risk estimated from random sample of 5,000 subjects, taken from cohort at baseline in 1987. Colon and rectal cancers identified by using combination of computerized linkage system to nine cancer registries in the Netherlands and a nationwide pathology database. A semi-quantitative FFQ that included 150 food items covered habitual food habits during the year before the start of the study.	After 11.3 years of follow-up, 1,225 colon and 418 rectal cancer cases available for analysis. RR for colorectal cancer comparing the highest vs. the lowest quintile levels of GL and GI were 0.83 (95% CI: 0.64, 1.08; P=0.37) and 0.81 (95% CI: 0.61, 1.08, P=0.27) for men and 1.00 (95% CI: 0.73, 1.36, P=0.81) and 1.20 (95% CI: 0.85, 1.67; P=0.53) for women. In men, GI associated with a ↓ risk of distal colon cancer (P=0.03).

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Search plan and results

Inclusion criteria

- June 2004 to March 2009 for cancer, and January 2000 to September 2009 for CVD and type 2 diabetes
- Human subjects
- English language
- International
- *Sample size*: Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate*: Less than 20%; preference for smaller dropout rates
- *Ages*: Children, two to 18 years; adults, 19 years and older
- *Populations*: Healthy and those with elevated chronic disease risk.

Exclusion criteria

- Reviews (narrative and systematic); meta-analyses
- Studies examining intermediate outcomes, not incidence of disease
- Medical treatment or therapy, including medical treatment of diabetes
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Animal studies
- In vitro studies
- Articles not peer reviewed (Websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed:
  Cancer: "Neoplasms"[Mesh] AND ("Glycemic Index"[Mesh] OR "glycemic load"[All Fields])

- PubMed, Embase, BIOSIS:
  Cardiovascular Disease: ("Glycemic Index"[Mesh] OR "glycemic load") AND (“Cardiovascular diseases”[Mesh])

- PubMed, Embase, BIOSIS:
  Type 2 Diabetes: ("Glycemic Index"[Mesh] OR "glycemic load") AND (“Diabetes Mellitus, Type 2”[Mesh])

Date searched: 03/20/2009; updated 09/19/2009 and 09/22/2009 for CVD and T2D

Summary of articles identified to review

- Total hits from all electronic database searches: 491
- Total articles identified to review from electronic databases: 133
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 46
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 46
- Number of Articles Reviewed but Excluded: 87

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Included articles (References)

What is the relationship between glycemic index or glycemic load and cancer?

1. Augustin LS, Galeone C, Dal Maso L, Pelucchi C, Ramazzotti V, Jenkins DJ, Montella M, Talamini R, Negri E, Franceschi S, La Vecchia C. Glycemic index, glycemic load and risk of prostate cancer. *Int J Cancer.* 2004 Nov 10; 112(3): 446-450. PMID: 15382070.
2. Bertuccio P, Praud D, Chatenoud L, Lucenteforte E, Bosetti C, Pelucchi C, Rossi M, Negri E, La Vecchia C. Dietary glycemic load and gastric cancer risk in Italy. *Br J Cancer.* 2009 Feb 10; 100(3): 558-561. PMID: 19190635.
3. Cust AE, Slimani N, Kaaks R, van Bakel M, Biessy C, Ferrari P, Laville M, Tjønneland A, Olsen A, Overvad K, Lajous M, Clavel-Chapelon F, Boutron-Ruault MC, Linseisen J, Rohrmann S, Nöthlings U, Boeing H, Palli D, Sieri S, Panico S, Tumino R, Sacerdote C, Skeie G, Engeset D, Gram IT, Quirós JR, Jakszyn P, Sánchez MJ, Larrañaga N, Navarro C, Ardanaz E, Wirfält E, Berglund G, Lundin E, Hallmans G, Bueno-de-Mesquita HB, Du H, Peeters PH, Bingham S, Khaw KT, Allen NE, Key TJ, Jenab M, Riboli E. Dietary carbohydrates, glycemic index, glycemic load, and endometrial cancer risk within the European Prospective Investigation into Cancer and Nutrition cohort. *Am J Epidemiol.* 2007 Oct 15; 166(8): 912-923. Epub 2007 Aug 1. PMID: 17670911.
4. Flood A, Peters U, Jenkins DJ, Chatterjee N, Subar AF, Church TR, Bresalier R, Weissfeld JL, Hayes RB, Schatzkin A; Prostate, Lung, Colorectal, Ovarian (PLCO) Project Team. Carbohydrate, glycemic index, and glycemic load and colorectal adenomas in the Prostate, Lung, Colorectal, and Ovarian Screening Study. *Am J Clin Nutr.* 2006 Nov; 84(5): 1, 184-1, 192. PMID: 17093173.
5. George SM, Mayne ST, Leitzmann MF, Park Y, Schatzkin A, Flood A, Hollenbeck A, Subar AF. Dietary glycemic index, glycemic load, and risk of cancer: A prospective cohort study. *Am J Epidemiol.* 2009 Feb 15; 169(4): 462-472. Epub 2008 Dec 18. PMID: 19095757.
6. Giles GG, Simpson JA, English DR, Hodge AM, Gertig DM, Macinnis RJ, Hopper JL. Dietary carbohydrate, fibre, glycaemic index, glycaemic load and the risk of postmenopausal breast cancer. *Int J Cancer.* 2006 Apr 1; 118(7): 1, 843-1, 847. PMID: 16217755.
7. Heinen MM, Verhage BA, Lumey L, Brants HA, Goldbohm RA, van den Brandt PA. Glycemic load, glycemic index, and pancreatic cancer risk in the Netherlands Cohort Study. *Am J Clin Nutr.* 2008 Apr; 87(4): 970-977. PMID: 18400721.
8. Howarth NC, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. The association of glycemic load and carbohydrate intake with colorectal cancer risk in the Multiethnic Cohort Study. *Am J Clin Nutr.* 2008 Oct; 88(4): 1, 074-1, 082. PMID: 18842796.
9. Johnson KJ, Anderson KE, Harnack L, Hong CP, Folsom AR. No association between dietary glycemic index or load and pancreatic cancer incidence in postmenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2005 Jun; 14(6): 1, 574-1, 575. PMID: 15941976.
10. Kabat GC, Shikany JM, Beresford SA, Caan B, Neuhouser ML, Tinker LF, Rohan TE. Dietary carbohydrate, glycemic index, and glycemic load in relation to colorectal cancer risk in the Women's Health Initiative. *Cancer Causes*

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Control. 2008 Dec; 19(10): 1, 291-1, 298. Epub 2008 Jul 10. PMID: 18618276.
11. Lajous M, Willett W, Lazcano-Ponce E, Sanchez-Zamorano LM, Hernandez-Avila M, Romieu I. Glycemic load, glycemic index, and the risk of breast cancer among Mexican women. *Cancer Causes Control.* 2005 Dec; 16(10): 1, 165-1, 169. PMID: 16215866.
12. Lajous M, Boutron-Ruault MC, Fabre A, Clavel-Chapelon F, Romieu I. Carbohydrate intake, glycemic index, glycemic load, and risk of postmenopausal breast cancer in a prospective study of French women. *Am J Clin Nutr.* 2008 May; 87(5): 1, 384-1, 391. PMID: 18469262.
13. Larsson SC, Bergkvist L, Wolk A. Glycemic load, glycemic index and carbohydrate intake in relation to risk of stomach cancer: a prospective study. *Int J Cancer.* 2006 Jun 15; 118(12): 3, 167-3, 169. PMID: 16395707.
14. Larsson SC, Giovannucci E, Wolk A. Dietary carbohydrate, glycemic index, and glycemic load in relation to risk of colorectal cancer in women. *Am J Epidemiol.* 2007 Feb 1; 165(3): 256-261. Epub 2006 Nov 21. PMID: 17118965
15. Larsson SC, Friberg E, Wolk A. Carbohydrate intake, glycemic index and glycemic load in relation to risk of endometrial cancer: A prospective study of Swedish women. *Int J Cancer.* 2007 Mar 1; 120(5): 1, 103-1, 137. PMID: 17131331.
16. McCann SE, McCann WE, Hong CC, Marshall JR, Edge SB, Trevisan M, Muti P, Freudenheim JL. Dietary patterns related to glycemic index and load and risk of premenopausal and postmenopausal breast cancer in the Western New York Exposure and Breast Cancer Study. *Am J Clin Nutr.* 2007 Aug; 86(2): 465-471. PMID: 17684220.
17. McCarl M, Harnack L, Limburg PJ, Anderson KE, Folsom AR. Incidence of colorectal cancer in relation to glycemic index and load in a cohort of women. *Cancer Epidemiol Biomarkers Prev.* 2006 May; 15(5): 892-896. PMID: 16702366.
18. Michaud DS, Fuchs CS, Liu S, Willett WC, Colditz GA, Giovannucci E. Dietary glycemic load, carbohydrate, sugar, and colorectal cancer risk in men and women. *Cancer Epidemiol Biomarkers Prev.* 2005 Jan; 14(1): 138-147. PMID: 15668487.
19. Nöthlings U, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. Dietary glycemic load, added sugars, and carbohydrates as risk factors for pancreatic cancer: The Multiethnic Cohort Study. *Am J Clin Nutr.* 2007 Nov; 86(5): 1, 495-1, 501. PMID: 17991664.
20. Patel AV, McCullough ML, Pavluck AL, Jacobs EJ, Thun MJ, Calle EE. Glycemic load, glycemic index, and carbohydrate intake in relation to pancreatic cancer risk in a large US cohort. *Cancer Causes Control.* 2007 Apr; 18(3): 287-294. Epub 2007 Jan 11. PMID: 17219014.
21. Randi G, Ferraroni M, Talamini R, Garavello W, Deandrea S, Decarli A, Franceschi S, La Vecchia C. Glycemic index, glycemic load and thyroid cancer risk. *Ann Oncol.* 2008 Feb; 19(2): 380-383. Epub 2007 Oct 19. PMID: 17951595.
22. Sieri S, Pala V, Brighenti F, Pellegrini N, Muti P, Micheli A, Evangelista A, Grioni S, Contiero P, Berrino F, Krogh V. Dietary glycemic index, glycemic load, and the risk of breast cancer in an Italian prospective cohort study. *Am J Clin Nutr.* 2007 Oct; 86(4): 1, 160-1, 166. PMID: 17921397.
23. Silvera SA, Rohan TE, Jain M, Terry PD, Howe GR, Miller AB. Glycaemic index, glycaemic load and risk of endometrial cancer: A prospective cohort

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

study. *Public Health Nutr.* 2005 Oct; 8(7): 912-919. PMID: 16277808.
24. Silvera SA, Rohan TE, Jain M, Terry PD, Howe GR, Miller AB. Glycemic index, glycemic load, and pancreatic cancer risk (Canada). *Cancer Causes Control.* 2005 May; 16(4): 431-436. PMID: 15953985.
25. Silvera SA, Jain M, Howe GR, Miller AB, Rohan TE. Dietary carbohydrates and breast cancer risk: A prospective study of the roles of overall glycemic index and glycemic load. *Int J Cancer.* 2005 Apr 20; 114(4): 653-658. Erratum in: *Int J Cancer.* 2006 May 1; 118(9): 2, 372. PMID: 15609324.
26. Silvera SA, Jain M, Howe GR, Miller AB, Rohan TE. Glycaemic index, glycaemic load and ovarian cancer risk: a prospective cohort study. *Public Health Nutr.* 2007 Oct; 10(10): 1, 076-1, 081. Epub 2007 Mar 2. PMID: 17381931.
27. Strayer L, Jacobs DR Jr, Schairer C, Schatzkin A, Flood A. Dietary carbohydrate, glycemic index, and glycemic load and the risk of colorectal cancer in the BCDDP cohort. *Cancer Causes Control.* 2007 Oct; 18(8): 853-863. Epub 2007 Jun 29. PMID: 17605083.
28. Weijenberg MP, Mullie PF, Brants HA, Heinen MM, Goldbohm RA, van den Brandt PA. Dietary glycemic load, glycemic index and colorectal cancer risk: Results from the Netherlands Cohort Study. *Int J Cancer.* 2008 Feb 1; 122(3): 620-629. PMID: 17935129.

What is the relationship between glycemic index or glycemic load and type 2 diabetes?

1. Barclay AW, Flood VM, Rochtchina E, Mitchell P, Brand-Miller JC. Glycemic index, dietary fiber, and risk of type 2 diabetes in a cohort of older Australians. *Diabetes Care.* 2007 Nov; 30(11): 2, 811-2, 813. Epub 2007 Aug 21. No abstract available. PMID: 17712022.
2. Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. *Am J Clin Nutr.* 2008 Feb; 87(2): 339-346. PMID: 18258623.
3. Hodge AM, English DR, O'Dea K, Giles GG. Glycemic index and dietary fiber and the risk of type 2 diabetes. *Diabetes Care.* 2004 Nov; 27(11): 2, 701-2, 706. PMID: 15505008.
4. Krishnan S, Rosenberg L, Singer M, Hu FB, Djoussé L, Cupples LA, Palmer JR. Glycemic index, glycemic load, and cereal fiber intake and risk of type 2 diabetes in US black women. *Arch Intern Med.* 2007 Nov 26; 167(21): 2, 304-2, 309. PMID: 18039988.
5. Mosdøl A, Witte DR, Frost G, Marmot MG, Brunner EJ. Dietary glycemic index and glycemic load are associated with high-density-lipoprotein cholesterol at baseline but not with increased risk of diabetes in the Whitehall II study. *Am J Clin Nutr.* 2007 Oct; 86(4): 988-994. PMID: 17921375.
6. Sahyoun NR, Anderson AL, Tylavsky FA, Lee JS, Sellmeyer DE, Harris TB; Health, Aging, and Body Composition Study. Dietary glycemic index and glycemic load and the risk of type 2 diabetes in older adults. *Am J Clin Nutr.* 2008 Jan; 87(1): 126-131. PMID: 18175745.
7. Schulz M, Liese AD, Fang F, Gilliard TS, Karter AJ. Is the association between dietary glycemic index and type 2 diabetes modified by waist circumference? *Diabetes Care.* 2006 May; 29(5): 1, 102-1, 104. PMID: 16644644.
8. Schulze MB, Liu S, Rimm EB, Manson JE, Willett WC, Hu FB. Glycemic index,

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glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. *Am J Clin Nutr.* 2004 Aug; 80(2): 348-356. PMID: 15277155.
9. Stevens J, Ahn K, Juhaeri, Houston D, Steffan L, Couper D. Dietary fiber intake and glycemic index and incidence of diabetes in African-American and white adults: The ARIC study. *Diabetes Care.* 2002 Oct; 25(10): 1, 715-1, 721. PMID: 12351467.
10. Villegas R, Liu S, Gao YT, Yang G, Li H, Zheng W, Shu XO. Prospective study of dietary carbohydrates, glycemic index, glycemic load, and incidence of type 2 diabetes mellitus in middle-aged Chinese women. *Arch Intern Med.* 2007 Nov 26; 167(21): 2, 310-2, 316. PMID: 18039989.

What is the relationship between glycemic index or glycemic load and type 2 diabetes?

1. Barclay AW, Flood VM, Rochtchina E, Mitchell P, Brand-Miller JC. Glycemic index, dietary fiber, and risk of type 2 diabetes in a cohort of older Australians. *Diabetes Care.* 2007 Nov; 30(11): 2, 811-2, 813. Epub 2007 Aug 21. No abstract available. PMID: 17712022.
2. Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. *Am J Clin Nutr.* 2008 Feb; 87(2): 339-346. PMID: 18258623.
3. Hodge AM, English DR, O'Dea K, Giles GG. Glycemic index and dietary fiber and the risk of type 2 diabetes. *Diabetes Care.* 2004 Nov; 27(11): 2, 701-2, 706. PMID: 15505008.
4. Krishnan S, Rosenberg L, Singer M, Hu FB, Djoussé L, Cupples LA, Palmer JR. Glycemic index, glycemic load, and cereal fiber intake and risk of type 2 diabetes in US black women. *Arch Intern Med.* 2007 Nov 26; 167(21): 2, 304-2, 309. PMID: 18039988.
5. Mosdøl A, Witte DR, Frost G, Marmot MG, Brunner EJ. Dietary glycemic index and glycemic load are associated with high-density-lipoprotein cholesterol at baseline but not with increased risk of diabetes in the Whitehall II study. *Am J Clin Nutr.* 2007 Oct; 86(4): 988-994. PMID: 17921375.
6. Sahyoun NR, Anderson AL, Tylavsky FA, Lee JS, Sellmeyer DE, Harris TB; Health, Aging, and Body Composition Study. Dietary glycemic index and glycemic load and the risk of type 2 diabetes in older adults. *Am J Clin Nutr.* 2008 Jan; 87(1): 126-131. PMID: 18175745.
7. Schulz M, Liese AD, Fang F, Gilliard TS, Karter AJ. Is the association between dietary glycemic index and type 2 diabetes modified by waist circumference? *Diabetes Care.* 2006 May; 29(5): 1, 102-1, 104. PMID: 16644644.
8. Schulze MB, Liu S, Rimm EB, Manson JE, Willett WC, Hu FB. Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. *Am J Clin Nutr.* 2004 Aug; 80(2): 348-356. PMID: 15277155.
9. Stevens J, Ahn K, Juhaeri, Houston D, Steffan L, Couper D. Dietary fiber intake and glycemic index and incidence of diabetes in African-American and white adults: The ARIC study. *Diabetes Care.* 2002 Oct; 25(10): 1, 715-1, 721. PMID: 12351467.
10. Villegas R, Liu S, Gao YT, Yang G, Li H, Zheng W, Shu XO. Prospective study of dietary carbohydrates, glycemic index, glycemic load, and incidence of type 2

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diabetes mellitus in middle-aged Chinese women. *Arch Intern Med.* 2007 Nov 26; 167(21): 2, 310-2, 316. PMID: 18039989.

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What is the relationship between glycemic index or glycemic load and cardiovascular disease?

1. Beulens JW, de Bruijne LM, Stolk RP, Peeters PH, Bots ML, Grobbee DE, van der Schouw YT. High dietary glycemic load and glycemic index increase risk of cardiovascular disease among middle-aged women: A population-based follow-up study. *J Am Coll Cardiol.* 2007 Jul 3; 50(1): 14-21. Epub 2007 Jun 18. PMID: 17601539.
2. Halton TL, Willett WC, Liu S, Manson JE, Albert CM, Rexrode K, Hu FB. Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med.* 2006 Nov 9; 355(19): 1, 991-2, 002. PMID: 17093250.
3. Kaushik S, Wang JJ, Wong TY, Flood V, Barclay A, Brand-Miller J, Mitchell P. Glycemic index, retinal vascular caliber, and stroke mortality. *Stroke.* 2009 Jan; 40(1): 206-212. Epub 2008 Oct 23. PMID: 18948616.
4. Levitan EB, Mittleman MA, Håkansson N, Wolk A. Dietary glycemic index, dietary glycemic load, and cardiovascular disease in middle-aged and older Swedish men. *Am J Clin Nutr.* 2007 Jun; 85(6): 1, 521-1, 526. PMID: 17556687.
5. Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, Hennekens CH, Manson JE. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr.* 2000 Jun; 71(6): 1, 455-1, 461. PMID: 10837285.
6. Oh K, Hu FB, Cho E, Rexrode KM, Stampfer MJ, Manson JE, Liu S, Willett WC. Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women. *Am J Epidemiol.* 2005 Jan 15; 161(2): 161-169. PMID: 15632266.
7. Tavani A, Bosetti C, Negri E, Augustin LS, Jenkins DJ, La Vecchia C. Carbohydrates, dietary glycaemic load and glycaemic index, and risk of acute myocardial infarction. *Heart.* 2003 Jul; 89(7): 722-726. PMID: 12807839; PMCID: PMC1767713.
8. van Dam RM, Visscher AW, Feskens EJ, Verhoef P, Kromhout D. Dietary glycemic index in relation to metabolic risk factors and incidence of coronary heart disease: The Zutphen Elderly Study. *Eur J Clin Nutr.* 2000 Sep; 54(9): 726-731. PMID: 11002385.

Excluded articles

Article	Reason for Exclusion
Amano Y, Kawakubo K, Lee JS, Tang AC, Sugiyama M, Mori K. Correlation between dietary glycemic index and cardiovascular disease risk factors among Japanese women. *Eur J Clin Nutr.* 2004 Nov; 58(11): 1, 472-1, 478. PMID: 15127092.	Does not include incidence of disease in analyses.
Barclay AW, Brand-Miller JC, Mitchell P. Macronutrient intake, glycaemic index and glycaemic load of older Australian subjects with and without diabetes: Baseline data from the Blue Mountains Eye study. *Br J Nutr.* 2006 Jul; 96(1): 117-123. PMID: 16869999.	Does not answer question; compares dietary intake of older adults with and without diabetes.

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Barclay AW, Petocz P, McMillan-Price J, Flood VM, Prvan T, Mitchell P, Brand-Miller JC. Glycemic index, glycemic load, and chronic disease risk: A meta-analysis of observational studies. *Am J Clin Nutr.* 2008 Mar; 87(3): 627-637. Review. PMID: 18326601.	Study design is meta-analysis.
Barkoukis H, Marchetti CM, Nolan B, Sistrun SN, Krishnan RK, Kirwan JP. A high glycemic meal suppresses the postprandial leptin response in normal healthy adults.*Ann Nutr Metab.* 2007; 51(6): 512-518. Epub 2007 Dec 10. PMID: 18073462.	Does not include incidence of disease in analyses.
Benoit SR, Fleming R, Philis-Tsimikas A, Ji M. Predictors of glycemic control among patients with Type 2 diabetes: A longitudinal study. *BMC Public Health.* 2005 Apr 17; 5: 36. PMID: 15833140.	Participants diagnosed with type 2 diabetes.
Beulens JWJ, Van Der Schouw YT. Increased risk of cardiovascular disease among middle-aged women due to glycemic load. *Cardiol Rev.* 2008 Feb; 25(2): 19-22.	Results reported based on the same dataset as Beulens (2007).
Biddinger SB, Ludwig DS. The insulin-like growth factor axis: A potential link between glycemic index and cancer. *Am J Clin Nutr.* 2005 Aug; 82(2): 277-278. PMID: 16087968.	Publication is editorial.
Brand-Miller J, Dickinson S, Barclay A, Celermajer D. The glycemic index and cardiovascular disease risk. *Curr Atheroscler Rep.* 2007 Dec; 9(6): 479-485. Review. PMID: 18377788.	Study design is narrative review.
Brand-Miller J, Hayne S, Petocz P, Colagiuri S. Low-glycemic index diets in the management of diabetes: A meta-analysis of randomized controlled trials. *Diabetes Care.* 2003 Aug; 26(8): 2, 261-2, 267. PMID: 12882846.	Study design is meta-analysis.
Brand-Miller JC, Stockmann K, Atkinson F, Petocz P, Denyer G. Glycemic index, postprandial glycemia, and the shape of the curve in healthy subjects: Analysis of a database of more than 1, 000 foods. *Am J Clin Nutr.* 2009 Jan; 89(1): 97-105. Epub 2008 Dec 3. PMID: 19056599.	Does not answer question; examined relationship between glycemic index and postprandial glycemia.
Brillon DJ, Sison CP, Salbe AD, Poretsky L. Reproducibility of a glycemic response to mixed meals in type 2 diabetes mellitus. *Horm Metab Res.* 2006 Aug; 38(8): 536-542. PMID: 16941281.	Does not include incidence of disease in analyses.

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Burani J, Longo PJ. Low-glycemic index carbohydrates: an effective behavioral change for glycemic control and weight management in patients with type 1 and 2 diabetes.*Diabetes Educ.* 2006 Jan-Feb; 32(1): 78-88. PMID: 16439496.	Participants diagnosed with type 2 diabetes.
Buscemi S, Verga S, Cottone S, Azzolina V, Buscemi B, Gioia D, Cerasola G. Glycaemic variability and inflammation in subjects with metabolic syndrome. *Acta Diabetol.* 2009 Mar; 46(1): 55-61. Epub 2008 Sep 26. PMID: 18818862.	Participants diagnosed with metabolic syndrome.
Colombani PC. Glycemic index and load-dynamic dietary guidelines in the context of diseases. *Physiol Behav.* 2004 Dec 30; 83(4): 603-610. Review. PMID: 15621065.	Study design is narrative review.
Darbinian JA, Ferrara AM, Van Den Eeden SK, Quesenberry CP Jr, Fireman B, Habel LA. Glycemic status and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2008 Mar; 17(3): 628-635. PMID: 18349280.	Does not include glycemic index or load in analyses.
de Rekeneire N, Rooks RN, Simonsick EM, Shorr RI, Kuller LH, Schwartz AV, Harris TB; Health, Aging and Body Composition Study. Racial differences in glycemic control in a well-functioning older diabetic population: Findings from the Health, Aging and Body Composition Study. *Diabetes Care.* 2003 Jul; 26(7): 1, 986-1, 992. Erratum in: *Diabetes Care.* 2003 Dec; 26(12): 3, 368. PMID: 12832300.	Participants diagnosed with type 2 diabetes.
Dickinson S, Brand-Miller J. Glycemic index, postprandial glycemia and cardiovascular disease. *Curr Opin Lipidol.* 2005 Feb; 16(1): 69-75. Review. PMID: 15650566.	Study design is narrative review.
Dickinson S, Hancock DP, Petocz P, Ceriello A, Brand-Miller J. High-glycemic index carbohydrate increases nuclear factor-kappaB activation in mononuclear cells of young, lean healthy subjects. *Am J Clin Nutr.* 2008 May; 87(5): 1, 188-1, 193. PMID: 18469238.	Does not include incidence of disease in analyses.

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Du H, van der A DL, van Bakel MM, van der Kallen CJ, Blaak EE, van Greevenbroek MM, Jansen EH, Nijpels G, Stehouwer CD, Dekker JM, Feskens EJ. Glycemic index and glycemic load in relation to food and nutrient intake and metabolic risk factors in a Dutch population. *Am J Clin Nutr.* 2008 Mar; 87(3): 655-661. PMID: 18326604.	Does not include incidence of disease in analyses.
Ebbeling CB, Leidig MM, Sinclair KB, Seger-Shippee LG, Feldman HA, Ludwig DS. Effects of an ad libitum low-glycemic load diet on cardiovascular disease risk factors in obese young adults. *Am J Clin Nutr.* 2005 May; 81(5): 976-982. PMID: 15883418.	Does not include incidence of disease in analyses.
Franz MJ. Is there a role for the glycemic index in coronary heart disease prevention or treatment? *Curr Atheroscler Rep.* 2008 Dec; 10(6): 497-502. Review. PMID: 18937897.	Study design is narrative review.
Gastrich MD, Lasser N L, Wien M, Bachmann G. Dietary complex carbohydrates and low glycemic index/load decrease levels of specific metabolic syndrome/cardiovascular disease risk factors. *Topics in Clinical Nutrition.* 2008; 23(1): 76-96.	Study design is systematic review.
Gellar L, Nansel TR. High and low glycemic index mixed meals and blood glucose in youth with type 2 diabetes or impaired glucose tolerance. *J Pediatr.* 2009 Mar; 154(3): 455-458.	Participants diagnosed with type 2 diabetes or impaired glucose tolerance.
Gnagnarella P, Gandini S, La Vecchia C, Maisonneuve P. Glycemic index, glycemic load, and cancer risk: a meta-analysis. *Am J Clin Nutr.* 2008 Jun; 87(6): 1, 793-1, 801. PMID: 18541570.	Study design is meta-analysis.
Graber AL, Shintani AK, Wolff K, Brown A, Elasy TA. Glycemic relapse in type 2 diabetes.*Endocr Pract.* 2006 Mar-Apr; 12(2): 145-151. PMID: 16690461.	Participants diagnosed with type 2 diabetes.
Hare-Bruun H, Nielsen BM, Grau K, Oxlund AL, Heitmann BL. Should glycemic index and glycemic load be considered in dietary recommendations? *Nutr Rev.* 2008 Oct; 66(10): 569-590. Review. PMID: 18826453.	Study design is narrative review.

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Henry CJ, Lightowler HJ, Tydeman EA, Skeath R. Use of low-glycaemic index bread to reduce 24-hour blood glucose: Implications for dietary advice to non-diabetic and diabetic subjects. *Int J Food Sci Nutr.* 2006 May-Jun; 57(3-4): 273-278. PMID: 17127477.	Does not include incidence of disease in analyses.
Jenkins DJ, Kendall CW, Augustin LS, Martini MC, Axelsen M, Faulkner D, Vidgen E, Parker T, Lau H, Connelly PW, Teitel J, Singer W, Vandenbroucke AC, Leiter LA, Josse RG. Effect of wheat bran on glycemic control and risk factors for cardiovascular disease in type 2 diabetes. *Diabetes Care.* 2002 Sep; 25(9): 1, 522-1, 528. PMID: 12196421.	Participants diagnosed with type 2 diabetes.
Jenkins DJ, Kendall CW, McKeown-Eyssen G, Josse RG, Silverberg J, Booth GL, Vidgen E, Josse AR, Nguyen TH, Corrigan S, Banach MS, Ares S, Mitchell S, Emam A, Augustin LS, Parker TL, Leiter LA. Effect of a low-glycemic index or a high-cereal fiber diet on type 2 diabetes: a randomized trial. *JAMA.* 2008 Dec 17; 300(23): 2, 742-2, 753. PMID: 19088352.	Participants diagnosed with type 2 diabetes.
Jimenez-Cruz A, Bacardi-Gascon M, Turnbull WH, Rosales-Garay P, Severino-Lugo I. A flexible, low-glycemic index mexican-style diet in overweight and obese subjects with type 2 diabetes improves metabolic parameters during a 6-week treatment period. *Diabetes Care.* 2003 Jul; 26(7): 1, 967-1, 970. PMID: 12832297.	Participants diagnosed with type 2 diabetes.
Jiménez-Cruz A, Gutiérrez-González AN, Bacardi-Gascon M. Low glycemic index lunch on satiety in overweight and obese people with type 2 diabetes. *Nutr Hosp.* 2005 Sep-Oct; 20(5): 348-350. PMID: 16229403.	Participants diagnosed with type 2 diabetes.
Kelly S, Frost G, Whittaker V, Summerbell C. Low glycaemic index diets for coronary heart disease. *Cochrane Database Syst Rev.* 2004 Oct 18; (4): CD004467. Review. PMID: 15495112.	Study design is systematic review.
Levitan EB, Cook NR, Stampfer MJ, Ridker PM, Rexrode KM, Buring JE, Manson JE, Liu S. Dietary glycemic index, dietary glycemic load, blood lipids, and C-reactive protein.*Metabolism.* 2008 Mar; 57(3): 437-443. PMID: 18249220; PMCID: PMC2262400.	Does not include incidence of disease in analyses.

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

Levitan EB, Mittleman MA, Wolk A. Dietary glycemic index, dietary glycemic load and mortality among men with established cardiovascular disease. *Eur J Clin Nutr.* 2009 Apr; 63(4): 552-557. Epub 2007 Dec 19. PMID: 18091767.	Participants diagnosed with cardiovascular disease.
Liese AD, Schulz M, Fang F, Wolever TM, D'Agostino RB Jr, Sparks KC, Mayer-Davis EJ. Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women. *Diabetes Care.* 2005 Dec; 28(12): 2, 832-2, 838. PMID: 16306541.	Does not include incidence of disease in analyses.
Liu S, Manson JE, Buring JE, Stampfer MJ, Willett WC, Ridker PM. Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity C-reactive protein in middle-aged women. *Am J Clin Nutr.* 2002 Mar; 75(3): 492-498. PMID: 11864854.	Does not include incidence of disease in analyses.
Liu S, Manson JE, Stampfer MJ, Holmes MD, Hu FB, Hankinson SE, Willett WC. Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women. *Am J Clin Nutr.* 2001 Mar; 73(3): 560-566. PMID: 11237932.	Does not include incidence of disease in analyses.
Liu S. Lowering dietary glycemic load for weight control and cardiovascular health: a matter of quality. *Arch Intern Med.* 2006 Jul 24; 166(14): 1, 438-1, 439. PMID: 16864751.	Publication is editorial.
Livesey G, Taylor R, Hulshof T, Howlett J. Glycemic response and health: A systematic review and meta-analysis: Relations between dietary glycemic properties and health outcomes. *Am J Clin Nutr.* 2008 Jan; 87(1): 258S-268S. Review. PMID: 18175766.	Study design is systematic review.
Lukaczer D, Liska DJ, Lerman RH, Darland G, Schiltz B, Tripp M, Bland JS. Effect of a low glycemic index diet with soy protein and phytosterols on CVD risk factors in postmenopausal women. *Nutrition.* 2006 Feb; 22(2): 104-113. PMID: 16459222.	Does not include incidence of disease in analyses.

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Ma Y, Olendzki BC, Merriam PA, Chiriboga DE, Culver AL, Li W, Hébert JR, Ockene IS, Griffith JA, Pagoto SL. A randomized clinical trial comparing low-glycemic index vs. ADA dietary education among individuals with type 2 diabetes. *Nutrition.* 2008 Jan; 24(1): 45-56. PMID: 18070658.	Participants diagnosed with type 2 diabetes.
Maki KC, Rains TM, Kaden VN, Raneri KR, Davidson MH. Effects of a reduced-glycemic-load diet on body weight, body composition, and cardiovascular disease risk markers in overweight and obese adults. *Am J Clin Nutr.* 2007 Mar; 85(3): 724-734. PMID: 17344493.	Does not include incidence of disease in analyses.
Mann JI. Evidence-based nutrition recommendations for the treatment and prevention of type 2 diabetes and the metabolic syndrome. *Food Nutr Bull.* 2006 Jun; 27(2): 161-166. Review. PMID: 16786982.	Publication provides recommendations.
Martínez-Ortiz JA, Fung TT, Baylin A, Hu FB, Campos H. Dietary patterns and risk of nonfatal acute myocardial infarction in Costa Rican adults. *Eur J Clin Nutr.* 2006 Jun; 60(6): 770-777. Epub 2006 Feb 8. PMID: 16465200.	Does not include glycemic index or load in analyses.
McMillan-Price J, Petocz P, Atkinson F, O'neill K, Samman S, Steinbeck K, Caterson I, Brand-Miller J. Comparison of four diets of varying glycemic load on weight loss and cardiovascular risk reduction in overweight and obese young adults: A randomized controlled trial. *Arch Intern Med.* 2006 Jul 24; 166(14): 1, 466-1, 475. PMID: 16864756.	Does not include incidence of disease in analyses.
Mead A, Atkinson G, Albin D, Alphey D, Baic S, Boyd O, Cadigan L, Clutton L, Craig L, Flanagan C, Greene P, Griffiths E, Lee NJ, Li M, McKechnie L, Ottaway J, Paterson K, Perrin L, Rigby P, Stone D, Vine R, Whitehead J, Wray L, Hooper L; UK Heart Health Group; Thoracic Dietitians Interest Group (Specialist group of the British Dietetic Association). Dietetic guidelines on food and nutrition in the secondary prevention of cardiovascular disease: Evidence from systematic reviews of randomized controlled trials (second update, January 2006). *J Hum Nutr Diet.* 2006 Dec; 19(6): 401-419. Review. PMID: 17105538.	Study design is review.

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Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med.* 2009 Apr 13; 169(7): 659-669. Review. PMID: 19364995.	Study design is systematic review.
Miles JM. A role for the glycemic index in preventing or treating diabetes? *Am J Clin Nutr.* 2008 Jan; 87(1): 1-2. PMID: 18175728.	Publication is perspective.
Miller CK, Gutschall M. A randomized trial about glycemic index and glycemic load improves outcomes among adults with type 2 diabetes. *Health Educ Behav.* 2009 Jun; 36(3): 615-626. Epub 2008 May 9. PMID: 18469161.	Participants diagnosed with type 2 diabetes.
Miller CK, Gutshcall MD, Mitchell DC. Change in food choices following a glycemic load intervention in adults with type 2 diabetes. *J Am Diet Assoc.* 2009 Feb; 109(2): 319-324. PMID: 19167961.	Participants diagnosed with type 2 diabetes.
Milton JE, Briche B, Brown IJ, Hickson M, Robertson CE, Frost GS. Relationship of glycaemic index with cardiovascular risk factors: Analysis of the National Diet and Nutrition Survey for people aged 65 and older. *Public Health Nutr.* 2007 Nov; 10(11): 1, 321-1, 335. Epub 2007 Apr 24. PMID: 17456246.	Does not include incidence of disease in analyses.
Mogos T, Dondoi C. Evaluation of glycemic control of type II diabetes mellitus treated only with diet. *Rom J Intern Med.* 2007; 45(2): 205-208. PMID: 18333376.	Participants diagnosed with type 2 diabetes.
Montori VM. Should patients with type 2 diabetes focus on glycemic control to reduce their cardiovascular risk? *Pol Arch Med Wewn.* 2008 Sep; 118(9): 502-507. Review. PMID: 18846985.	Study design is narrative review.
Mulholland HG, Murray LJ, Cardwell CR, Cantwell MM. Dietary glycaemic index, glycaemic load and breast cancer risk: a systematic review and meta-analysis. *Br J Cancer.* 2008 Oct 7; 99(7): 1, 170-1, 175. Epub 2008 Aug 26. Review. PMID: 18728653.	Study design is systematic review/meta-analysis.

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Mulholland HG, Murray LJ, Cardwell CR, Cantwell MM. Glycemic index, glycemic load, and risk of digestive tract neoplasms: A systematic review and meta-analysis. *Am J Clin Nutr.* 2009 Feb; 89(2): 568-576. Epub 2008 Dec 16. Review. PMID: 19088152.	Study design is systematic review/meta-analysis.
Murakami K, Okubo H, Sasaki S. Effect of dietary factors on incidence of type 2 diabetes: A systematic review of cohort studies. *J Nutr Sci Vitaminol (Tokyo).* 2005 Aug; 51(4): 292-310. Review. PMID: 16262005.	Study design is systematic review.
Murakami K, Sasaki S, Takahashi Y, Okubo H, Hosoi Y, Horiguchi H, Oguma E, Kayama F. Dietary glycemic index and load in relation to metabolic risk factors in Japanese female farmers with traditional dietary habits. *Am J Clin Nutr.* 2006 May; 83(5): 1, 161-1, 169. PMID: 16685061.	Does not include incidence of disease in analyses.
Nansel TR, Gellar L, Zeitzoff L. Acceptability of lower glycemic index foods in the diabetes camp setting. *J Nutr Educ Behav.* 2006 May-Jun; 38(3): 143-150. PMID: 16731448.	Participants diagnosed with type 2 diabetes.
Oh K, Willett WC, Fuchs CS, Giovannucci EL. Glycemic index, glycemic load, and carbohydrate intake in relation to risk of distal colorectal adenoma in women. *Cancer Epidemiol Biomarkers Prev.* 2004 Jul; 13(7): 1, 192-1, 198. PMID: 15247130.	Results reported based on the same dataset as Michaud (2005).
Ostman EM, Frid AH, Groop LC, Björck IM. A dietary exchange of common bread for tailored bread of low glycaemic index and rich in dietary fibre improved insulin economy in young women with impaired glucose tolerance. *Eur J Clin Nutr.* 2006 Mar; 60(3): 334-341. PMID: 16234828.	Does not include incidence of disease in analyses.
Panlasigui LN, Thompson LU. Blood glucose lowering effects of brown rice in normal and diabetic subjects. *Int J Food Sci Nutr.* 2006 May-Jun; 57(3-4): 151-158. PMID: 17127465.	Does not meet inclusion criteria for sample size.
Papanikolaou Y, Palmer H, Binns MA, Jenkins DJ, Greenwood CE. Better cognitive performance following a low-glycaemic-index compared with a high-glycaemic-index carbohydrate meal in adults with type 2 diabetes. *Diabetologia.* 2006 May; 49(5): 855-862. Epub 2006 Mar 1. PMID: 16508776.	Participants diagnosed with type 2 diabetes.

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Pereira MA, Swain J, Goldfine AB, Rifai N, Ludwig DS. Effects of a low-glycemic load diet on resting energy expenditure and heart disease risk factors during weight loss. *JAMA.* 2004 Nov 24; 292(20): 2, 482-2, 490. PMID: 15562127.	Does not include incidence of disease in analyses.
Philippou E, McGowan BM, Brynes AE, Dornhorst A, Leeds AR, Frost GS. The effect of a 12-week low glycaemic index diet on heart disease risk factors and 24-hour glycaemic response in healthy middle-aged volunteers at risk of heart disease: A pilot study. *Eur J Clin Nutr.* 2008 Jan; 62(1): 145-149. Epub 2007 Feb 21. PMID: 17311054.	Does not meet inclusion criteria for sample size.
Pi-Sunyer X. Glycemic index in early type 2 diabetes. *Am J Clin Nutr.* 2008 Jan; 87(1): 3-4. PMID: 18175729.	Publication is perspective.
Pittas AG, Roberts SB, Das SK, Gilhooly CH, Saltzman E, Golden J, Stark PC, Greenberg AS. The effects of the dietary glycemic load on type 2 diabetes risk factors during weight loss. *Obesity (Silver Spring).* 2006 Dec; 14(12): 2, 200-2, 209. PMID: 17189547.	Does not include incidence of disease in analyses.
Qi L, Meigs JB, Liu S, Manson JE, Mantzoros C, Hu FB. Dietary fibers and glycemic load, obesity, and plasma adiponectin levels in women with type 2 diabetes. *Diabetes Care.* 2006 Jul; 29(7): 1, 501-1, 505. PMID: 16801569.	Participants diagnosed with type 2 diabetes.
Qi L, Rimm E, Liu S, Rifai N, Hu FB. Dietary glycemic index, glycemic load, cereal fiber, and plasma adiponectin concentration in diabetic men. *Diabetes Care.* 2005 May; 28(5): 1, 022-1, 028. PMID: 15855561.	Participants diagnosed with type 2 diabetes.
Rendell M, Vanderhoof J, Venn M, Shehan MA, Arndt E, Rao CS, Gill G, Newman RK, Newman CW. Effect of a barley breakfast cereal on blood glucose and insulin response in normal and diabetic patients. *Plant Foods Hum Nutr.* 2005 Jun; 60(2): 63-67. PMID: 16021833.	Does not include incidence of disease in analyses.
Riccardi G, Rivellese AA, Giacco R. Role of glycemic index and glycemic load in the healthy state, in prediabetes, and in diabetes. *Am J Clin Nutr.* 2008 Jan; 87(1): 269S-274S. Review. PMID: 18175767.	Study design is narrative review.

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Roberts SB, Pittas AG. The role of glycemic index in type 2 diabetes. *Nutr Clin Care.* 2003 May-Sep; 6(2): 73-78. Review. PMID: 14692295.	Study design is narrative review.
Sahyoun NR, Anderson AL, Kanaya AM, Koh-Banerjee P, Kritchevsky SB, de Rekeneire N, Tylavsky FA, Schwartz AV, Lee JS, Harris TB. Dietary glycemic index and load, measures of glucose metabolism, and body fat distribution in older adults. *Am J Clin Nutr.* 2005 Sep; 82(3): 547-552. PMID: 16155266.	Does not include incidence of disease in analyses.
Shani M, Taylor TR, Vinker S, Lustman A, Erez R, Elhayany A, Lahad A. Characteristics of diabetics with poor glycemic control who achieve good control. *J Am Board Fam Med.* 2008 Nov-Dec; 21(6): 490-496. PMID: 18988715.	Participants diagnosed with type 2 diabetes.
Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, Howard BV, Kirkman MS, Kosiborod M, Reaven P, Sherwin RS; American Diabetes Association; American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials: A position statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association. *J Am Coll Cardiol.* 2009 Jan 20; 53(3): 298-304. Review. PMID: 19147051.	Publication is position statement.
Slama G, Elgrably F, Kabir M, Rizkalla S. Low glycemic index foods should play a role in improving overall glycemic control in type-1 and type-2 diabetic patients and, more specifically, in correcting excessive postprandial hyperglycemia. *Nestle Nutr Workshop Ser Clin Perform Programme.* 2006; 11: 73-79; discussion, 79-81. Review. PMID: 16820732.	Study design is narrative review.
Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med.* 2000 Jul 6; 343(1): 16-22. PMID: 10882764.	Does not include glycemic index or load in analyses (part of composite dietary score).
Tapola N, Karvonen H, Niskanen L, Mikola M, Sarkkinen E. Glycemic responses of oat bran products in type 2 diabetic patients. *Nutr Metab Cardiovasc Dis.* 2005 Aug; 15(4): 255-261. PMID: 16054549.	Participants diagnosed with type 2 diabetes.

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Terry J, Terry P. [Glycemic index--relevant in the treatment of overweight and diabetes]*Lakartidningen.* 2006 Feb 15-21; 103(7): 466-470; discussion 471-473. Swedish. PMID: 16535876.	Study not published in English.
Thomas D, Elliott EJ. Low glycaemic index, or low glycaemic load, diets for diabetes mellitus.*Cochrane Database Syst Rev.* 2009 Jan 21; (1): CD006296. Review. PMID: 19160276.	Participants diagnosed with diabetes.
Thomas DE, Elliott EJ, Baur L. Low glycaemic index or low glycaemic load diets for overweight and obesity. *Cochrane Database Syst Rev.* 2007 Jul 18; (3): CD005105. Review. PMID: 17636786.	Study design is systematic review.
Tokuyama Y, Ishizuka T, Matsui K, Egashira T, Kanatsuka A. Predictors of glycemic control in Japanese subjects with type 2 diabetes mellitus. *Metabolism.* 2008 Apr; 57(4): 453-457. PMID: 18328344.	Participants diagnosed with type 2 diabetes.
Ukleja A, Kunachowicz H, Pachocka L. The use of glycaemic index in the prevention of cardiovascular diseases. *Rocz Panstw Zakl Hig.* 2007; 58(1): 145-151. Review. PMID: 17711103.	Study design is narrative review.
Whiting PH, Kalansooriya A, Holbrook I, Haddad F, Jennings PE. The relationship between chronic glycaemic control and oxidative stress in type 2 diabetes mellitus. *Br J Biomed Sci.* 2008; 65(2): 71-74. PMID: 19055108.	Participants diagnosed with type 2 diabetes.
Willett W, Manson J, Liu S. Glycemic index, glycemic load, and risk of type 2 diabetes. *Am J Clin Nutr.* 2002 Jul; 76(1): 274S-280S. Review. PMID: 12081851.	Study design is review.
Wilson T, Meyers SL, Singh AP, Limburg PJ, Vorsa N. Favorable glycemic response of type 2 diabetics to low-calorie cranberry juice. *J Food Sci.* 2008 Nov; 73(9): H241-H245. PMID: 19021808.	Participants diagnosed with type 2 diabetes.

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Wolever TM, Gibbs AL, Mehling C, Chiasson JL, Connelly PW, Josse RG, Leiter LA, Maheux P, Rabasa-Lhoret R, Rodger NW, Ryan EA. The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-year controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: No effect on glycated hemoglobin but reduction in C-reactive protein. *Am J Clin Nutr.* 2008 Jan; 87(1): 114-125. PMID: 18175744.	Participants diagnosed with type 2 diabetes.
Wolever TM, Mehling C, Chiasson JL, Josse RG, Leiter LA, Maheux P, Rabasa-Lhoret R, Rodger NW, Ryan EA. Low glycaemic index diet and disposition index in type 2 diabetes (the Canadian trial of carbohydrates in diabetes): a randomised controlled trial. *Diabetologia.* 2008 Sep; 51(9): 1, 607-1, 615. Epub 2008 Jul 22. PMID: 18648764.	Participants diagnosed with type 2 diabetes.

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CHAPTER 4. GLYCEMIC INDEX/LOAD – TYPE 2 DIABETES

WHAT IS THE RELATIONSHIP BETWEEN GLYCEMIC INDEX OR GLYCEMIC LOAD AND TYPE 2 DIABETES?

Conclusion statement

A moderate body of inconsistent evidence supports a relationship between high glycemic index and type 2 diabetes.

Strong, convincing evidence shows little association between glycemic load and type 2 diabetes.

Grade

GI: Moderate; GL: Strong

Evidence summary overview

Evidence is mixed as to whether there is an association between a high glycemic index and type 2 diabetes (T2D). Little evidence suggests that a high glycemic load is associated with T2D. This conclusion is based on 10 longitudinal prospective observational studies published since 2000 (Barclay, 2007; Halton, 2008; Hodge, 2004; Krishnan, 2007; Mosdol, 2007; Sahyoun, 2008; Schulz, 2006; Schulze, 2004; Stevens, 2002; Villegas, 2007). No randomized controlled trials(RCTs) were reported. Of the 10 prospective observational studies, glycemic index was positively associated with T2D in five reports (Halton, 2008; Krishnan, 2007; Schulz, 2006; Schultze, 2006; Villegas, 2007). Four other longitudinal studies reported no association of glycemic index with T2D (Barclay 2007; Mosdol 2007; Sahyoun 2008; Steven 2002). One longitudinal study reported an inverse association (Hodge, 2004).

Of the 10 prospective observational studies, one study reported a significant, positive association between glycemic load and risk of T2D during 20 years of follow-up in comparison of extreme deciles (Halton, 2008). Six studies found no relationship (Barclay, 2007; Hodge, 2004; Krishnan, 2007; Sahyoun, 2008; Schulz, 2006; Stevens, 2002). Two studies found an inverse association (Mosdol, 2007; Villegas, 2007).

Evidence summary paragraphs

Barclay, 2007 (neutral quality), a prospective cohort study, examined the link between glycemic index (GI) and fiber and incidence of T2D in an older Australian population. The study began in 1991 and 4,433 subjects aged more than 49 years were identified. Of these, 3,654 participated in a detailed examination in 1992 to 1994; 2,335 participated in a five-year follow-up; and 1,952 participated in a 10-year follow-up. Subjects were Caucasian and representative of the older Australian population. Diagnosis of T2D was either self-reported with current use of diabetes medication or fasting glucose concentration of more than 126mg per dL. Diabetes incidence was measured based on subjects without T2D at baseline who were diagnosed with T2D at subsequent follow-up stages. Glycemic index was evaluated based on a 145-item semi-quantitative, Willett-derived, food-frequency questionnaire (FFQ) that was validated by these authors for ranking subjects accurately according to GI [Barclay et al, 2007 (Public Health Nutrition)]. It should be noted, however, that in validating the FFQ, the authors found the FFQ could rank subjects according to

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total carbohydrate, sugar, starch and fiber intake and GI, but not as well for glycemic load (GL). During ten years of follow-up, 138 cases of T2D were identified out of the 1,833 subjects. Total carbohydrate, starch, sugar and total fiber intake were not correlated with T2D incidence in age- and sex-adjusted models or the multivariate-adjusted model. However, vegetable fiber had a negative association with risk of T2D in the age- and sex-adjusted and multivariate analysis models. For all ages combined, there was a trend toward a positive correlation between GI and T2D risk, although this was not statistically significant. However, in the age-stratified and multivariate analyses, there was a positive correlation between GI and T2D risk for individuals less than 70 years at baseline, but not those older than 70 years at baseline. Overall, the authors concluded that vegetable fiber was independently associated with decreased incidence of T2D over a 10-year period in older Australians; whereas, in a secondary analysis, there was a positive association between GI and T2D incidence in older Australian subjects less than 70 years at baseline. Limitations of this study include the FFQ that these authors reported previously was not well-suited for grouping subjects by GL.

Halton, 2008 (positive quality), a prospective cohort study (Nurses' Health Study) in the US, examined the association between low-carbohydrate-diet score and risk of T2D. In addition, the relationship between dietary glycemic load and risk of T2D was examined. Participants were 85,059 women (98% white) aged 30 to 55 years at baseline. Participants were followed from 1980 to 2000. Diet was assessed using FFQs and T2D status was self-reported. During 20 years of follow-up, 4,670 cases of T2D were documented. There was a significant, positive association between glycemic load and risk of T2D in comparison of extreme deciles (multivariate RR: 2.47; 95% CI: 1.75, 3.47; P<0.0001).

Hodge, 2004 (positive quality), a prospective cohort study, examined the association between glycemic index (GI), glycemic load (GL) and T2D. Participants were 31,641 men and women (40 to 69 years old at baseline) from the Melbourne Collaborative Cohort Study. Participants completed baseline questionnaires between 1990 and 1994. Dietary information was collected using a 121-item, self-administered FFQ developed for the cohort study. Incident cases of diabetes were self-reported on a questionnaire mailed to participants four years after baseline. Confirmation of diagnosis was sought from medical practitioners. A total of 365 cases of T2D were reported (76% of cases confirmed). Dietary GI was positively associated with diabetes. When body mass index (BMI) and waist to hip ratio (WHR) were included in the model, the association was attenuated. In participants with BMI less than 25kg/m^2, GI was inversely associated with diabetes (OR=0.29; 95% CI: 0.10, 0.91). In people with BMI less than 30kg/m^2, GI was not associated with diabetes (1.00; 95% CI: 0.68, 1.46), whereas in those with BMI 30kg/m^2 or more, a positive association (1.64; 95% CI: 1.22, 2.21) was observed (interaction, P=0.01). Glycemic load showed little association with diabetes. The authors concluded that reducing GI while maintaining carbohydrate intake may reduce the risk of T2D.

Krishnan, 2007 (positive quality), a prospective cohort study, examined the association of glycemic index (GI), glycemic load (GL) and cereal fiber intake and risk of T2D in a cohort of black women. Data from the Black Women's Health Study (BWHS), a prospective cohort study of 59,000 black women in the US, was used for this analysis. After exclusion criteria were applied, 40,078 women remained in the study. The study began in 1995 when women between the ages of 30 to 69 years

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were recruited by postal questionnaires, resulting in the recruitment of women from all regions of the US. This report was based on a follow-up from 1995 to 2003. Diet was assessed at baseline in 1995 with a 68-item modified version of the Block National Cancer Institute (NCI) FFQ that had been modified to include foods unique to the black population. The Cox proportional hazards models were used to calculate the incidence rate ratios (IRR) and 95% confidence intervals (CI). During the 123,499 person-years follow-up, there were 1,938 cases of T2D reported. Glycemic load was inversely associated with risk of T2D in the age-adjusted model; however, after adjustment for BMI, energy intake, family history of T2D, smoking and physical activity (Model 1), the inverse association was lost. Further adjustment for fiber intake, total fat intake and total protein intake (Model 2) resulted in an IRR of 1.22 (95% CI: 0.98, 1.51), comparing the highest to the lowest quintile. Glycemic index was positively associated with T2D risk for all models; for Model 2, the IRR was 1.23 (95% CI: 1.05, 1.44) for the highest to lowest quintiles of GI. Lastly, cereal fiber intake was inversely associated with T2D risk in all models; the IRR was 0.82 (95% CI: 0.70, 0.96). Overall, both GI and GL were positively associated with increased risk of T2D and cereal fiber intake was negatively associated. These associations were valid in both overweight and non-overweight individuals, but stronger in thinner women. For women with a BMI less than 25kg/m^2, there was an approximate two-fold increase in risk of T2D for the highest quintile of GI and a 59% decrease for the highest quintile for fiber intake. The authors concluded that risk of T2D was statistically significantly associated with GI, but not with GL. Furthermore, their recommendations only address fiber (i.e., increasing cereal fiber in the diet may be protective against T2D, a disease that is of high incidence in this population of black women). Potential problems with this study were the difficulty in assessing GL (e.g., as cereal fiber intake increases, GL also increases). Furthermore, in the study population, those in the higher quintiles for GL also were more health conscious as indicated by lower cigarette and alcohol consumption, more physical activity, lower BMI and lower fat intake and, according to the authors, this may explain the initial positive association between GL and T2D incidence. However, when the above confounders were taken into account in their model, the direction of the association changed. The authors also warn that when their data was stratified according to BMI and they found that women with BMI less than 25kg/m^2had a stronger association between GL and cereal fiber and T2D risk, that the stratification according to less than 25 and higher than 25kg/m^2 may have produced this outcome “by chance.” They make a point that their results should not be interpreted to mean that overweight and obese women should not reduce their intake of refined carbohydrates for prevention of T2D.

Mosdol, 2007 (neutral quality), a prospective cohort study (Whitehall II Study) in the United Kingdom, examined the associations between glycemic index and glycemic load with clinical variables at baseline and incidence of T2D. Participants were 7,321 white adults (71% men) aged 39 to 63 years at baseline. Participants were followed for seven phases from 1995 to 1998 (phase 1) through 2003 to 2004 (phase 7). Diet was assessed using an FFQ for Western diets. Type 2 diabetes was self-reported throughout the study. In addition, two-hour glucose tolerance tests were conducted at clinical exams during phases three, five and seven (five-year intervals). During 13 years of follow-up, 329 incident cases of T2D were identified. Glycemic index was not associated with risk even after further adjustments for employment grade (measure of SES), physical activity, smoking status, alcohol intake, fiber intake and carbohydrate intake; and WHR and BMI. Hazard ratios across tertiles of glycemic

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load showed a significant, inverse association with T2D risk in the base model. Sex-specific tertiles of glycemic load were 1.00, 0.92 (95% CI: 0.71, 1.19), and 0.70 (95% CI: 0.54, 0.92) (adjusted for sex, age, and energy-misreporting; P=0.01). The association remained after adjustment for employment grade, physical activity, smoking and alcohol, but it was NS after further adjustment for carbohydrate and fiber intakes or in a model additionally adjusted for WHR and BMI. Higher glycemic index and glycemic load were not associated with increased risk of incident diabetes. Higher glycemic load was associated with a decreased risk of T2D in some models.

Sayhoun, 2008 (positive quality), a prospective cohort study drawn from the Health, Aging, and Body Composition (Health ABC) Study, consisted of a random sample of Medicare-eligible individuals (aged 70 to 79) from Pittsburgh PA and Memphis TN. Participants (N=1,898; women, N=1,027; men, N=871) were eligible for the study if they remained in the same area for more than three years and had no life-threatening cancers and could conduct basic daily activities unassisted. The relevance of studying an elderly population is that the incidence of T2D has doubled over the last 20 years, and people more than 60 years account for approximately half of this increase. The results in this report were drawn from the first six years of the Health ABC Study. Dietary intake was measured in the second year of the Health ABC study using a FFQ based on the Block questionnaire (Block Dietary Data Systems, Berkeley, CA), which included age-appropriate foods. A computer SAS program was developed to calculate GI and GL of the foods eaten by participants in the study. Diagnosis of T2D was based on: 1) Physician's report, 2) Use of insulin or hypoglycemic medications, and 3) Blood glucose levels higher than 126mg per dL measured in years two, four and six. Subjects were grouped based on quintiles of GI and GL. Multivariate logistic regression was used to determine risk of T2D by quintile of energy adjusted dietary GI and GL. The data showed that neither dietary GI nor GL were significantly associated with risk of developing T2D, either before or after controlling for age, sex, race, clinical site, education, physical activity, baseline fasting glucose, BMI, alcohol consumption and smoking. For GI, the means of Q2 to Q5 were not significantly different from Q1 [OR (95% CI), P=0.7152 and P=0.8628, for unadjusted and adjusted, respectively]. For GL the means of Q2 to Q5 were NS different from Q1 [OR (95% CI), P=0.1234 and P=0.1147, for unadjusted and adjusted, respectively]. This study also showed that dietary GI and GL were negatively correlated with total fat, saturated fat and alcohol consumption; both GI and GL were positively correlated with carbohydrate and GL was positively associated with fruit and fiber intake. Notably, low dietary GI and GL patterns were not necessarily compatible with current dietary guidelines. Limitations of the study involved limitations of the GI and GL indices themselves, in that these indices may not provide enough information on the overall composition of the diet, type of carbohydrate in the diet, and dietary risk of T2D. Another specific limitation of this study was that, due to a cohort of similar age and functional status, there was a relative narrow range of GI and GL status and the quintile means fell within a narrow range (approximately 50 to 60). The authors concluded that the homogeneity of the study population may have diminished the associations between dietary GI and GL and risk of developing T2D.

Schulz, 2006 (neutral quality), a prospective cohort study, evaluated the impact of GI and GL on risk of T2D in the multiethnic Insulin Resistance Atherosclerosis Study (IRAS), focusing on the relationship between GI and GL on abdominal obesity and waist circumference (WC) measurements. In a previous study, this group showed that abdominal adiposity was associated with decreased insulin sensitivity in this same

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population. Subjects (1,600) for the study were recruited from four clinical centers between 1992 to 1994, with equal representation across gender, age (40 to 49, 50 to 59, 60 to 69 years), ethnicity (African American, Hispanic and non-Hispanic white) and glucose tolerance ranges (normal, IGT, and T2D). This cohort was followed up after five years. Dietary intake was assessed using a one-year, semi-quantitative, 114-item food frequency interview. This study included 892 subjects who were free from T2D at baseline and who returned for follow-up examination. At five-year follow-up, subjects diagnosed with T2D according to the World Health Organization (WHO) criteria were considered for the incidence of T2D in this cohort: 146 cases of T2D were identified. Multiple logistic regression analysis was used to assess the relationship between GI and GL and T2D risk. The average GI and GL for diabetic subjects was 59.5 and 127.9, respectively, NS different from non-diabetic subjects, 58.6 and 121.8, respectively. In multivariate regression models, GI and GL were not associated with increased risk of T2D. Stratification by abdominal obesity status at baseline showed a positive association between GI and T2D risk among non-abdominally obese subjects, whereas, there was no association in subjects with abdominal obesity. Interestingly, stratification by five-year waist change showed a positive association between GI and T2D risk in subjects who experienced an increase in waist circumference. This association was strongest among subjects without abdominal obesity at baseline: a one-unit increase in GI increased T2D risk by 12% (OR=1.12; 95% CI: 1.03, 1.21) in subjects with waist increase without abdominal obesity at baseline. No significant association was found between GL and T2D risk with stratification by either abdominal obesity or waist change. The authors conclude that an increase in dietary GI increases the risk of T2D in non-abdominally obese subjects and subjects with increased WC. Furthermore, this association is stronger in subjects who were both non-abdominally obese at baseline and showed WC increase over the duration of the study. A major limitation of this study was the IRAS subject population which, due to sampling design, has a one-third incidence of impaired glucose tolerance (IGT) and a cohort that is much more overweight (mean BMI=28.4kg/m^2) than an average American cohort.

Schulze, 2004 (positive-quality) examined the association of GI, GL and dietary fiber on T2D risk in young women from the Nurses' Health Study II, a prospective cohort study of 116,671 nurses in the US who were 24 to 44 years at baseline. This cohort was followed up with biennial mailed questionnaires on lifestyle factors and health outcomes. After exclusion, 91,249 women were included for the analysis. In 1991, these 91,249 women completed a semi-quantitative FFQ and were followed for eight years for T2D incidence. A similar FFQ was used 1995 to update dietary intake data. The Cox proportional hazards analysis method, stratified on five-year age categories, was used to estimate relative risks (RR) for each category of intake (quintiles). During the 716,300 person-years follow-up, 741 T2D cases were diagnosed. Increasing GI was strongly associated with a progressively higher risk of T2D; the RR from the age-adjusted quintiles, highest to lowest GI, was 1.79 (95% CI: 1.43, 2.25). This association remained high after further adjustments for BMI, alcohol consumption, smoking, family T2D history and numerous other covariates including different dietary and fat intakes. On the other hand, in age-adjusted analysis, both GL and total carbohydrate intake were inversely correlated with T2D risk; however, this significant association disappeared after adjustment for BMI and the other covariates listed above. There was a significant inverse association between total dietary fiber intake and T2D risk; the RR from the age-adjusted quintiles, highest to lowest GI, was 0.53 (95% CI: 0.42, 0.67), with cereal fiber having the strongest

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association with decreased T2D risk; the RR from the age-adjusted quintiles, highest to lowest GI, was 0.32 (95% CI: 0.25, 0.45). However, the inverse association between total fiber intake and T2D risk was attenuated by further adjustment with the above covariates beyond adjustment for age and BMI; whereas the inverse association between cereal fiber intake and T2D risk was maintained. Lastly, the data were also stratified to assess whether the associations with GI, GL and total carbohydrate intake were modified by BMI, physical activity and family T2D history. No major changes were observed for BMI. For physical activity, women in the lower two quintiles of activity scores had RRs of 2.01 for GI (highest to lowest quintile comparison) (95% CI: 1.38, 2.93) and 1.65 for GL (95% CI: 1.01, 2.70). Among women with no family history of T2D, the RR for GL and T2D was 1.02 (95% CI: 0.64, 1.63), but among women with a family history of T2D, the RR was 2.04 (95% CI: 1.13, 3.66).

Stevens, 2002 (positive quality), a prospective cohort study (Atherosclerosis Risk in Communities [ARIC] Study) in the US, examined the association of dietary fiber and glycemic index with T2D in African American and white adults. Participants were 12,251 adults (9,529 white, 2,722 African American) aged 45 to 64 years at baseline. The cohort study was initiated in 1987 to 1989 and included a maximum of four clinical trials that took place at approximately three-year intervals. Diet was assessed with an interviewer administered FFQ and T2D status was determined by fasting blood glucose (FBG), non-fasting glucose level, self-report or use of diabetes medication. During nine years of follow-up, 1,447 cases of diabetes were reported. After adjustment for age, BMI, education, smoking status, physical activity, sex and field center, there was NS association of glycemic index or glycemic load with incident diabetes. The HR for extreme quintiles of GL was 1.10 (95% CI: 0.90, 1.39) in white adults and 0.97 (95% CI: 0.73, 1.35) in African American adults in the fully adjusted model.

Villegas, 2007 (positive quality) was a five-year prospective cohort study of 64,227 middle-aged Chinese women with no history of diabetes or other adult degenerative disease. Food-frequency questionnaires were used for in-person interviews conducted on dietary intake and physical activity. These were conducted at baseline and at the first follow-up interview. The FFQ was designed for, and validated in, this population in Shanghai (Shanghai Women's Health Study FFQ). A total of 1,608 were diagnosed with T2D, as recorded in follow-up interviews using criteria of the American Diabetes Association (ADA). Associations between total carbohydrate intake, glycemic index (GI), glycemic load (GL) and specific food groups and T2D incidence were evaluated using multivariable Cox proportional hazards models. Findings showed that high carbohydrate intake and rice consumption were positively associated with T2D incidence. Comparing the highest vs. the lowest quintiles of intake, the multivariable-adjusted estimates of risk were 1.28 (95% CI: 1.09, 1.50) and 1.78 (95% CI: 1.48, 2.15) for carbohydrate and rice consumption, respectively. The percentage of energy from carbohydrates was also associated with increased risk of T2D; estimated risk of 1.37 in highest to lowest quintile comparison (95% CI: 1.11, 1.69), as was GI [estimated risk of 1.21 in highest to lowest quintile comparison (95% CI: 1.03, 1.43)] and GL [estimated risk of 1.34 in highest to lowest quintile comparison (95% CI: 1.13, 1.58)]. Overall, the intake of rice was associated with the greatest increase risk of T2D.

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Overview table

Author, Year, Study Design, Class, Rating	Population/Subjects	Methodology	Significant Outcomes
Barclay AW, Flood VM et al, 2007 Study Design: Prospective Cohort Study Class: B Neutral Quality	N=1,833 total. Study begun in 1991, subjects were 49 years at the start. Subjects were mostly caucasian, representative of older Australian population.	Diabetes incidence measured based on subjects without T2D at baseline who were diagnosed with T2D at subsequent follow-up in 1992 to 1994, five years and 10 years.	During ten years follow-up, 138 cases of T2D identified out of 1,833 subjects. Total CHO, starch, sugar and total fiber intake were not correlated with T2D incidence in age-and sex-adjusted models or the multivariate-adjusted model. Vegetable fiber had significant negative association with risk of T2D in the age- and sex-adjusted models: HR=0.72 (95% CI: 0.57, 0.93) P=0.010; <70 years at baseline [HR=0.72 (95% CI: 0.54, 0.96) P=0.027]. In multivariate model: HR=0.76 (95% CI: 0.57, 0.99) P=0.048. NS when stratified by age with multivariate analysis adjustment. In age-stratified and multivariate analyses, there was a positive correlation between GI and T2D incidence for individuals <70 years, but not those >70 years at baseline [HR=1.75 (95% CI: 1.05, 2.92) P=0.031].

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Halton TL, Liu S et al, 2008 Study Design: Prospective cohort Class: B Positive Quality	N=85,059 women. Nurses' Health Study. Age: 30 to 55 years at baseline. 98% white. Location: United States.	Followed from 1980 to 2000. Diet assessed with FFQ in 1980, 1984, 1986, 1990, 1994 and 1998. T2D self-reported (with follow-up by additional questionnaire).	During 20 years of follow-up 4,670 cases of T2D were reported. Significant positive association between glycemic load and risk of T2D in comparison of extreme deciles (multivariate RR: 2.47; 95% CI: 1.75, 3.47; P<0.0001).
Hodge AM, English DR et al, 2004 Study Design: Prospective Cohort Study Class: B Positive Quality	N=31,641 men and women from the Melbourne Collaborative Cohort Study. Age: 40 to 69 years at baseline.	Participants completed baseline questionnaires (including FFQ) between 1990 and 1994. Incident cases of diabetes were self-reported on a questionnaire mailed to participants four years after baseline. Confirmation of diagnosis was sought from medical practitioners. Dietary information was collected using a 121-item, self-administered FFQ developed for the cohort study.	365 cases of T2D were reported (76% of cases confirmed). Dietary GI was positively associated with diabetes. When BMI and WHR were included in the model, the association was attenuated. In participants with BMI <25kg/m^2, GI was inversely associated with diabetes (OR=0.29, 95% CI: 0.10, 0.91). In people with BMI <30kg/m^2, GI was not associated with diabetes (1.00, 95% CI: 0.68, 1.46), whereas in those with BMI of ≥30kg/m^2, a positive association (1.64, 95% CI: 1.22, 2.21) was observed (interaction, P=0.01). GL showed little association with diabetes.

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Krishnan S, Rosenberg L et al, 2007 Study Design: Prospective Cohort Study Class: B Positive Quality	N=40,078 women from BWHS. Study began in 1995. Women ages 30 to 69 years recruited by mail from all regions of US.	Examined association of GI, GL and cereal fiber intake and risk of T2D in cohort of women from BWHS. Follow-up 1995 to 2003. Diet assessed at baseline with 68-item modified Block National Cancer Institute (NCI) FFQ modified to include foods unique to black population. Cox proportional hazards models were used to calculate incidence rate ratios (IRR) and 95% CI.	For 123,499 person-years follow-up: 1,938 T2D cases. GL inversely associated with risk of T2D in age-adjusted model; after adjustment for BMI, energy intake, family history of T2D, smoking and physical activity (Model 1), inverse association lost. Further adjustment of GL for fiber intake, total fat intake and total protein intake (Model 2) resulted in an IRR of 1.22 (95% CI: 0.98, 1.51), comparing highest to lowest GL quintiles. GI positively associated with T2D risk for all models; for Model 2, the IRR was 1.23 (95% CI: 1.05, 1.44) for the highest to lowest GI quintiles. Cereal fiber inversely associated with T2D risk in all models; the IRR was 0.82 (95% CI: 0.70, 0.96).

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Mosdol et al 2007 Study Design: Prospective cohort Class: B Neutral Quality	N=7,321 white adults (71% men). Whitehall II Study. Age: 39 to 63 years at baseline. Location: United Kingdom.	Participants followed for seven phases from 1995 to 1998 (phase one) through 2003 to 2004 (phase seven). Diet assessed with FFQ for Western diets. T2D self-reported throughout study and two-hour GTT conducted at clinical exams during phases three, five and seven (five-year intervals).	During 13 years of follow-up, 329 incident cases of T2D were identified. GI not associated with risk even after further adjustments for employment grade (measure of SES), physical activity, smoking status, alcohol intake, fiber intake and CHO intake; and WHR and BMI. HRs across tertiles of glycemic load showed a significant, inverse association with T2D risk in base model. Sex-specific tertiles of glycemic load were 1.00, 0.92 (95% CI: 0.71, 1.19) and 0.70 (95% CI: 0.54, 0.92) (adjusted for sex, age and energy-misreporting; P=0.01). The association remained after adjustment for employment grade, physical activity, smoking and alcohol, but it was NS after further adjustment for CHO and fiber intakes or in a model additionally adjusted for WHR and BMI.

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Sahyoun N, Anderson A et al, 2008 Study Design: Prospective Cohort Study Class: B Positive Quality	N=1,890 total (1,027 women; 871 men). Age: 70 to 79 years. Recruited for the Health ABC Study of elderly Americans from Pittsburgh, PA and Memphis, TN.	Study from first six years of Health ABC Study. Dietary intake was measured in second year of Health ABC study using a FFQ based on the Block questionnaire with age-appropriate foods. Health information was collected at two, four and six years. Subjects were grouped based on quintiles of GI and GL. Multivariate logistic regression was used to determine risk of T2D by quintile of energy adjusted dietary GI and GL.	Neither dietary GI nor GL were significantly associated with risk of developing T2D. GI: Means of Q2 to Q5 were NS different from Q1 [OR (95% CI), P=0.7152 and P=0.8628, for unadjusted and adjusted, respectively]. GL: Means of Q2 to Q5 were NS different from Q1 [OR (95% CI), P=0.1234 and P=0.1147, for unadjusted and adjusted, respectively].

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Schulz M, Liese AD et al, 2006 Study Design: Prospective Cohort Study Class: B Neutral Quality	N=1,600 IRAS subjects. Subjects recruited at four clinical centers from 1992 to 1994. 892 subjects free from T2D at baseline. Equal across gender, age (40 to 49, 50 to 59, 60 to 69 years), ethnicity and glucose tolerance (norm, IGT and T2D). Five-year follow-up.	Multiple logistic regression analysis was used to assess the relationship between GI and GL and T2D risk. Cases further stratified according to abdominal obesity (WC >102cm men; >99cm women) and "change in waist" (↓ = Δ in waist of ≥2cm; stable = ±2cm; ↑ ≥2cm). Adjusted for age, ethnicity, baseline BMI, family history of T2D, smoking, glucose tolerance status, education and energy intake.	At five-year follow-up, subjects diagnosed with T2D according to WHO criteria: 146 cases. Average GI and GL for T2D subjects was 59.5 and 127.9, respectively, NS different from non-T2D subjects, 58.6 and 121.8, respectively. Multivariate regression analysis: GI (β=0.0234, P=0.2); GL (β=-0.0018, P=0.6). Stratification by abdominal obesity at baseline: Positive association between GI and T2D risk among non-abdominally obese subjects [OR first to third tertile=1.90 (95% CI: 0.89, 4.00)]. No association in subjects with abdominal obesity. Stratification by five-year waist Δ: Positive association between GI and T2D risk in subjects with ↑ in WC [OR first to third tertile=1.70 (95% CI: 0.84, 3.47)]. Association was strongest in subjects without abdominal obesity: A one-unit ↑ in GI ↑ T2D risk by 12% [OR 1.12 (95% CI: 1.03, 1.21)] in subjects with waist ↑ without abdominal obesity. NS association between GL and T2D with stratification by either abdominal obesity or waist Δ.

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Schulze MB, Liu S et al, 2004 Study Design: Prospective Cohort Study Class: B Positive Quality	N=116,671 women from Nurses' Health Study II. N=91,249, after exclusion. Age: 24 to 44 years at baseline.	Examined association of GI, GL and dietary fiber on T2D risk in young women. In 1991, 91,249 women completed a semi-quantitative FFQ and followed for eight years. The Cox proportional hazards analysis method, stratified by five-year age categories, used for RR for each category of intake (quintiles).	During 716,300 person-years follow-up, 741 T2D cases were diagnosed. ↑ GI strongly associated with progressively ↑ risk of T2D; RR=1.79 (95% CI: 1.43, 2.25). Association remained ↑ after adjustments for BMI, alcohol, smoking, family T2D history and other covariates including dietary and fat intakes. GL and total CHO were inversely correlated with T2D risk; however, association disappeared after adjustment for BMI and other covariates. Significant inverse association between total dietary fiber and T2D risk; RR=0.53 (95% CI: 0.42, 0.67), with cereal fiber having the strongest association, RR= 0.32 (95% CI: 0.25, 0.45). Data further stratified for associations modified by BMI, physical activity and family T2D history: No major Δs were observed for BMI. For physical activity, women in the lower two quintiles of activity had RRs of 2.01 for GI (95% CI: 1.38, 2.93) and 1.65 for GL (95% CI: 1.01, 2.70). Among women with no family history of T2D, RR=1.02 for GL and T2D (95% CI: 0.64, 1.63), but women with family history of T2D, RR = 2.04 (95% CI: 1.13, 3.66).

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Stevens J, Ahn K et al 2002 Study Design: Prospective cohort Class: B Positive Quality	N=12,251 adults (9,529 white; 2,722 African American). Atherosclerosis Risk in Communities (ARIC) study. Age: 45 to 64 years at baseline. Location: United States.	Initiated in 1987 to 1989 and included a maximum of four clinical exams that took place at ~three-year intervals. Diet assessed by interviewer-administered FFQ. Diabetes status determined by FBG, non-fasting glucose level, self-report or use of diabetes medication.	During nine years of follow-up, 1,447 cases of diabetes were reported. After adjustment for age, BMI, education, smoking status, physical activity, sex and field center; there was NS association of glycemic index or glycemic load with incident diabetes. The HR for extreme quintiles of GL was 1.10 (95% CI: 0.90, 1.39) in white adults and 0.97 (95% CI: 0.73, 1.35) in African American adults in the fully adjusted model.
Villegas R, Liu S et al, 2007 Study Design: Prospective Cohort Study Class: B Positive Quality	N=64,227 middle-aged Chinese women with no history of diabetes.	Duration: Five years. FFQ used for in-person interviews conducted on dietary intake and physical activity, conducted at baseline and at the first follow-up. Associations between total CHO intake, GI, GL and specific food groups and T2D incidence were evaluated using multivariable Cox proportional hazards model.	High CHO intake and rice consumption were positively associated with T2D risk. The RR comparing the highest to lowest quintiles was 1.28 (95% CI: 1.09, 1.50) and 1.78 (95% CI: 1.48, 2.15) for CHO and rice consumption, respectively. GI and GL were also positively associated with ↑ risk of T2D; RR=1.21 (95% CI: 1.03, 1.43) and RR=1.34 (95% CI: 1.13, 1.58) for GI and GL, respectively.

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Search plan and results

Inclusion criteria

- June 2004 to March 2009 for cancer, and January 2000 to September 2009 for CVD and type 2 diabetes
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children, two to 18 years; adults, 19 years and older
- *Populations:* Healthy and those with elevated chronic disease risk.

Exclusion criteria

- Reviews (narrative and systematic); meta-analyses
- Studies examining intermediate outcomes, not incidence of disease
- Medical treatment or therapy, including medical treatment of diabetes
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Animal studies
- In vitro studies
- Articles not peer reviewed (Websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed:
  Cancer: "Neoplasms"[Mesh] AND ("Glycemic Index"[Mesh] OR "glycemic load"[All Fields])

- PubMed, Embase, BIOSIS:
  Cardiovascular Disease: ("Glycemic Index"[Mesh] OR "glycemic load") AND (“Cardiovascular diseases”[Mesh])

- PubMed, Embase, BIOSIS:
  Type 2 Diabetes: ("Glycemic Index"[Mesh] OR "glycemic load") AND (“Diabetes Mellitus, Type 2”[Mesh])

Date searched: 03/20/2009; updated 09/19/2009 and 09/22/2009 for CVD and T2D

Summary of articles identified to review

- Total hits from all electronic database searches: 491
- Total articles identified to review from electronic databases: 133
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 46
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 46
- Number of Articles Reviewed but Excluded: 87

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Included articles (References)

What is the relationship between glycemic index or glycemic load and cancer?

1. Augustin LS, Galeone C, Dal Maso L, Pelucchi C, Ramazzotti V, Jenkins DJ, Montella M, Talamini R, Negri E, Franceschi S, La Vecchia C. Glycemic index, glycemic load and risk of prostate cancer. *Int J Cancer.* 2004 Nov 10; 112(3): 446-450. PMID: 15382070.
2. Bertuccio P, Praud D, Chatenoud L, Lucenteforte E, Bosetti C, Pelucchi C, Rossi M, Negri E, La Vecchia C. Dietary glycemic load and gastric cancer risk in Italy. *Br J Cancer.* 2009 Feb 10; 100(3): 558-561. PMID: 19190635.
3. Cust AE, Slimani N, Kaaks R, van Bakel M, Biessy C, Ferrari P, Laville M, Tjønneland A, Olsen A, Overvad K, Lajous M, Clavel-Chapelon F, Boutron-Ruault MC, Linseisen J, Rohrmann S, Nöthlings U, Boeing H, Palli D, Sieri S, Panico S, Tumino R, Sacerdote C, Skeie G, Engeset D, Gram IT, Quirós JR, Jakszyn P, Sánchez MJ, Larrañaga N, Navarro C, Ardanaz E, Wirfält E, Berglund G, Lundin E, Hallmans G, Bueno-de-Mesquita HB, Du H, Peeters PH, Bingham S, Khaw KT, Allen NE, Key TJ, Jenab M, Riboli E. Dietary carbohydrates, glycemic index, glycemic load, and endometrial cancer risk within the European Prospective Investigation into Cancer and Nutrition cohort. *Am J Epidemiol.* 2007 Oct 15; 166(8): 912-923. Epub 2007 Aug 1. PMID: 17670911.
4. Flood A, Peters U, Jenkins DJ, Chatterjee N, Subar AF, Church TR, Bresalier R, Weissfeld JL, Hayes RB, Schatzkin A; Prostate, Lung, Colorectal, Ovarian (PLCO) Project Team. Carbohydrate, glycemic index, and glycemic load and colorectal adenomas in the Prostate, Lung, Colorectal, and Ovarian Screening Study. *Am J Clin Nutr.* 2006 Nov; 84(5): 1, 184-1, 192. PMID: 17093173.
5. George SM, Mayne ST, Leitzmann MF, Park Y, Schatzkin A, Flood A, Hollenbeck A, Subar AF. Dietary glycemic index, glycemic load, and risk of cancer: A prospective cohort study. *Am J Epidemiol.* 2009 Feb 15; 169(4): 462-472. Epub 2008 Dec 18. PMID: 19095757.
6. Giles GG, Simpson JA, English DR, Hodge AM, Gertig DM, Macinnis RJ, Hopper JL. Dietary carbohydrate, fibre, glycaemic index, glycaemic load and the risk of postmenopausal breast cancer. *Int J Cancer.* 2006 Apr 1; 118(7): 1, 843-1, 847. PMID: 16217755.
7. Heinen MM, Verhage BA, Lumey L, Brants HA, Goldbohm RA, van den Brandt PA. Glycemic load, glycemic index, and pancreatic cancer risk in the Netherlands Cohort Study. *Am J Clin Nutr.* 2008 Apr; 87(4): 970-977. PMID: 18400721.
8. Howarth NC, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. The association of glycemic load and carbohydrate intake with colorectal cancer risk in the Multiethnic Cohort Study. *Am J Clin Nutr.* 2008 Oct; 88(4): 1, 074-1, 082. PMID: 18842796.
9. Johnson KJ, Anderson KE, Harnack L, Hong CP, Folsom AR. No association between dietary glycemic index or load and pancreatic cancer incidence in postmenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2005 Jun; 14(6): 1, 574-1, 575. PMID: 15941976.
10. Kabat GC, Shikany JM, Beresford SA, Caan B, Neuhouser ML, Tinker LF, Rohan TE. Dietary carbohydrate, glycemic index, and glycemic load in relation to colorectal cancer risk in the Women's Health Initiative. *Cancer Causes*

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

Control. 2008 Dec; 19(10): 1, 291-1, 298. Epub 2008 Jul 10. PMID: 18618276.
11. Lajous M, Willett W, Lazcano-Ponce E, Sanchez-Zamorano LM, Hernandez-Avila M, Romieu I. Glycemic load, glycemic index, and the risk of breast cancer among Mexican women. *Cancer Causes Control.* 2005 Dec; 16(10): 1, 165-1, 169. PMID: 16215866.
12. Lajous M, Boutron-Ruault MC, Fabre A, Clavel-Chapelon F, Romieu I. Carbohydrate intake, glycemic index, glycemic load, and risk of postmenopausal breast cancer in a prospective study of French women. *Am J Clin Nutr.* 2008 May; 87(5): 1, 384-1, 391. PMID: 18469262.
13. Larsson SC, Bergkvist L, Wolk A. Glycemic load, glycemic index and carbohydrate intake in relation to risk of stomach cancer: a prospective study. *Int J Cancer.* 2006 Jun 15; 118(12): 3, 167-3, 169. PMID: 16395707.
14. Larsson SC, Giovannucci E, Wolk A. Dietary carbohydrate, glycemic index, and glycemic load in relation to risk of colorectal cancer in women. *Am J Epidemiol.* 2007 Feb 1; 165(3): 256-261. Epub 2006 Nov 21. PMID: 17118965
15. Larsson SC, Friberg E, Wolk A. Carbohydrate intake, glycemic index and glycemic load in relation to risk of endometrial cancer: A prospective study of Swedish women. *Int J Cancer.* 2007 Mar 1; 120(5): 1, 103-1, 137. PMID: 17131331.
16. McCann SE, McCann WE, Hong CC, Marshall JR, Edge SB, Trevisan M, Muti P, Freudenheim JL. Dietary patterns related to glycemic index and load and risk of premenopausal and postmenopausal breast cancer in the Western New York Exposure and Breast Cancer Study. *Am J Clin Nutr.* 2007 Aug; 86(2): 465-471. PMID: 17684220.
17. McCarl M, Harnack L, Limburg PJ, Anderson KE, Folsom AR. Incidence of colorectal cancer in relation to glycemic index and load in a cohort of women. *Cancer Epidemiol Biomarkers Prev.* 2006 May; 15(5): 892-896. PMID: 16702366.
18. Michaud DS, Fuchs CS, Liu S, Willett WC, Colditz GA, Giovannucci E. Dietary glycemic load, carbohydrate, sugar, and colorectal cancer risk in men and women. *Cancer Epidemiol Biomarkers Prev.* 2005 Jan; 14(1): 138-147. PMID: 15668487.
19. Nöthlings U, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. Dietary glycemic load, added sugars, and carbohydrates as risk factors for pancreatic cancer: The Multiethnic Cohort Study. *Am J Clin Nutr.* 2007 Nov; 86(5): 1, 495-1, 501. PMID: 17991664.
20. Patel AV, McCullough ML, Pavluck AL, Jacobs EJ, Thun MJ, Calle EE. Glycemic load, glycemic index, and carbohydrate intake in relation to pancreatic cancer risk in a large US cohort. *Cancer Causes Control.* 2007 Apr; 18(3): 287-294. Epub 2007 Jan 11. PMID: 17219014.
21. Randi G, Ferraroni M, Talamini R, Garavello W, Deandrea S, Decarli A, Franceschi S, La Vecchia C. Glycemic index, glycemic load and thyroid cancer risk. *Ann Oncol.* 2008 Feb; 19(2): 380-383. Epub 2007 Oct 19. PMID: 17951595.
22. Sieri S, Pala V, Brighenti F, Pellegrini N, Muti P, Micheli A, Evangelista A, Grioni S, Contiero P, Berrino F, Krogh V. Dietary glycemic index, glycemic load, and the risk of breast cancer in an Italian prospective cohort study. *Am J Clin Nutr.* 2007 Oct; 86(4): 1, 160-1, 166. PMID: 17921397.
23. Silvera SA, Rohan TE, Jain M, Terry PD, Howe GR, Miller AB. Glycaemic index, glycaemic load and risk of endometrial cancer: A prospective cohort

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

study. *Public Health Nutr.* 2005 Oct; 8(7): 912-919. PMID: 16277808.
24. Silvera SA, Rohan TE, Jain M, Terry PD, Howe GR, Miller AB. Glycemic index, glycemic load, and pancreatic cancer risk (Canada). *Cancer Causes Control.* 2005 May; 16(4): 431-436. PMID: 15953985.
25. Silvera SA, Jain M, Howe GR, Miller AB, Rohan TE. Dietary carbohydrates and breast cancer risk: A prospective study of the roles of overall glycemic index and glycemic load. *Int J Cancer.* 2005 Apr 20; 114(4): 653-658. Erratum in: *Int J Cancer.* 2006 May 1; 118(9): 2, 372. PMID: 15609324.
26. Silvera SA, Jain M, Howe GR, Miller AB, Rohan TE. Glycaemic index, glycaemic load and ovarian cancer risk: a prospective cohort study. *Public Health Nutr.* 2007 Oct; 10(10): 1, 076-1, 081. Epub 2007 Mar 2. PMID: 17381931.
27. Strayer L, Jacobs DR Jr, Schairer C, Schatzkin A, Flood A. Dietary carbohydrate, glycemic index, and glycemic load and the risk of colorectal cancer in the BCDDP cohort. *Cancer Causes Control.* 2007 Oct; 18(8): 853-863. Epub 2007 Jun 29. PMID: 17605083.
28. Weijenberg MP, Mullie PF, Brants HA, Heinen MM, Goldbohm RA, van den Brandt PA. Dietary glycemic load, glycemic index and colorectal cancer risk: Results from the Netherlands Cohort Study. *Int J Cancer.* 2008 Feb 1; 122(3): 620-629. PMID: 17935129.

What is the relationship between glycemic index or glycemic load and type 2 diabetes?

1. Barclay AW, Flood VM, Rochtchina E, Mitchell P, Brand-Miller JC. Glycemic index, dietary fiber, and risk of type 2 diabetes in a cohort of older Australians. *Diabetes Care.* 2007 Nov; 30(11): 2, 811-2, 813. Epub 2007 Aug 21. No abstract available. PMID: 17712022.
2. Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. *Am J Clin Nutr.* 2008 Feb; 87(2): 339-346. PMID: 18258623.
3. Hodge AM, English DR, O'Dea K, Giles GG. Glycemic index and dietary fiber and the risk of type 2 diabetes. *Diabetes Care.* 2004 Nov; 27(11): 2, 701-2, 706. PMID: 15505008.
4. Krishnan S, Rosenberg L, Singer M, Hu FB, Djoussé L, Cupples LA, Palmer JR. Glycemic index, glycemic load, and cereal fiber intake and risk of type 2 diabetes in US black women. *Arch Intern Med.* 2007 Nov 26; 167(21): 2, 304-2, 309. PMID: 18039988.
5. Mosdøl A, Witte DR, Frost G, Marmot MG, Brunner EJ. Dietary glycemic index and glycemic load are associated with high-density-lipoprotein cholesterol at baseline but not with increased risk of diabetes in the Whitehall II study. *Am J Clin Nutr.* 2007 Oct; 86(4): 988-994. PMID: 17921375.
6. Sahyoun NR, Anderson AL, Tylavsky FA, Lee JS, Sellmeyer DE, Harris TB; Health, Aging, and Body Composition Study. Dietary glycemic index and glycemic load and the risk of type 2 diabetes in older adults. *Am J Clin Nutr.* 2008 Jan; 87(1): 126-131. PMID: 18175745.
7. Schulz M, Liese AD, Fang F, Gilliard TS, Karter AJ. Is the association between dietary glycemic index and type 2 diabetes modified by waist circumference? *Diabetes Care.* 2006 May; 29(5): 1, 102-1, 104. PMID: 16644644.
8. Schulze MB, Liu S, Rimm EB, Manson JE, Willett WC, Hu FB. Glycemic index,

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glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. *Am J Clin Nutr.* 2004 Aug; 80(2): 348-356. PMID: 15277155.
9. Stevens J, Ahn K, Juhaeri, Houston D, Steffan L, Couper D. Dietary fiber intake and glycemic index and incidence of diabetes in African-American and white adults: The ARIC study. *Diabetes Care.* 2002 Oct; 25(10): 1, 715-1, 721. PMID: 12351467.
10. Villegas R, Liu S, Gao YT, Yang G, Li H, Zheng W, Shu XO. Prospective study of dietary carbohydrates, glycemic index, glycemic load, and incidence of type 2 diabetes mellitus in middle-aged Chinese women. *Arch Intern Med.* 2007 Nov 26; 167(21): 2, 310-2, 316. PMID: 18039989.

What is the relationship between glycemic index or glycemic load and cardiovascular disease?

1. Beulens JW, de Bruijne LM, Stolk RP, Peeters PH, Bots ML, Grobbee DE, van der Schouw YT. High dietary glycemic load and glycemic index increase risk of cardiovascular disease among middle-aged women: A population-based follow-up study. *J Am Coll Cardiol.* 2007 Jul 3; 50(1): 14-21. Epub 2007 Jun 18. PMID: 17601539.
2. Halton TL, Willett WC, Liu S, Manson JE, Albert CM, Rexrode K, Hu FB. Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med.* 2006 Nov 9; 355(19): 1, 991-2, 002. PMID: 17093250.
3. Kaushik S, Wang JJ, Wong TY, Flood V, Barclay A, Brand-Miller J, Mitchell P. Glycemic index, retinal vascular caliber, and stroke mortality. *Stroke.* 2009 Jan; 40(1): 206-212. Epub 2008 Oct 23. PMID: 18948616.
4. Levitan EB, Mittleman MA, Håkansson N, Wolk A. Dietary glycemic index, dietary glycemic load, and cardiovascular disease in middle-aged and older Swedish men. *Am J Clin Nutr.* 2007 Jun; 85(6): 1, 521-1, 526. PMID: 17556687.
5. Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, Hennekens CH, Manson JE. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr.* 2000 Jun; 71(6): 1, 455-1, 461. PMID: 10837285.
6. Oh K, Hu FB, Cho E, Rexrode KM, Stampfer MJ, Manson JE, Liu S, Willett WC. Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women. *Am J Epidemiol.* 2005 Jan 15; 161(2): 161-169. PMID: 15632266.
7. Tavani A, Bosetti C, Negri E, Augustin LS, Jenkins DJ, La Vecchia C. Carbohydrates, dietary glycaemic load and glycaemic index, and risk of acute myocardial infarction. *Heart.* 2003 Jul; 89(7): 722-726. PMID: 12807839; PMCID: PMC1767713.
8. van Dam RM, Visscher AW, Feskens EJ, Verhoef P, Kromhout D. Dietary glycemic index in relation to metabolic risk factors and incidence of coronary heart disease: The Zutphen Elderly Study. *Eur J Clin Nutr.* 2000 Sep; 54(9): 726-731. PMID: 11002385.

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Excluded articles

Article	Reason for Exclusion
Amano Y, Kawakubo K, Lee JS, Tang AC, Sugiyama M, Mori K. Correlation between dietary glycemic index and cardiovascular disease risk factors among Japanese women. *Eur J Clin Nutr.* 2004 Nov; 58(11): 1, 472-1, 478. PMID: 15127092.	Does not include incidence of disease in analyses.
Barclay AW, Brand-Miller JC, Mitchell P. Macronutrient intake, glycaemic index and glycaemic load of older Australian subjects with and without diabetes: Baseline data from the Blue Mountains Eye study. *Br J Nutr.* 2006 Jul; 96(1): 117-123. PMID: 16869999.	Does not answer question; compares dietary intake of older adults with and without diabetes.
Barclay AW, Petocz P, McMillan-Price J, Flood VM, Prvan T, Mitchell P, Brand-Miller JC. Glycemic index, glycemic load, and chronic disease risk: A meta-analysis of observational studies. *Am J Clin Nutr.* 2008 Mar; 87(3): 627-637. Review. PMID: 18326601.	Study design is meta-analysis.
Barkoukis H, Marchetti CM, Nolan B, Sistrun SN, Krishnan RK, Kirwan JP. A high glycemic meal suppresses the postprandial leptin response in normal healthy adults.*Ann Nutr Metab.* 2007; 51(6): 512-518. Epub 2007 Dec 10. PMID: 18073462.	Does not include incidence of disease in analyses.
Benoit SR, Fleming R, Philis-Tsimikas A, Ji M. Predictors of glycemic control among patients with Type 2 diabetes: A longitudinal study. *BMC Public Health.* 2005 Apr 17; 5: 36. PMID: 15833140.	Participants diagnosed with type 2 diabetes.
Beulens JWJ, Van Der Schouw YT. Increased risk of cardiovascular disease among middle-aged women due to glycemic load. *Cardiol Rev.* 2008 Feb; 25(2): 19-22.	Results reported based on the same dataset as Beulens (2007).
Biddinger SB, Ludwig DS. The insulin-like growth factor axis: A potential link between glycemic index and cancer. *Am J Clin Nutr.* 2005 Aug; 82(2): 277-278. PMID: 16087968.	Publication is editorial.

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Brand-Miller J, Dickinson S, Barclay A, Celermajer D. The glycemic index and cardiovascular disease risk. *Curr Atheroscler Rep.* 2007 Dec; 9(6): 479-485. Review. PMID: 18377788.	Study design is narrative review.
Brand-Miller J, Hayne S, Petocz P, Colagiuri S. Low-glycemic index diets in the management of diabetes: A meta-analysis of randomized controlled trials. *Diabetes Care.* 2003 Aug; 26(8): 2, 261-2, 267. PMID: 12882846.	Study design is meta-analysis.
Brand-Miller JC, Stockmann K, Atkinson F, Petocz P, Denyer G. Glycemic index, postprandial glycemia, and the shape of the curve in healthy subjects: Analysis of a database of more than 1, 000 foods. *Am J Clin Nutr.* 2009 Jan; 89(1): 97-105. Epub 2008 Dec 3. PMID: 19056599.	Does not answer question; examined relationship between glycemic index and postprandialglycemia.
Brillon DJ, Sison CP, Salbe AD, Poretsky L. Reproducibility of a glycemic response to mixed meals in type 2 diabetes mellitus. *Horm Metab Res.* 2006 Aug; 38(8): 536-542. PMID: 16941281.	Does not include incidence of disease in analyses.
Burani J, Longo PJ. Low-glycemic index carbohydrates: an effective behavioral change for glycemic control and weight management in patients with type 1 and 2 diabetes.*Diabetes Educ.* 2006 Jan-Feb; 32(1): 78-88. PMID: 16439496.	Participants diagnosed with type 2 diabetes.
Buscemi S, Verga S, Cottone S, Azzolina V, Buscemi B, Gioia D, Cerasola G. Glycaemic variability and inflammation in subjects with metabolic syndrome. *Acta Diabetol.* 2009 Mar; 46(1): 55-61. Epub 2008 Sep 26. PMID: 18818862.	Participants diagnosed with metabolic syndrome.
Colombani PC. Glycemic index and load-dynamic dietary guidelines in the context of diseases. *Physiol Behav.* 2004 Dec 30; 83(4): 603-610. Review. PMID: 15621065.	Study design is narrative review.
Darbinian JA, Ferrara AM, Van Den Eeden SK, Quesenberry CP Jr, Fireman B, Habel LA. Glycemic status and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2008 Mar; 17(3): 628-635. PMID: 18349280.	Does not include glycemic index or load in analyses.

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de Rekeneire N, Rooks RN, Simonsick EM, Shorr RI, Kuller LH, Schwartz AV, Harris TB; Health, Aging and Body Composition Study. Racial differences in glycemic control in a well-functioning older diabetic population: Findings from the Health, Aging and Body Composition Study. *Diabetes Care.* 2003 Jul; 26(7): 1, 986-1, 992. Erratum in: *Diabetes Care.* 2003 Dec; 26(12): 3, 368. PMID: 12832300.	Participants diagnosed with type 2 diabetes.
Dickinson S, Brand-Miller J. Glycemic index, postprandial glycemia and cardiovascular disease. *Curr Opin Lipidol.* 2005 Feb; 16(1): 69-75. Review. PMID: 15650566.	Study design is narrative review.
Dickinson S, Hancock DP, Petocz P, Ceriello A, Brand-Miller J. High-glycemic index carbohydrate increases nuclear factor-kappaB activation in mononuclear cells of young, lean healthy subjects. *Am J Clin Nutr.* 2008 May; 87(5): 1, 188-1, 193. PMID: 18469238.	Does not include incidence of disease in analyses.
Du H, van der A DL, van Bakel MM, van der Kallen CJ, Blaak EE, van Greevenbroek MM, Jansen EH, Nijpels G, Stehouwer CD, Dekker JM, Feskens EJ. Glycemic index and glycemic load in relation to food and nutrient intake and metabolic risk factors in a Dutch population. *Am J Clin Nutr.* 2008 Mar; 87(3): 655-661. PMID: 18326604.	Does not include incidence of disease in analyses.
Ebbeling CB, Leidig MM, Sinclair KB, Seger-Shippee LG, Feldman HA, Ludwig DS. Effects of an ad libitum low-glycemic load diet on cardiovascular disease risk factors in obese young adults. *Am J Clin Nutr.* 2005 May; 81(5): 976-982. PMID: 15883418.	Does not include incidence of disease in analyses.
Franz MJ. Is there a role for the glycemic index in coronary heart disease prevention or treatment? *Curr Atheroscler Rep.* 2008 Dec; 10(6): 497-502. Review. PMID: 18937897.	Study design is narrative review.
Gastrich MD, Lasser N L, Wien M, Bachmann G. Dietary complex carbohydrates and low glycemic index/load decrease levels of specific metabolic syndrome/cardiovascular disease risk factors. *Topics in Clinical Nutrition.* 2008; 23(1): 76-96.	Study design is systematic review.

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Gellar L, Nansel TR. High and low glycemic index mixed meals and blood glucose in youth with type 2 diabetes or impaired glucose tolerance. *J Pediatr.* 2009 Mar; 154(3): 455-458.	Participants diagnosed with type 2 diabetes or impaired glucose tolerance.
Gnagnarella P, Gandini S, La Vecchia C, Maisonneuve P. Glycemic index, glycemic load, and cancer risk: a meta-analysis. *Am J Clin Nutr.* 2008 Jun; 87(6): 1, 793-1, 801. PMID: 18541570.	Study design is meta-analysis.
Graber AL, Shintani AK, Wolff K, Brown A, Elasy TA. Glycemic relapse in type 2 diabetes.*Endocr Pract.* 2006 Mar-Apr; 12(2): 145-151. PMID: 16690461.	Participants diagnosed with type 2 diabetes.
Hare-Bruun H, Nielsen BM, Grau K, Oxlund AL, Heitmann BL. Should glycemic index and glycemic load be considered in dietary recommendations? *Nutr Rev.* 2008 Oct; 66(10): 569-590. Review. PMID: 18826453.	Study design is narrative review.
Henry CJ, Lightowler HJ, Tydeman EA, Skeath R. Use of low-glycaemic index bread to reduce 24-hour blood glucose: Implications for dietary advice to non-diabetic and diabetic subjects. *Int J Food Sci Nutr.* 2006 May-Jun; 57(3-4): 273-278. PMID: 17127477.	Does not include incidence of disease in analyses.
Jenkins DJ, Kendall CW, Augustin LS, Martini MC, Axelsen M, Faulkner D, Vidgen E, Parker T, Lau H, Connelly PW, Teitel J, Singer W, Vandenbroucke AC, Leiter LA, Josse RG. Effect of wheat bran on glycemic control and risk factors for cardiovascular disease in type 2 diabetes. *Diabetes Care.* 2002 Sep; 25(9): 1, 522-1, 528. PMID: 12196421.	Participants diagnosed with type 2 diabetes.
Jenkins DJ, Kendall CW, McKeown-Eyssen G, Josse RG, Silverberg J, Booth GL, Vidgen E, Josse AR, Nguyen TH, Corrigan S, Banach MS, Ares S, Mitchell S, Emam A, Augustin LS, Parker TL, Leiter LA. Effect of a low-glycemic index or a high-cereal fiber diet on type 2 diabetes: a randomized trial. *JAMA.* 2008 Dec 17; 300(23): 2, 742-2, 753. PMID: 19088352.	Participants diagnosed with type 2 diabetes.

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Jimenez-Cruz A, Bacardi-Gascon M, Turnbull WH, Rosales-Garay P, Severino-Lugo I. A flexible, low-glycemic index mexican-style diet in overweight and obese subjects with type 2 diabetes improves metabolic parameters during a 6-week treatment period. *Diabetes Care.* 2003 Jul; 26(7): 1, 967-1, 970. PMID: 12832297.	Participants diagnosed with type 2 diabetes.
Jiménez-Cruz A, Gutiérrez-González AN, Bacardi-Gascon M. Low glycemic index lunch on satiety in overweight and obese people with type 2 diabetes. *Nutr Hosp.* 2005 Sep-Oct; 20(5): 348-350. PMID: 16229403.	Participants diagnosed with type 2 diabetes.
Kelly S, Frost G, Whittaker V, Summerbell C. Low glycaemic index diets for coronary heart disease. *Cochrane Database Syst Rev.* 2004 Oct 18; (4): CD004467. Review. PMID: 15495112.	Study design is systematic review.
Levitan EB, Cook NR, Stampfer MJ, Ridker PM, Rexrode KM, Buring JE, Manson JE, Liu S. Dietary glycemic index, dietary glycemic load, blood lipids, and C-reactive protein.*Metabolism.* 2008 Mar; 57(3): 437-443. PMID: 18249220; PMCID: PMC2262400.	Does not include incidence of disease in analyses.
Levitan EB, Mittleman MA, Wolk A. Dietary glycemic index, dietary glycemic load and mortality among men with established cardiovascular disease. *Eur J Clin Nutr.* 2009 Apr; 63(4): 552-557. Epub 2007 Dec 19. PMID: 18091767.	Participants diagnosed with cardiovascular disease.
Liese AD, Schulz M, Fang F, Wolever TM, D'Agostino RB Jr, Sparks KC, Mayer-Davis EJ. Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women. *Diabetes Care.* 2005 Dec; 28(12): 2, 832-2, 838. PMID: 16306541.	Does not include incidence of disease in analyses.
Liu S, Manson JE, Buring JE, Stampfer MJ, Willett WC, Ridker PM. Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity C-reactive protein in middle-aged women. *Am J Clin Nutr.* 2002 Mar; 75(3): 492-498. PMID: 11864854.	Does not include incidence of disease in analyses.

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Liu S, Manson JE, Stampfer MJ, Holmes MD, Hu FB, Hankinson SE, Willett WC. Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women. *Am J Clin Nutr.* 2001 Mar; 73(3): 560-566. PMID: 11237932.	Does not include incidence of disease in analyses.
Liu S. Lowering dietary glycemic load for weight control and cardiovascular health: a matter of quality. *Arch Intern Med.* 2006 Jul 24; 166(14): 1, 438-1, 439. PMID: 16864751.	Publication is editorial.
Livesey G, Taylor R, Hulshof T, Howlett J. Glycemic response and health: A systematic review and meta-analysis: Relations between dietary glycemic properties and health outcomes. *Am J Clin Nutr.* 2008 Jan; 87(1): 258S-268S. Review. PMID: 18175766.	Study design is systematic review.
Lukaczer D, Liska DJ, Lerman RH, Darland G, Schiltz B, Tripp M, Bland JS. Effect of a low glycemic index diet with soy protein and phytosterols on CVD risk factors in postmenopausal women. *Nutrition.* 2006 Feb; 22(2): 104-113. PMID: 16459222.	Does not include incidence of disease in analyses.
Ma Y, Olendzki BC, Merriam PA, Chiriboga DE, Culver AL, Li W, Hébert JR, Ockene IS, Griffith JA, Pagoto SL. A randomized clinical trial comparing low-glycemic index vs. ADA dietary education among individuals with type 2 diabetes. *Nutrition.* 2008 Jan; 24(1): 45-56. PMID: 18070658.	Participants diagnosed with type 2 diabetes.
Maki KC, Rains TM, Kaden VN, Raneri KR, Davidson MH. Effects of a reduced-glycemic-load diet on body weight, body composition, and cardiovascular disease risk markers in overweight and obese adults. *Am J Clin Nutr.* 2007 Mar; 85(3): 724-734. PMID: 17344493.	Does not include incidence of disease in analyses.
Mann JI. Evidence-based nutrition recommendations for the treatment and prevention of type 2 diabetes and the metabolic syndrome. *Food Nutr Bull.* 2006 Jun; 27(2): 161-166. Review. PMID: 16786982.	Publication provides recommendations.

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Martínez-Ortiz JA, Fung TT, Baylin A, Hu FB, Campos H. Dietary patterns and risk of nonfatal acute myocardial infarction in Costa Rican adults. *Eur J Clin Nutr.* 2006 Jun; 60(6): 770-777. Epub 2006 Feb 8. PMID: 16465200.	Does not include glycemic index or load in analyses.
McMillan-Price J, Petocz P, Atkinson F, O'neill K, Samman S, Steinbeck K, Caterson I, Brand-Miller J. Comparison of four diets of varying glycemic load on weight loss and cardiovascular risk reduction in overweight and obese young adults: A randomized controlled trial. *Arch Intern Med.* 2006 Jul 24; 166(14): 1, 466-1, 475. PMID: 16864756.	Does not include incidence of disease in analyses.
Mead A, Atkinson G, Albin D, Alphey D, Baic S, Boyd O, Cadigan L, Clutton L, Craig L, Flanagan C, Greene P, Griffiths E, Lee NJ, Li M, McKechnie L, Ottaway J, Paterson K, Perrin L, Rigby P, Stone D, Vine R, Whitehead J, Wray L, Hooper L; UK Heart Health Group; Thoracic Dietitians Interest Group (Specialist group of the British Dietetic Association). Dietetic guidelines on food and nutrition in the secondary prevention of cardiovascular disease: Evidence from systematic reviews of randomized controlled trials (second update, January 2006). *J Hum Nutr Diet.* 2006 Dec; 19(6): 401-419. Review. PMID: 17105538.	Study design is review.
Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med.* 2009 Apr 13; 169(7): 659-669. Review. PMID: 19364995.	Study design is systematic review.
Miles JM. A role for the glycemic index in preventing or treating diabetes? *Am J Clin Nutr.* 2008 Jan; 87(1): 1-2. PMID: 18175728.	Publication is perspective.
Miller CK, Gutschall M. A randomized trial about glycemic index and glycemic load improves outcomes among adults with type 2 diabetes. *Health Educ Behav.* 2009 Jun; 36(3): 615-626. Epub 2008 May 9. PMID: 18469161.	Participants diagnosed with type 2 diabetes.

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Miller CK, Gutshcall MD, Mitchell DC. Change in food choices following a glycemic load intervention in adults with type 2 diabetes. *J Am Diet Assoc.* 2009 Feb; 109(2): 319-324. PMID: 19167961.	Participants diagnosed with type 2 diabetes.
Milton JE, Briche B, Brown IJ, Hickson M, Robertson CE, Frost GS. Relationship of glycaemic index with cardiovascular risk factors: Analysis of the National Diet and Nutrition Survey for people aged 65 and older. *Public Health Nutr.* 2007 Nov; 10(11): 1, 321-1, 335. Epub 2007 Apr 24. PMID: 17456246.	Does not include incidence of disease in analyses.
Mogos T, Dondoi C. Evaluation of glycemic control of type II diabetes mellitus treated only with diet. *Rom J Intern Med.* 2007; 45(2): 205-208. PMID: 18333376.	Participants diagnosed with type 2 diabetes.
Montori VM. Should patients with type 2 diabetes focus on glycemic control to reduce their cardiovascular risk? *Pol Arch Med Wewn.* 2008 Sep; 118(9): 502-507. Review. PMID: 18846985.	Study design is narrative review.
Mulholland HG, Murray LJ, Cardwell CR, Cantwell MM. Dietary glycaemic index, glycaemic load and breast cancer risk: a systematic review and meta-analysis. *Br J Cancer.* 2008 Oct 7; 99(7): 1, 170-1, 175. Epub 2008 Aug 26. Review. PMID: 18728653.	Study design is systematic review/meta-analysis.
Mulholland HG, Murray LJ, Cardwell CR, Cantwell MM. Glycemic index, glycemic load, and risk of digestive tract neoplasms: A systematic review and meta-analysis. *Am J Clin Nutr.* 2009 Feb; 89(2): 568-576. Epub 2008 Dec 16. Review. PMID: 19088152.	Study design is systematic review/meta-analysis.
Murakami K, Okubo H, Sasaki S. Effect of dietary factors on incidence of type 2 diabetes: A systematic review of cohort studies. *J Nutr Sci Vitaminol (Tokyo).* 2005 Aug; 51(4): 292-310. Review. PMID: 16262005.	Study design is systematic review.

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Murakami K, Sasaki S, Takahashi Y, Okubo H, Hosoi Y, Horiguchi H, Oguma E, Kayama F. Dietary glycemic index and load in relation to metabolic risk factors in Japanese female farmers with traditional dietary habits. *Am J Clin Nutr.* 2006 May; 83(5): 1, 161-1, 169. PMID: 16685061.	Does not include incidence of disease in analyses.
Nansel TR, Gellar L, Zeitzoff L. Acceptability of lower glycemic index foods in the diabetes camp setting. *J Nutr Educ Behav.* 2006 May-Jun; 38(3): 143-150. PMID: 16731448.	Participants diagnosed with type 2 diabetes.
Oh K, Willett WC, Fuchs CS, Giovannucci EL. Glycemic index, glycemic load, and carbohydrate intake in relation to risk of distal colorectal adenoma in women. *Cancer Epidemiol Biomarkers Prev.* 2004 Jul; 13(7): 1, 192-1, 198. PMID: 15247130.	Results reported based on the same dataset as Michaud (2005).
Ostman EM, Frid AH, Groop LC, Björck IM. A dietary exchange of common bread for tailored bread of low glycaemic index and rich in dietary fibre improved insulin economy in young women with impaired glucose tolerance. *Eur J Clin Nutr.* 2006 Mar; 60(3): 334-341. PMID: 16234828.	Does not include incidence of disease in analyses.
Panlasigui LN, Thompson LU. Blood glucose lowering effects of brown rice in normal and diabetic subjects. *Int J Food Sci Nutr.* 2006 May-Jun; 57(3-4): 151-158. PMID: 17127465.	Does not meet inclusion criteria for sample size.
Papanikolaou Y, Palmer H, Binns MA, Jenkins DJ, Greenwood CE. Better cognitive performance following a low-glycaemic-index compared with a high-glycaemic-index carbohydrate meal in adults with type 2 diabetes. *Diabetologia.* 2006 May; 49(5): 855-862. Epub 2006 Mar 1. PMID: 16508776.	Participants diagnosed with type 2 diabetes.
Pereira MA, Swain J, Goldfine AB, Rifai N, Ludwig DS. Effects of a low-glycemic load diet on resting energy expenditure and heart disease risk factors during weight loss. *JAMA.* 2004 Nov 24; 292(20): 2, 482-2, 490. PMID: 15562127.	Does not include incidence of disease in analyses.

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Philippou E, McGowan BM, Brynes AE, Dornhorst A, Leeds AR, Frost GS. The effect of a 12-week low glycaemic index diet on heart disease risk factors and 24-hour glycaemic response in healthy middle-aged volunteers at risk of heart disease: A pilot study. *Eur J Clin Nutr.* 2008 Jan; 62(1): 145-149. Epub 2007 Feb 21. PMID: 17311054.	Does not meet inclusion criteria for sample size.
Pi-Sunyer X. Glycemic index in early type 2 diabetes. *Am J Clin Nutr.* 2008 Jan; 87(1): 3-4. PMID: 18175729.	Publication is perspective.
Pittas AG, Roberts SB, Das SK, Gilhooly CH, Saltzman E, Golden J, Stark PC, Greenberg AS. The effects of the dietary glycemic load on type 2 diabetes risk factors during weight loss. *Obesity (Silver Spring).* 2006 Dec; 14(12): 2, 200-2, 209. PMID: 17189547.	Does not include incidence of disease in analyses.
Qi L, Meigs JB, Liu S, Manson JE, Mantzoros C, Hu FB. Dietary fibers and glycemic load, obesity, and plasma adiponectin levels in women with type 2 diabetes. *Diabetes Care.* 2006 Jul; 29(7): 1, 501-1, 505. PMID: 16801569.	Participants diagnosed with type 2 diabetes.
Qi L, Rimm E, Liu S, Rifai N, Hu FB. Dietary glycemic index, glycemic load, cereal fiber, and plasma adiponectin concentration in diabetic men. *Diabetes Care.* 2005 May; 28(5): 1, 022-1, 028. PMID: 15855561.	Participants diagnosed with type 2 diabetes.
Rendell M, Vanderhoof J, Venn M, Shehan MA, Arndt E, Rao CS, Gill G, Newman RK, Newman CW. Effect of a barley breakfast cereal on blood glucose and insulin response in normal and diabetic patients. *Plant Foods Hum Nutr.* 2005 Jun; 60(2): 63-67. PMID: 16021833.	Does not include incidence of disease in analyses.
Riccardi G, Rivellese AA, Giacco R. Role of glycemic index and glycemic load in the healthy state, in prediabetes, and in diabetes. *Am J Clin Nutr.* 2008 Jan; 87(1): 269S-274S. Review. PMID: 18175767.	Study design is narrative review.
Roberts SB, Pittas AG. The role of glycemic index in type 2 diabetes. *Nutr Clin Care.* 2003 May-Sep; 6(2): 73-78. Review. PMID: 14692295.	Study design is narrative review.

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Sahyoun NR, Anderson AL, Kanaya AM, Koh-Banerjee P, Kritchevsky SB, de Rekeneire N, Tylavsky FA, Schwartz AV, Lee JS, Harris TB. Dietary glycemic index and load, measures of glucose metabolism, and body fat distribution in older adults. *Am J Clin Nutr.* 2005 Sep; 82(3): 547-552. PMID: 16155266.	Does not include incidence of disease in analyses.
Shani M, Taylor TR, Vinker S, Lustman A, Erez R, Elhayany A, Lahad A. Characteristics of diabetics with poor glycemic control who achieve good control. *J Am Board Fam Med.* 2008 Nov-Dec; 21(6): 490-496. PMID: 18988715.	Participants diagnosed with type 2 diabetes.
Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, Howard BV, Kirkman MS, Kosiborod M, Reaven P, Sherwin RS; American Diabetes Association; American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials: A position statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association. *J Am Coll Cardiol.* 2009 Jan 20; 53(3): 298-304. Review. PMID: 19147051.	Publication is position statement.
Slama G, Elgrably F, Kabir M, Rizkalla S. Low glycemic index foods should play a role in improving overall glycemic control in type-1 and type-2 diabetic patients and, more specifically, in correcting excessive postprandial hyperglycemia. *Nestle Nutr Workshop Ser Clin Perform Programme.* 2006; 11: 73-79; discussion, 79-81. Review. PMID: 16820732.	Study design is narrative review.
Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med.* 2000 Jul 6; 343(1): 16-22. PMID: 10882764.	Does not include glycemic index or load in analyses (part of composite dietary score).
Tapola N, Karvonen H, Niskanen L, Mikola M, Sarkkinen E. Glycemic responses of oat bran products in type 2 diabetic patients. *Nutr Metab Cardiovasc Dis.* 2005 Aug; 15(4): 255-261. PMID: 16054549.	Participants diagnosed with type 2 diabetes.

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Terry J, Terry P. [Glycemic index--relevant in the treatment of overweight and diabetes]*Lakartidningen.* 2006 Feb 15-21; 103(7): 466-470; discussion 471-473. Swedish. PMID: 16535876.	Study not published in English.
Thomas D, Elliott EJ. Low glycaemic index, or low glycaemic load, diets for diabetes mellitus.*Cochrane Database Syst Rev.* 2009 Jan 21; (1): CD006296. Review. PMID: 19160276.	Participants diagnosed with diabetes.
Thomas DE, Elliott EJ, Baur L. Low glycaemic index or low glycaemic load diets for overweight and obesity. *Cochrane Database Syst Rev.* 2007 Jul 18; (3): CD005105. Review. PMID: 17636786.	Study design is systematic review.
Tokuyama Y, Ishizuka T, Matsui K, Egashira T, Kanatsuka A. Predictors of glycemic control in Japanese subjects with type 2 diabetes mellitus. *Metabolism.* 2008 Apr; 57(4): 453-457. PMID: 18328344.	Participants diagnosed with type 2 diabetes.
Ukleja A, Kunachowicz H, Pachocka L. The use of glycaemic index in the prevention of cardiovascular diseases. *Rocz Panstw Zakl Hig.* 2007; 58(1): 145-151. Review. PMID: 17711103.	Study design is narrative review.
Whiting PH, Kalansooriya A, Holbrook I, Haddad F, Jennings PE. The relationship between chronic glycaemic control and oxidative stress in type 2 diabetes mellitus. *Br J Biomed Sci.* 2008; 65(2): 71-74. PMID: 19055108.	Participants diagnosed with type 2 diabetes.
Willett W, Manson J, Liu S. Glycemic index, glycemic load, and risk of type 2 diabetes. *Am J Clin Nutr.* 2002 Jul; 76(1): 274S-280S. Review. PMID: 12081851.	Study design is review.
Wilson T, Meyers SL, Singh AP, Limburg PJ, Vorsa N. Favorable glycemic response of type 2 diabetics to low-calorie cranberry juice. *J Food Sci.* 2008 Nov; 73(9): H241-H245. PMID: 19021808.	Participants diagnosed with type 2 diabetes.

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Wolever TM, Gibbs AL, Mehling C, Chiasson JL, Connelly PW, Josse RG, Leiter LA, Maheux P, Rabasa-Lhoret R, Rodger NW, Ryan EA. The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-year controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: No effect on glycated hemoglobin but reduction in C-reactive protein. *Am J Clin Nutr.* 2008 Jan; 87(1): 114-125. PMID: 18175744.	Participants diagnosed with type 2 diabetes.
Wolever TM, Mehling C, Chiasson JL, Josse RG, Leiter LA, Maheux P, Rabasa-Lhoret R, Rodger NW, Ryan EA. Low glycaemic index diet and disposition index in type 2 diabetes (the Canadian trial of carbohydrates in diabetes): a randomised controlled trial. *Diabetologia.* 2008 Sep; 51(9): 1, 607-1, 615. Epub 2008 Jul 22. PMID: 18648764.	Participants diagnosed with type 2 diabetes.

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CHAPTER 5. GLYCEMIC INDEX/LOAD – CARDIOVASCULAR DISEASE

WHAT IS THE RELATIONSHIP BETWEEN GLYCEMIC INDEX OR GLYCEMIC LOAD AND CARDIOVASCULAR DISEASE?

Conclusion statement

Due to limited evidence, no conclusion can be drawn to assess the relationship between either glycemic index or load and cardiovascular disease.

Grade

Limited

Evidence summary overview

Although the evidence for an association between high glycemic index or high glycemic load and cardiovascular disease(CVD) is more negative than positive, the evidence available is inadequate to come to a firm conclusion on this question.

Eight reports have been published since 2000 (Beulens, 2007; Kaushik, 2009; Levitan, 2007; Liu, 2000; Halton, 2006; Oh, 2005; Tavani, 2003; van Dam, 2000). Of these, three are from the same Nurses' Health Study. After 10 years of follow-up, Liu et al (2000) reported glycemic index was associated with CVD. A high glycemic load was associated with CVD in women with a body mass index (BMI) greater than 23, but not with a BMI less than 23kg/m^2. After 20 years of follow-up, Halton (2006) reported both a high glycemic index and load to be associated with CVD. Oh (2005) reported on the associations between dietary carbohydrate, glycemic index, glycemic load and stroke. They found no association between glycemic index and stroke. They found a positive association between glycemic load and total stroke in women with a BMI greater than 25, but not in those with a BMI less than 25kg/m^2.

Five other reports are available. Of these, Beulens (2007) found a positive trend for an association between glycemic load and stroke, but not for glycemic index and stroke. He found a positive trend between glycemic index and CHD and between glycemic load and coronary heart disease (CHD) only for women with a BMI greater than 25kg/m^2.

Kauschik (2009) found an association between both glycemic index and glycemic load and death from stroke. Levitan (2007) found no association between glycemic index or glycemic load with myocardial infarction (MI), ischemic stroke or all-cause mortality. van Dam (2000) found no association of either glycemic index or glycemic load and CHD.

One case-control study (Tavani, 2003) reported on the relation between glycemic index and glycemic load and the risk of non-fatal acute MI. No significant (NS) association was found.

Evidence summary paragraphs

Beulens, 2007 (positive quality), a cohort study in the Netherlands, prospectively assessed whether high dietary glycemic load (GL) and glycemic index (GI) were associated with an increased risk of CVD in 15,714 Dutch women who were 49 to 70 years, without diabetes or CVD and were participants of the Prospect-EPIC cohort study. Subjects were followed for 9±2 years (141,633 person-years). A total of 556

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cases of CHD and 243 cases of cerebrovascular accident occurred. After adjustment for CVD risk factors and dietary variables, both GL with a hazard ratio (HR) of 1.47 (95% CI: 1.04, 2.09; P=0.03), and GI with HR of 1.33 (95% CI: 1.07, 1.67; P for trend = 0.02) were associated with increased risk of cerebrovascular accident. In women with BMI higher than 25kg/m^2, GL was associated with CVD (HR=1.78, 95% CI: 1.11, 2.85; P=0.04) but not with normal weight women. Glycemic index was associated with CHD (P=0.01) and not cerebrovascular accident; in addition, BMI did not modify the association of GI with CVD.

Kaushik, 2009 (positive quality), cohort study in Australia, prospectively investigated the links between diets with high glycemic index (GI), low cereal fiber (CF) and the greater risk of stroke-related mortality and retinal microvascular caliber in 2,712 Australians 49+ years and participants of the Blue Mountains Eye Study. Dietary GI was assessed at baseline using a validated food-frequency questionnaire (FFQ) and followed for 13 years. Ninety-five (3.5%) participants died from stroke. After adjusting for multiple stroke risk factors, increasing GI (HR=1.91; 95% CI: 1.01, 3.47) and decreasing CF (HR=2.13; 95% CI: 1.19, 3.80) predicted greater risk of stroke death, while there was no relationship between total fruit or vegetable fiber and risk of stroke-related death. Participants consuming food in the highest GI tertiles and lowest CF tertiles had a five-fold increased risk of stroke death (HR=5.06, 95% CI: 1.67, 15.22). High-GI and low-CF diets predict greater stroke mortality and wider retinal venular caliber.

Levitan, 2007 (positive quality), a cohort study in Sweden, prospectively examined the association between dietary glycemic index (GI) and glycemic load (GL) with CVD among 36,246 Swedish men who were 45 to 79 years old and free of diabetes or prior CVD. Dietary GI and GL were assessed at baseline and followed for six years. Dietary GI and dietary GL were not associated with MI (N=1,324), ischemic stroke (N=692), cardiovascular mortality (N=785) or all-cause mortality (N=2,959). However, dietary GL was associated with hemorrhagic stroke [N=165; RR=1.44 comparing extreme quartiles (95% CI: 0.91, 2.27; P=0.047)]. No association between dietary GL with all-cause mortality was observed. Among men with cereal fiber (CF) intake of 12.8g per day or men with lower CF intake, higher dietary GL was associated with an elevated risk (trends not statistically significant). Overall, dietary GI and GL were not associated with ischemic CVD or mortality, but dietary GL was associated with a greater risk of hemorrhagic stroke.

Lui, 2000 (positive quality) and Halton, 2006 (positive quality), both reported relationships between glycemic load and risk of CHD from the Nurses' Health Study. Lui, 2000, prospectively evaluated the relationship between the amount and type of carbohydrates consumed and the risk of CHD. The baseline population was 75,521 women aged 38 to 63 years in 1984. Dietary intake was assessed with an FFQ at baseline and repeated in 1986 and 1990. The primary endpoint considered was CHD, including fatal CHD and non-fatal MI. Non-fatal MI was confirmed by medical records; deaths were identified from the National Death Index and confirmed by medical records, autopsy reports or death certificates. During 10 years of follow-up, 761 cases of CHD were identified. Glycemic load was directly associated with risk of CHD after adjustment for age, smoking status, total energy intake and other coronary disease risk factors; RR of extreme quintiles of glycemic load was 1.98 (95% CI: 1.41, 2.77; P<0.0001). The increased risk of CHD with high glycemic load was most evident among women with BMI>23kg/m^2. Little relation was observed among women with

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BMI<23kg/m^2. Carbohydrate classified by glycemic index, as opposed to its traditional classification as either simple or complex, was a better predictor of CHD risk. Neither simple sugar nor starch was significantly related to CHD risk when they were included simultaneously in the same multivariate model. In contrast, glycemic index was significantly associated with the risk of CHD in a multivariate model with the same covariates (multivariate adjusted RR comparing extreme quintiles = 1.31; 95% CI: 1.02, 1.68; P=0.008). In a follow-up study, Halton, 2006 prospectively examined the association between low-carbohydrate diet score and the risk of CHD in women. In additional analyses, they examined the relationship between glycemic index or load and CHD. Participants were 82,802 women, aged 30 to 55 years at baseline, who were followed from 1980 to 2000. Dietary intake was assessed with an FFQ at six time points over the study period. The endpoints were non-fatal MI or fatal coronary events. Coronary heart disease was self-reported on questionnaires with confirmation from medical records. Deaths were identified from state records and the National Death Index, next of kin, or the US Postal Service. During 20 years of follow-up, 1,994 cases of CHD were identified. A high glycemic load was strongly associated with an increased risk of CHD (RR comparing extreme deciles = 1.90; 95% CI: 1.15, 3.15; P=0.003). Overall dietary glycemic index had a direct association with risk of CHD (RR comparing extreme deciles = 1.19; 95% CI: 0.91, 1.55; P=0.04).

Oh, 2005 (positive quality), cohort study in the US, prospectively examined associations between dietary carbohydrate, glycemic index (GI), glycemic load (GL) and risk of stroke in 78,779 women who were age 30 to 55 years, free of CVD and diabetes and participants of the Nurses' Health Study. Dietary information was collected for usual diet with a semi-quantitative FFQ. Among the women followed, 1,020 incident strokes were documented (515 ischemic, 279 hemorrhagic). After adjusting for non-dietary risk factors and cereal fiber (CF), carbohydrate intake was found to associate with elevated risk of hemorrhagic stroke when the extreme quintiles were compared (RR=2.05; 95% CI: 1.10, 3.83; P=0.02), but not with ischemic stroke. Carbohydrate intake and dietary GL were positively associated with total stroke among those women whose BMI was higher than 25kg/m^2 (RR=1.61; 95% CI: 1.15, 2.27; P=0.01), but associations for type of stroke were not statistically significant. Intake of CF was inversely associated with total stroke risk, RR=0.66 (95% CI: 0.52, 0.83; P=0.001) and with hemorrhagic stroke risk, RR=0.51 (95% CI: 0.33, 0.78; P=0.01). Dietary GI was not related to risks of total stroke or type of stroke within BMI categories.

van Dam, 2000 (positive quality), a cohort study in the Netherlands (Zutphen Elderly Study), prospectively examined the association between glycemic index and CHD risk in elderly men. Participants were 646 men, aged 64 to 84 years at baseline, who were followed between 1985 and 1995. Dietary intake was assessed with the cross-check dietary history method. Non-fatal MI information was obtained by physician-administered (in 1985 and 1990) or self-administered (in 1993 and 1995) standardized medical questionnaire. Death information was obtained from the participant's general practitioner and registries. During 4,527 person-years of follow-up, 94 cases of CHD were documented. The multivariate adjusted risk ratio for CHD was 1.11 (95% CI: 0.66, 1.87; P=0.70) for the extreme tertiles of glycemic index after correction for age, BMI, physical activity, cigarette smoking and dietary factors. The multivariate adjusted risk ratio was 1.06 (95% CI: 0.52, 2.14; P=0.88; not adjusted for carbohydrate intake) for the extreme tertiles of glycemic load. The authors concluded that glycemic index or load was not associated with incidence of CHD in

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elderly men without a history of diabetes or CHD.

Case-control Study:

Tavani, 2003 (neutral-quality), case-control study in Italy, examined the relation between glycemic index and glycemic load and the risk of non-fatal acute MI. Cases were 433 non-diabetic adults with a first episode of non-fatal acute MI, and controls were 448 adults admitted to the hospital for acute conditions unrelated to known or potential risk factors for acute MI. Dietary intake was assessed with a validated FFQ. The odds ratio (OR) in the highest compared to lowest tertile was 1.38 for glycemic index and 1.08 for glycemic load. Neither of these estimates was significant. A significant association was found for glycemic index in patients 60 years and older (OR for highest vs. lowest tertile = 1.81; 95% CI: 1.07, 3.07; P=0.03). A significant association was found for glycemic index in those with a BMI of 25kg/m^2 and higher (OR for highest vs. lowest tertile = 2.02; 95% CI: 1.21, 3.34; P=0.006). No other significant associations were observed for BMI, age or gender.

Overview table

Author, Year, Study Design, Class, Rating	Population/Subjects	Methodology	Significant Outcomes
Beulens JW, de Bruijne LM et al, 2007 Study Design: Prospective Cohort Study Class: B Positive Quality	N=15,714 women. Age: 49 to 70 years. EPIC Cohort. Location: Netherlands.	Association of glycemic index and glycemic load with incident CVD examined for more than nine years of follow-up. Dietary glycemic index and glycemic load calculated from intake data from FFQs.	141,633 person-years: CHD = 556 cases; CVA = 243 cases. After adjustment for CVD risk and dietary variables, hazard ratios (HR) for CVA: GL=1.47 (95% CI: 1.04, 2.09; P=0.03) GI=1.33 (95% CI: 1.07, 1.67; P=0.02). Women with BMI >25kg/m^2: GL=1.78 (95% CI: 1.11, 2.85; P=0.04) vs. normal weight women. Association of GI with CVD not modified by BMI. GI associated with CHD, not CVA (P=0.01).

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Halton et al 2006 Study Design: Prospective Cohort Study Class: B Positive Quality	N=82,802 women. Nurses' Health Study. Age: 30 to 55 years at baseline. Location: United States.	Followed from 1980 to 2000. Diet assessed with FFQ at six time points over study period. Endpoints: Non-fatal MI or fatal coronary events; CHD self-reported on questionnaires with confirmation from medical records; deaths identified from state records and the National Death Index, next of kin or US Postal Service.	During 20 years of follow-up, 1,994 cases of CHD were identified. A high glycemic load was strongly associated with an ↑ risk of CHD (RR comparing extreme deciles = 1.90; 95% CI: 1.15, 3.15; P=0.003). Overall dietary glycemic index had a direct association with risk of CHD (RR comparing extreme deciles = 1.19; 95% CI: 0.91, 1.55; P=0.04).
Kaushik S, Wang JJ et al, 2009 Study Design: Prospective Cohort Study Class: B Positive Quality	N=2,712 older participants. Age: 49 years or older. Blue Mountains Eye Study. Location: Australia.	Participants followed for 13 years; inpatients, cause-of-death and death registries for MI, ischemic and hemorrhagic stroke. Mean GI calculated from an Australian database. Retinal arteriolar and venular diameters measured from photographs. Mortality data derived from an Australian National Death Index.	After adjusting for multiple stroke risk factors, ↑ GI (HR=1.91; 95% CI: 1.01, 3.47) and ↓ CF (HR=2.13; 95% CI: 1.19, 3.80) predicted greater risk of stroke death, while there was no relationship between total fruit or vegetable fiber and risk of stroke-related death. Participants consuming food in the highest GI tertiles and lowest CF tertiles had a five-fold ↑ risk of stroke death (HR=5.06, 95% CI: 1.67, 15.22). High-GI and low-CF diets predict greater stroke mortality and wider retinal venular caliber.

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Levitan EB, Mittleman MA et al, 2007 Study Design: Prospective Cohort Study Class: B Positive Quality	N=36,246 men. Age: 45 to 79 years. Location: Sweden.	Baseline assessment: Dietary glycemic index and glycemic load with FFQs. Six-year followed up through inpatient, cause-of-death and death registries: MI, ischemic stroke, hemorrhagic stroke, cardiovascular mortality, all-cause mortality. Cox models with age as time scale to estimate RR adjusted for smoking, BMI, physical activity, demographic characteristics and nutritional factors.	After eight years, dietary glycemic index and glycemic load not linked with: MI (N=1,324) Ischemic stroke (N=692) CV mortality (N=785) All-cause mortality (N=2,959). Dietary glycemic index linked with hemorrhagic stroke (N=165; HR=1.44; 95% CI: 0.91 to 2.27; P=0.047).

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Liu et al 2000 Study Design: Prospective Cohort Study Class: B Positive Quality	N=75,521 women. Nurses' Health Study. Age: 38 to 63 years at baseline. Location: United States.	Followed from 1984 to 1994. Diet assessed with FFQ at baseline and repeated in 1986 and 1990. Endpoints: Non-fatal MI or fatal CHD; non-fatal MI confirmed by medical records; deaths identified from the National Death Index and confirmed by medical records, autopsy reports or death certificates.	During 10 years of follow-up, 761 cases of CHD were identified. Glycemic load was directly associated with risk of CHD after adjustment for age, smoking status, total energy intake and other coronary disease risk factors. RR of extreme quintiles of glycemic load was 1.98 (95% CI: 1.41, 2.77; P<0.0001). ↑ risk of CHD with high glycemic load was most evident among women with BMI >23kg/m^2. Little relation was observed among women with BMI <23 kg/m^2. CHO classified by glycemic index, as opposed to its classification as either simple or complex, was a better predictor of CHD risk. Neither simple sugar nor starch was significantly related to CHD risk when they were included simultaneously in the same multivariate model. In contrast, glycemic index was significantly associated with the risk of CHD in a multivariate model with the same covariates (multivariate adjusted RR comparing extreme quintiles = 1.31; 95% CI: 1.02, 1.68; P for trend = 0.008).

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Oh K, Hu FB et al, 2005 Study Design: Prospective cohort study Class: B Positive Quality	N=78,779 women. Nurses' Health Study. Location: United States.	1,980 semi-quantitative FFQ with 61 food items. Followed for 18 years. Stroke endpoint ascertained by medical records (blinded). Non-fatal medically reported strokes – probable (25%). Death ascertained by family reports, postal service and National Death Index. Fatal non-medically reported strokes – probable (32%).	Dietary glycemic load, positive association with total stroke in women with BMI >25kg/m^2(HR=1.61, 95% CI: 1.15, 2.27; P=0.01), but not type of stroke. Dietary glycemic index not related to risks of total stroke or type of stroke within BMI categories.

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Tavani et al 2003 Study Design: Case-Control Study Class: C Neutral Quality	N=433 cases. N=448 controls. Age: 25 to 79 years. Location: Italy.	Cases: Non-diabetic adults with a first episode of non-fatal acute MI. Controls: Adults admitted to hospital for acute conditions unrelated to known or potential risk factors for acute MI. Dietary intake assessed with validated FFQ.	OR in highest compared to lowest tertile was 1.38 (95% CI: 0.95, 2.00; P=0.10) for glycemic index and 1.08 (95% CI: 0.73, 1.60; P=0.69) for glycemic load (adjusted for sex, age, education, BMI, physical activity, tobacco, alcohol, cholesterol, HTN, hyperlipidemia and family history of IHD). A significant association was found for glycemic index in patients ≥60 years (OR for highest vs. lowest tertile = 1.81; 95% CI: 1.07, 3.07; P=0.03). A significant association was found for glycemic index in those with a BMI of ≥25kg/m^2 (OR for highest vs. lowest tertile = 2.02; 95% CI: 1.21, 3.34; P=0.006). No other significant associations were observed for BMI, age or gender.

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van Dam et al 2000 Study Design: Prospective Cohort Study/Cross-sectional Analysis Class: B Positive Quality	N=646 men. Zutphen Elderly Study. Age: 64 to 84 years at baseline. Location: Netherlands.	Followed between 1985 and 1995. Dietary intake assessed with the cross-check dietary history method. Non-fatal MI information obtained by physician-administered (in 1985 and 1990) or self-administered (in 1993 and 1995) standardized medical questionnaire. Death information obtained from the participant's general practitioner and registries.	During 4,527 person-years of follow-up, 94 cases of CHD were documented. The multivariate adjusted risk ratio for CHD was 1.11 (95% CI: 0.66, 1.87; P=0.70) for the extreme tertiles of glycemic index after correction for age, BMI, physical activity, cigarette smoking and dietary factors. The multivariate adjusted risk ratio was 1.06 (95% CI: 0.52, 2.14; P=0.88; not adjusted for CHO intake) for the extreme tertiles of glycemic load.

Search plan and results

Inclusion criteria

- June 2004 to March 2009 for cancer, and January 2000 to September 2009 for CVD and type 2 diabetes
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Children, two to 18 years; adults, 19 years and older
- *Populations:* Healthy and those with elevated chronic disease risk.

Exclusion criteria

- Reviews (narrative and systematic); meta-analyses
- Studies examining intermediate outcomes, not incidence of disease
- Medical treatment or therapy, including medical treatment of diabetes
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Animal studies
- In vitro studies

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- Articles not peer reviewed (Websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed:
  Cancer: "Neoplasms"[Mesh] AND ("Glycemic Index"[Mesh] OR "glycemic load"[All Fields])

- PubMed, Embase, BIOSIS:
  Cardiovascular Disease: ("Glycemic Index"[Mesh] OR "glycemic load") AND (“Cardiovascular diseases”[Mesh])

- PubMed, Embase, BIOSIS:
  Type 2 Diabetes: ("Glycemic Index"[Mesh] OR "glycemic load") AND (“Diabetes Mellitus, Type 2”[Mesh])

Date searched: 03/20/2009; updated 09/19/2009 and 09/22/2009 for CVD and T2D

Summary of articles identified to review

- Total hits from all electronic database searches: 491
- Total articles identified to review from electronic databases: 133
- Articles identified via handsearch or other means: 0
- Number of Primary Articles Identified: 46
- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 46
- Number of Articles Reviewed but Excluded: 87

Included articles (References)

What is the relationship between glycemic index or glycemic load and cancer?

1. Augustin LS, Galeone C, Dal Maso L, Pelucchi C, Ramazzotti V, Jenkins DJ, Montella M, Talamini R, Negri E, Franceschi S, La Vecchia C. Glycemic index, glycemic load and risk of prostate cancer. *Int J Cancer.* 2004 Nov 10; 112(3): 446-450. PMID: 15382070.
2. Bertuccio P, Praud D, Chatenoud L, Lucenteforte E, Bosetti C, Pelucchi C, Rossi M, Negri E, La Vecchia C. Dietary glycemic load and gastric cancer risk in Italy. *Br J Cancer.* 2009 Feb 10; 100(3): 558-561. PMID: 19190635.
3. Cust AE, Slimani N, Kaaks R, van Bakel M, Biessy C, Ferrari P, Laville M, Tjønneland A, Olsen A, Overvad K, Lajous M, Clavel-Chapelon F, Boutron-Ruault MC, Linseisen J, Rohrmann S, Nöthlings U, Boeing H, Palli D, Sieri S, Panico S, Tumino R, Sacerdote C, Skeie G, Engeset D, Gram IT, Quirós JR, Jakszyn P, Sánchez MJ, Larrañaga N, Navarro C, Ardanaz E, Wirfält E, Berglund G, Lundin E, Hallmans G, Bueno-de-Mesquita HB, Du H, Peeters PH, Bingham S, Khaw KT, Allen NE, Key TJ, Jenab M, Riboli E. Dietary carbohydrates, glycemic index, glycemic load, and endometrial cancer risk within the European Prospective Investigation into Cancer and Nutrition cohort. *Am J Epidemiol.* 2007 Oct 15; 166(8): 912-923. Epub 2007 Aug 1. PMID: 17670911.
4. Flood A, Peters U, Jenkins DJ, Chatterjee N, Subar AF, Church TR, Bresalier R, Weissfeld JL, Hayes RB, Schatzkin A; Prostate, Lung, Colorectal, Ovarian (PLCO) Project Team. Carbohydrate, glycemic index, and glycemic load and

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

colorectal adenomas in the Prostate, Lung, Colorectal, and Ovarian Screening Study. *Am J Clin Nutr.* 2006 Nov; 84(5): 1, 184-1, 192. PMID: 17093173.

5. George SM, Mayne ST, Leitzmann MF, Park Y, Schatzkin A, Flood A, Hollenbeck A, Subar AF. Dietary glycemic index, glycemic load, and risk of cancer: A prospective cohort study. *Am J Epidemiol.* 2009 Feb 15; 169(4): 462-472. Epub 2008 Dec 18. PMID: 19095757.
6. Giles GG, Simpson JA, English DR, Hodge AM, Gertig DM, Macinnis RJ, Hopper JL. Dietary carbohydrate, fibre, glycaemic index, glycaemic load and the risk of postmenopausal breast cancer. *Int J Cancer.* 2006 Apr 1; 118(7): 1, 843-1, 847. PMID: 16217755.
7. Heinen MM, Verhage BA, Lumey L, Brants HA, Goldbohm RA, van den Brandt PA. Glycemic load, glycemic index, and pancreatic cancer risk in the Netherlands Cohort Study. *Am J Clin Nutr.* 2008 Apr; 87(4): 970-977. PMID: 18400721.
8. Howarth NC, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. The association of glycemic load and carbohydrate intake with colorectal cancer risk in the Multiethnic Cohort Study. *Am J Clin Nutr.* 2008 Oct; 88(4): 1, 074-1, 082. PMID: 18842796.
9. Johnson KJ, Anderson KE, Harnack L, Hong CP, Folsom AR. No association between dietary glycemic index or load and pancreatic cancer incidence in postmenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2005 Jun; 14(6): 1, 574-1, 575. PMID: 15941976.
10. Kabat GC, Shikany JM, Beresford SA, Caan B, Neuhouser ML, Tinker LF, Rohan TE. Dietary carbohydrate, glycemic index, and glycemic load in relation to colorectal cancer risk in the Women's Health Initiative. *Cancer Causes Control.* 2008 Dec; 19(10): 1, 291-1, 298. Epub 2008 Jul 10. PMID: 18618276.
11. Lajous M, Willett W, Lazcano-Ponce E, Sanchez-Zamorano LM, Hernandez-Avila M, Romieu I. Glycemic load, glycemic index, and the risk of breast cancer among Mexican women. *Cancer Causes Control.* 2005 Dec; 16(10): 1, 165-1, 169. PMID: 16215866.
12. Lajous M, Boutron-Ruault MC, Fabre A, Clavel-Chapelon F, Romieu I. Carbohydrate intake, glycemic index, glycemic load, and risk of postmenopausal breast cancer in a prospective study of French women. *Am J Clin Nutr.* 2008 May; 87(5): 1, 384-1, 391. PMID: 18469262.
13. Larsson SC, Bergkvist L, Wolk A. Glycemic load, glycemic index and carbohydrate intake in relation to risk of stomach cancer: a prospective study. *Int J Cancer.* 2006 Jun 15; 118(12): 3, 167-3, 169. PMID: 16395707.
14. Larsson SC, Giovannucci E, Wolk A. Dietary carbohydrate, glycemic index, and glycemic load in relation to risk of colorectal cancer in women. *Am J Epidemiol.* 2007 Feb 1; 165(3): 256-261. Epub 2006 Nov 21. PMID: 17118965
15. Larsson SC, Friberg E, Wolk A. Carbohydrate intake, glycemic index and glycemic load in relation to risk of endometrial cancer: A prospective study of Swedish women. *Int J Cancer.* 2007 Mar 1; 120(5): 1, 103-1, 137. PMID: 17131331.
16. McCann SE, McCann WE, Hong CC, Marshall JR, Edge SB, Trevisan M, Muti P, Freudenheim JL. Dietary patterns related to glycemic index and load and risk of premenopausal and postmenopausal breast cancer in the Western New York Exposure and Breast Cancer Study. *Am J Clin Nutr.* 2007 Aug; 86(2): 465-471. PMID: 17684220.
17. McCarl M, Harnack L, Limburg PJ, Anderson KE, Folsom AR. Incidence of

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

colorectal cancer in relation to glycemic index and load in a cohort of women. *Cancer Epidemiol Biomarkers Prev.* 2006 May; 15(5): 892-896. PMID: 16702366.
18. Michaud DS, Fuchs CS, Liu S, Willett WC, Colditz GA, Giovannucci E. Dietary glycemic load, carbohydrate, sugar, and colorectal cancer risk in men and women. *Cancer Epidemiol Biomarkers Prev.* 2005 Jan; 14(1): 138-147. PMID: 15668487.
19. Nöthlings U, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. Dietary glycemic load, added sugars, and carbohydrates as risk factors for pancreatic cancer: The Multiethnic Cohort Study. *Am J Clin Nutr.* 2007 Nov; 86(5): 1, 495-1, 501. PMID: 17991664.
20. Patel AV, McCullough ML, Pavluck AL, Jacobs EJ, Thun MJ, Calle EE. Glycemic load, glycemic index, and carbohydrate intake in relation to pancreatic cancer risk in a large US cohort. *Cancer Causes Control.* 2007 Apr; 18(3): 287-294. Epub 2007 Jan 11. PMID: 17219014.
21. Randi G, Ferraroni M, Talamini R, Garavello W, Deandrea S, Decarli A, Franceschi S, La Vecchia C. Glycemic index, glycemic load and thyroid cancer risk. *Ann Oncol.* 2008 Feb; 19(2): 380-383. Epub 2007 Oct 19. PMID: 17951595.
22. Sieri S, Pala V, Brighenti F, Pellegrini N, Muti P, Micheli A, Evangelista A, Grioni S, Contiero P, Berrino F, Krogh V. Dietary glycemic index, glycemic load, and the risk of breast cancer in an Italian prospective cohort study. *Am J Clin Nutr.* 2007 Oct; 86(4): 1, 160-1, 166. PMID: 17921397.
23. Silvera SA, Rohan TE, Jain M, Terry PD, Howe GR, Miller AB. Glycaemic index, glycaemic load and risk of endometrial cancer: A prospective cohort study. *Public Health Nutr.* 2005 Oct; 8(7): 912-919. PMID: 16277808.
24. Silvera SA, Rohan TE, Jain M, Terry PD, Howe GR, Miller AB. Glycemic index, glycemic load, and pancreatic cancer risk (Canada). *Cancer Causes Control.* 2005 May; 16(4): 431-436. PMID: 15953985.
25. Silvera SA, Jain M, Howe GR, Miller AB, Rohan TE. Dietary carbohydrates and breast cancer risk: A prospective study of the roles of overall glycemic index and glycemic load. *Int J Cancer.* 2005 Apr 20; 114(4): 653-658. Erratum in: *Int J Cancer.* 2006 May 1; 118(9): 2, 372. PMID: 15609324.
26. Silvera SA, Jain M, Howe GR, Miller AB, Rohan TE. Glycaemic index, glycaemic load and ovarian cancer risk: a prospective cohort study. *Public Health Nutr.* 2007 Oct; 10(10): 1, 076-1, 081. Epub 2007 Mar 2. PMID: 17381931.
27. Strayer L, Jacobs DR Jr, Schairer C, Schatzkin A, Flood A. Dietary carbohydrate, glycemic index, and glycemic load and the risk of colorectal cancer in the BCDDP cohort. *Cancer Causes Control.* 2007 Oct; 18(8): 853-863. Epub 2007 Jun 29. PMID: 17605083.
28. Weijenberg MP, Mullie PF, Brants HA, Heinen MM, Goldbohm RA, van den Brandt PA. Dietary glycemic load, glycemic index and colorectal cancer risk: Results from the Netherlands Cohort Study. *Int J Cancer.* 2008 Feb 1; 122(3): 620-629. PMID: 17935129.

What is the relationship between glycemic index or glycemic load and type 2 diabetes?

1. Barclay AW, Flood VM, Rochtchina E, Mitchell P, Brand-Miller JC. Glycemic index, dietary fiber, and risk of type 2 diabetes in a cohort of older

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Australians. *Diabetes Care.* 2007 Nov; 30(11): 2, 811-2, 813. Epub 2007 Aug 21. No abstract available. PMID: 17712022.
2. Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. *Am J Clin Nutr.* 2008 Feb; 87(2): 339-346. PMID: 18258623.
3. Hodge AM, English DR, O'Dea K, Giles GG. Glycemic index and dietary fiber and the risk of type 2 diabetes. *Diabetes Care.* 2004 Nov; 27(11): 2, 701-2, 706. PMID: 15505008.
4. Krishnan S, Rosenberg L, Singer M, Hu FB, Djoussé L, Cupples LA, Palmer JR. Glycemic index, glycemic load, and cereal fiber intake and risk of type 2 diabetes in US black women. *Arch Intern Med.* 2007 Nov 26; 167(21): 2, 304-2, 309. PMID: 18039988.
5. Mosdøl A, Witte DR, Frost G, Marmot MG, Brunner EJ. Dietary glycemic index and glycemic load are associated with high-density-lipoprotein cholesterol at baseline but not with increased risk of diabetes in the Whitehall II study. *Am J Clin Nutr.* 2007 Oct; 86(4): 988-994. PMID: 17921375.
6. Sahyoun NR, Anderson AL, Tylavsky FA, Lee JS, Sellmeyer DE, Harris TB; Health, Aging, and Body Composition Study. Dietary glycemic index and glycemic load and the risk of type 2 diabetes in older adults. *Am J Clin Nutr.* 2008 Jan; 87(1): 126-131. PMID: 18175745.
7. Schulz M, Liese AD, Fang F, Gilliard TS, Karter AJ. Is the association between dietary glycemic index and type 2 diabetes modified by waist circumference? *Diabetes Care.* 2006 May; 29(5): 1, 102-1, 104. PMID: 16644644.
8. Schulze MB, Liu S, Rimm EB, Manson JE, Willett WC, Hu FB. Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. *Am J Clin Nutr.* 2004 Aug; 80(2): 348-356. PMID: 15277155.
9. Stevens J, Ahn K, Juhaeri, Houston D, Steffan L, Couper D. Dietary fiber intake and glycemic index and incidence of diabetes in African-American and white adults: The ARIC study. *Diabetes Care.* 2002 Oct; 25(10): 1, 715-1, 721. PMID: 12351467.
10. Villegas R, Liu S, Gao YT, Yang G, Li H, Zheng W, Shu XO. Prospective study of dietary carbohydrates, glycemic index, glycemic load, and incidence of type 2 diabetes mellitus in middle-aged Chinese women. *Arch Intern Med.* 2007 Nov 26; 167(21): 2, 310-2, 316. PMID: 18039989.

What is the relationship between glycemic index or glycemic load and cardiovascular disease?

1. Beulens JW, de Bruijne LM, Stolk RP, Peeters PH, Bots ML, Grobbee DE, van der Schouw YT. High dietary glycemic load and glycemic index increase risk of cardiovascular disease among middle-aged women: A population-based follow-up study. *J Am Coll Cardiol.* 2007 Jul 3; 50(1): 14-21. Epub 2007 Jun 18. PMID: 17601539.
2. Halton TL, Willett WC, Liu S, Manson JE, Albert CM, Rexrode K, Hu FB. Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med.* 2006 Nov 9; 355(19): 1, 991-2, 002. PMID: 17093250.
3. Kaushik S, Wang JJ, Wong TY, Flood V, Barclay A, Brand-Miller J, Mitchell P. Glycemic index, retinal vascular caliber, and stroke mortality. *Stroke.* 2009 Jan; 40(1): 206-212. Epub 2008 Oct 23. PMID: 18948616.

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4. Levitan EB, Mittleman MA, Håkansson N, Wolk A. Dietary glycemic index, dietary glycemic load, and cardiovascular disease in middle-aged and older Swedish men. *Am J Clin Nutr.* 2007 Jun; 85(6): 1, 521-1, 526. PMID: 17556687.
5. Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, Hennekens CH, Manson JE. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr.* 2000 Jun; 71(6): 1, 455-1, 461. PMID: 10837285.
6. Oh K, Hu FB, Cho E, Rexrode KM, Stampfer MJ, Manson JE, Liu S, Willett WC. Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women. *Am J Epidemiol.* 2005 Jan 15; 161(2): 161-169. PMID: 15632266.
7. Tavani A, Bosetti C, Negri E, Augustin LS, Jenkins DJ, La Vecchia C. Carbohydrates, dietary glycaemic load and glycaemic index, and risk of acute myocardial infarction. *Heart.* 2003 Jul; 89(7): 722-726. PMID: 12807839; PMCID: PMC1767713.
8. van Dam RM, Visscher AW, Feskens EJ, Verhoef P, Kromhout D. Dietary glycemic index in relation to metabolic risk factors and incidence of coronary heart disease: The Zutphen Elderly Study. *Eur J Clin Nutr.* 2000 Sep; 54(9): 726-731. PMID: 11002385.

Excluded articles

Article	Reason for Exclusion
Amano Y, Kawakubo K, Lee JS, Tang AC, Sugiyama M, Mori K. Correlation between dietary glycemic index and cardiovascular disease risk factors among Japanese women. *Eur J Clin Nutr.* 2004 Nov; 58(11): 1, 472-1, 478. PMID: 15127092.	Does not include incidence of disease in analyses.
Barclay AW, Brand-Miller JC, Mitchell P. Macronutrient intake, glycaemic index and glycaemic load of older Australian subjects with and without diabetes: Baseline data from the Blue Mountains Eye study. *Br J Nutr.* 2006 Jul; 96(1): 117-123. PMID: 16869999.	Does not answer question; compares dietary intake of older adults with and without diabetes.
Barclay AW, Petocz P, McMillan-Price J, Flood VM, Prvan T, Mitchell P, Brand-Miller JC. Glycemic index, glycemic load, and chronic disease risk: A meta-analysis of observational studies. *Am J Clin Nutr.* 2008 Mar; 87(3): 627-637. Review. PMID: 18326601.	Study design is meta-analysis.

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Barkoukis H, Marchetti CM, Nolan B, Sistrun SN, Krishnan RK, Kirwan JP. A high glycemic meal suppresses the postprandial leptin response in normal healthy adults.*Ann Nutr Metab.* 2007; 51(6): 512-518. Epub 2007 Dec 10. PMID: 18073462.	Does not include incidence of disease in analyses.
Benoit SR, Fleming R, Philis-Tsimikas A, Ji M. Predictors of glycemic control among patients with Type 2 diabetes: A longitudinal study. *BMC Public Health.* 2005 Apr 17; 5: 36. PMID: 15833140.	Participants diagnosed with type 2 diabetes.
Beulens JWJ, Van Der Schouw YT. Increased risk of cardiovascular disease among middle-aged women due to glycemic load. *Cardiol Rev.* 2008 Feb; 25(2): 19-22.	Results reported based on the same dataset as Beulens (2007).
Biddinger SB, Ludwig DS. The insulin-like growth factor axis: A potential link between glycemic index and cancer. *Am J Clin Nutr.* 2005 Aug; 82(2): 277-278. PMID: 16087968.	Publication is editorial.
Brand-Miller J, Dickinson S, Barclay A, Celermajer D. The glycemic index and cardiovascular disease risk. *Curr Atheroscler Rep.* 2007 Dec; 9(6): 479-485. Review. PMID: 18377788.	Study design is narrative review.
Brand-Miller J, Hayne S, Petocz P, Colagiuri S. Low-glycemic index diets in the management of diabetes: A meta-analysis of randomized controlled trials. *Diabetes Care.* 2003 Aug; 26(8): 2, 261-2, 267. PMID: 12882846.	Study design is meta-analysis.
Brand-Miller JC, Stockmann K, Atkinson F, Petocz P, Denyer G. Glycemic index, postprandial glycemia, and the shape of the curve in healthy subjects: Analysis of a database of more than 1, 000 foods. *Am J Clin Nutr.* 2009 Jan; 89(1): 97-105. Epub 2008 Dec 3. PMID: 19056599.	Does not answer question; examined relationship between glycemic index and postprandialglycemia.
Brillon DJ, Sison CP, Salbe AD, Poretsky L. Reproducibility of a glycemic response to mixed meals in type 2 diabetes mellitus. *Horm Metab Res.* 2006 Aug; 38(8): 536-542. PMID: 16941281.	Does not include incidence of disease in analyses.

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Burani J, Longo PJ. Low-glycemic index carbohydrates: an effective behavioral change for glycemic control and weight management in patients with type 1 and 2 diabetes.*Diabetes Educ.* 2006 Jan-Feb; 32(1): 78-88. PMID: 16439496.	Participants diagnosed with type 2 diabetes.
Buscemi S, Verga S, Cottone S, Azzolina V, Buscemi B, Gioia D, Cerasola G. Glycaemic variability and inflammation in subjects with metabolic syndrome. *Acta Diabetol.* 2009 Mar; 46(1): 55-61. Epub 2008 Sep 26. PMID: 18818862.	Participants diagnosed with metabolic syndrome.
Colombani PC. Glycemic index and load-dynamic dietary guidelines in the context of diseases. *Physiol Behav.* 2004 Dec 30; 83(4): 603-610. Review. PMID: 15621065.	Study design is narrative review.
Darbinian JA, Ferrara AM, Van Den Eeden SK, Quesenberry CP Jr, Fireman B, Habel LA. Glycemic status and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2008 Mar; 17(3): 628-635. PMID: 18349280.	Does not include glycemic index or load in analyses.
de Rekeneire N, Rooks RN, Simonsick EM, Shorr RI, Kuller LH, Schwartz AV, Harris TB; Health, Aging and Body Composition Study. Racial differences in glycemic control in a well-functioning older diabetic population: Findings from the Health, Aging and Body Composition Study. *Diabetes Care.* 2003 Jul; 26(7): 1, 986-1, 992. Erratum in: *Diabetes Care.* 2003 Dec; 26(12): 3, 368. PMID: 12832300.	Participants diagnosed with type 2 diabetes.
Dickinson S, Brand-Miller J. Glycemic index, postprandial glycemia and cardiovascular disease. *Curr Opin Lipidol.* 2005 Feb; 16(1): 69-75. Review. PMID: 15650566.	Study design is narrative review.
Dickinson S, Hancock DP, Petocz P, Ceriello A, Brand-Miller J. High-glycemic index carbohydrate increases nuclear factor-kappaB activation in mononuclear cells of young, lean healthy subjects. *Am J Clin Nutr.* 2008 May; 87(5): 1, 188-1, 193. PMID: 18469238.	Does not include incidence of disease in analyses.

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Du H, van der A DL, van Bakel MM, van der Kallen CJ, Blaak EE, van Greevenbroek MM, Jansen EH, Nijpels G, Stehouwer CD, Dekker JM, Feskens EJ. Glycemic index and glycemic load in relation to food and nutrient intake and metabolic risk factors in a Dutch population. *Am J Clin Nutr.* 2008 Mar; 87(3): 655-661. PMID: 18326604.	Does not include incidence of disease in analyses.
Ebbeling CB, Leidig MM, Sinclair KB, Seger-Shippee LG, Feldman HA, Ludwig DS. Effects of an ad libitum low-glycemic load diet on cardiovascular disease risk factors in obese young adults. *Am J Clin Nutr.* 2005 May; 81(5): 976-982. PMID: 15883418.	Does not include incidence of disease in analyses.
Franz MJ. Is there a role for the glycemic index in coronary heart disease prevention or treatment? *Curr Atheroscler Rep.* 2008 Dec; 10(6): 497-502. Review. PMID: 18937897.	Study design is narrative review.
Gastrich MD, Lasser N L, Wien M, Bachmann G. Dietary complex carbohydrates and low glycemic index/load decrease levels of specific metabolic syndrome/cardiovascular disease risk factors. *Topics in Clinical Nutrition.* 2008; 23(1): 76-96.	Study design is systematic review.
Gellar L, Nansel TR. High and low glycemic index mixed meals and blood glucose in youth with type 2 diabetes or impaired glucose tolerance. *J Pediatr.* 2009 Mar; 154(3): 455-458.	Participants diagnosed with type 2 diabetes or impaired glucose tolerance.
Gnagnarella P, Gandini S, La Vecchia C, Maisonneuve P. Glycemic index, glycemic load, and cancer risk: a meta-analysis. *Am J Clin Nutr.* 2008 Jun; 87(6): 1, 793-1, 801. PMID: 18541570.	Study design is meta-analysis.
Graber AL, Shintani AK, Wolff K, Brown A, Elasy TA. Glycemic relapse in type 2 diabetes.*Endocr Pract.* 2006 Mar-Apr; 12(2): 145-151. PMID: 16690461.	Participants diagnosed with type 2 diabetes.
Hare-Bruun H, Nielsen BM, Grau K, Oxlund AL, Heitmann BL. Should glycemic index and glycemic load be considered in dietary recommendations? *Nutr Rev.* 2008 Oct; 66(10): 569-590. Review. PMID: 18826453.	Study design is narrative review.

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Henry CJ, Lightowler HJ, Tydeman EA, Skeath R. Use of low-glycaemic index bread to reduce 24-hour blood glucose: Implications for dietary advice to non-diabetic and diabetic subjects. *Int J Food Sci Nutr.* 2006 May-Jun; 57(3-4): 273-278. PMID: 17127477.	Does not include incidence of disease in analyses.
Jenkins DJ, Kendall CW, Augustin LS, Martini MC, Axelsen M, Faulkner D, Vidgen E, Parker T, Lau H, Connelly PW, Teitel J, Singer W, Vandenbroucke AC, Leiter LA, Josse RG. Effect of wheat bran on glycemic control and risk factors for cardiovascular disease in type 2 diabetes. *Diabetes Care.* 2002 Sep; 25(9): 1, 522-1, 528. PMID: 12196421.	Participants diagnosed with type 2 diabetes.
Jenkins DJ, Kendall CW, McKeown-Eyssen G, Josse RG, Silverberg J, Booth GL, Vidgen E, Josse AR, Nguyen TH, Corrigan S, Banach MS, Ares S, Mitchell S, Emam A, Augustin LS, Parker TL, Leiter LA. Effect of a low-glycemic index or a high-cereal fiber diet on type 2 diabetes: a randomized trial. *JAMA.* 2008 Dec 17; 300(23): 2, 742-2, 753. PMID: 19088352.	Participants diagnosed with type 2 diabetes.
Jimenez-Cruz A, Bacardi-Gascon M, Turnbull WH, Rosales-Garay P, Severino-Lugo I. A flexible, low-glycemic index mexican-style diet in overweight and obese subjects with type 2 diabetes improves metabolic parameters during a 6-week treatment period. *Diabetes Care.* 2003 Jul; 26(7): 1, 967-1, 970. PMID: 12832297.	Participants diagnosed with type 2 diabetes.
Jiménez-Cruz A, Gutiérrez-González AN, Bacardi-Gascon M. Low glycemic index lunch on satiety in overweight and obese people with type 2 diabetes. *Nutr Hosp.* 2005 Sep-Oct; 20(5): 348-350. PMID: 16229403.	Participants diagnosed with type 2 diabetes.
Kelly S, Frost G, Whittaker V, Summerbell C. Low glycaemic index diets for coronary heart disease. *Cochrane Database Syst Rev.* 2004 Oct 18; (4): CD004467. Review. PMID: 15495112.	Study design is systematic review.

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Levitan EB, Cook NR, Stampfer MJ, Ridker PM, Rexrode KM, Buring JE, Manson JE, Liu S. Dietary glycemic index, dietary glycemic load, blood lipids, and C-reactive protein.*Metabolism.* 2008 Mar; 57(3): 437-443. PMID: 18249220; PMCID: PMC2262400.	Does not include incidence of disease in analyses.
Levitan EB, Mittleman MA, Wolk A. Dietary glycemic index, dietary glycemic load and mortality among men with established cardiovascular disease. *Eur J Clin Nutr.* 2009 Apr; 63(4): 552-557. Epub 2007 Dec 19. PMID: 18091767.	Participants diagnosed with cardiovascular disease.
Liese AD, Schulz M, Fang F, Wolever TM, D'Agostino RB Jr, Sparks KC, Mayer-Davis EJ. Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women. *Diabetes Care.* 2005 Dec; 28(12): 2, 832-2, 838. PMID: 16306541.	Does not include incidence of disease in analyses.
Liu S, Manson JE, Buring JE, Stampfer MJ, Willett WC, Ridker PM. Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity C-reactive protein in middle-aged women. *Am J Clin Nutr.* 2002 Mar; 75(3): 492-498. PMID: 11864854.	Does not include incidence of disease in analyses.
Liu S, Manson JE, Stampfer MJ, Holmes MD, Hu FB, Hankinson SE, Willett WC. Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women. *Am J Clin Nutr.* 2001 Mar; 73(3): 560-566. PMID: 11237932.	Does not include incidence of disease in analyses.
Liu S. Lowering dietary glycemic load for weight control and cardiovascular health: a matter of quality. *Arch Intern Med.* 2006 Jul 24; 166(14): 1, 438-1, 439. PMID: 16864751.	Publication is editorial.
Livesey G, Taylor R, Hulshof T, Howlett J. Glycemic response and health: A systematic review and meta-analysis: Relations between dietary glycemic properties and health outcomes. *Am J Clin Nutr.* 2008 Jan; 87(1): 258S-268S. Review. PMID: 18175766.	Study design is systematic review.

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Lukaczer D, Liska DJ, Lerman RH, Darland G, Schiltz B, Tripp M, Bland JS. Effect of a low glycemic index diet with soy protein and phytosterols on CVD risk factors in postmenopausal women. *Nutrition.* 2006 Feb; 22(2): 104-113. PMID: 16459222.	Does not include incidence of disease in analyses.
Ma Y, Olendzki BC, Merriam PA, Chiriboga DE, Culver AL, Li W, Hébert JR, Ockene IS, Griffith JA, Pagoto SL. A randomized clinical trial comparing low-glycemic index vs. ADA dietary education among individuals with type 2 diabetes. *Nutrition.* 2008 Jan; 24(1): 45-56. PMID: 18070658.	Participants diagnosed with type 2 diabetes.
Maki KC, Rains TM, Kaden VN, Raneri KR, Davidson MH. Effects of a reduced-glycemic-load diet on body weight, body composition, and cardiovascular disease risk markers in overweight and obese adults. *Am J Clin Nutr.* 2007 Mar; 85(3): 724-734. PMID: 17344493.	Does not include incidence of disease in analyses.
Mann JI. Evidence-based nutrition recommendations for the treatment and prevention of type 2 diabetes and the metabolic syndrome. *Food Nutr Bull.* 2006 Jun; 27(2): 161-166. Review. PMID: 16786982.	Publication provides recommendations.
Martínez-Ortiz JA, Fung TT, Baylin A, Hu FB, Campos H. Dietary patterns and risk of nonfatal acute myocardial infarction in Costa Rican adults. *Eur J Clin Nutr.* 2006 Jun; 60(6): 770-777. Epub 2006 Feb 8. PMID: 16465200.	Does not include glycemic index or load in analyses.
McMillan-Price J, Petocz P, Atkinson F, O'neill K, Samman S, Steinbeck K, Caterson I, Brand-Miller J. Comparison of four diets of varying glycemic load on weight loss and cardiovascular risk reduction in overweight and obese young adults: A randomized controlled trial. *Arch Intern Med.* 2006 Jul 24; 166(14): 1, 466-1, 475. PMID: 16864756.	Does not include incidence of disease in analyses.

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Mead A, Atkinson G, Albin D, Alphey D, Baic S, Boyd O, Cadigan L, Clutton L, Craig L, Flanagan C, Greene P, Griffiths E, Lee NJ, Li M, McKechnie L, Ottaway J, Paterson K, Perrin L, Rigby P, Stone D, Vine R, Whitehead J, Wray L, Hooper L; UK Heart Health Group; Thoracic Dietitians Interest Group (Specialist group of the British Dietetic Association). Dietetic guidelines on food and nutrition in the secondary prevention of cardiovascular disease: Evidence from systematic reviews of randomized controlled trials (second update, January 2006). *J Hum Nutr Diet.* 2006 Dec; 19(6): 401-419. Review. PMID: 17105538.	Study design is review.
Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med.* 2009 Apr 13; 169(7): 659-669. Review. PMID: 19364995.	Study design is systematic review.
Miles JM. A role for the glycemic index in preventing or treating diabetes? *Am J Clin Nutr.* 2008 Jan; 87(1): 1-2. PMID: 18175728.	Publication is perspective.
Miller CK, Gutschall M. A randomized trial about glycemic index and glycemic load improves outcomes among adults with type 2 diabetes. *Health Educ Behav.* 2009 Jun; 36(3): 615-626. Epub 2008 May 9. PMID: 18469161.	Participants diagnosed with type 2 diabetes.
Miller CK, Gutshcall MD, Mitchell DC. Change in food choices following a glycemic load intervention in adults with type 2 diabetes. *J Am Diet Assoc.* 2009 Feb; 109(2): 319-324. PMID: 19167961.	Participants diagnosed with type 2 diabetes.
Milton JE, Briche B, Brown IJ, Hickson M, Robertson CE, Frost GS. Relationship of glycaemic index with cardiovascular risk factors: Analysis of the National Diet and Nutrition Survey for people aged 65 and older. *Public Health Nutr.* 2007 Nov; 10(11): 1, 321-1, 335. Epub 2007 Apr 24. PMID: 17456246.	Does not include incidence of disease in analyses.
Mogos T, Dondoi C. Evaluation of glycemic control of type II diabetes mellitus treated only with diet. *Rom J Intern Med.* 2007; 45(2): 205-208. PMID: 18333376.	Participants diagnosed with type 2 diabetes.

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Montori VM. Should patients with type 2 diabetes focus on glycemic control to reduce their cardiovascular risk? *Pol Arch Med Wewn.* 2008 Sep; 118(9): 502-507. Review. PMID: 18846985.	Study design is narrative review.
Mulholland HG, Murray LJ, Cardwell CR, Cantwell MM. Dietary glycaemic index, glycaemic load and breast cancer risk: a systematic review and meta-analysis. *Br J Cancer.* 2008 Oct 7; 99(7): 1, 170-1, 175. Epub 2008 Aug 26. Review. PMID: 18728653.	Study design is systematic review/meta-analysis.
Mulholland HG, Murray LJ, Cardwell CR, Cantwell MM. Glycemic index, glycemic load, and risk of digestive tract neoplasms: A systematic review and meta-analysis. *Am J Clin Nutr.* 2009 Feb; 89(2): 568-576. Epub 2008 Dec 16. Review. PMID: 19088152.	Study design is systematic review/meta-analysis.
Murakami K, Okubo H, Sasaki S. Effect of dietary factors on incidence of type 2 diabetes: A systematic review of cohort studies. *J Nutr Sci Vitaminol (Tokyo).* 2005 Aug; 51(4): 292-310. Review. PMID: 16262005.	Study design is systematic review.
Murakami K, Sasaki S, Takahashi Y, Okubo H, Hosoi Y, Horiguchi H, Oguma E, Kayama F. Dietary glycemic index and load in relation to metabolic risk factors in Japanese female farmers with traditional dietary habits. *Am J Clin Nutr.* 2006 May; 83(5): 1, 161-1, 169. PMID: 16685061.	Does not include incidence of disease in analyses.
Nansel TR, Gellar L, Zeitzoff L. Acceptability of lower glycemic index foods in the diabetes camp setting. *J Nutr Educ Behav.* 2006 May-Jun; 38(3): 143-150. PMID: 16731448.	Participants diagnosed with type 2 diabetes.
Oh K, Willett WC, Fuchs CS, Giovannucci EL. Glycemic index, glycemic load, and carbohydrate intake in relation to risk of distal colorectal adenoma in women. *Cancer Epidemiol Biomarkers Prev.* 2004 Jul; 13(7): 1, 192-1, 198. PMID: 15247130.	Results reported based on the same dataset as Michaud (2005).

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Ostman EM, Frid AH, Groop LC, Björck IM. A dietary exchange of common bread for tailored bread of low glycaemic index and rich in dietary fibre improved insulin economy in young women with impaired glucose tolerance. *Eur J Clin Nutr.* 2006 Mar; 60(3): 334-341. PMID: 16234828.	Does not include incidence of disease in analyses.
Panlasigui LN, Thompson LU. Blood glucose lowering effects of brown rice in normal and diabetic subjects. *Int J Food Sci Nutr.* 2006 May-Jun; 57(3-4): 151-158. PMID: 17127465.	Does not meet inclusion criteria for sample size.
Papanikolaou Y, Palmer H, Binns MA, Jenkins DJ, Greenwood CE. Better cognitive performance following a low-glycaemic-index compared with a high-glycaemic-index carbohydrate meal in adults with type 2 diabetes. *Diabetologia.* 2006 May; 49(5): 855-862. Epub 2006 Mar 1. PMID: 16508776.	Participants diagnosed with type 2 diabetes.
Pereira MA, Swain J, Goldfine AB, Rifai N, Ludwig DS. Effects of a low-glycemic load diet on resting energy expenditure and heart disease risk factors during weight loss. *JAMA.* 2004 Nov 24; 292(20): 2, 482-2, 490. PMID: 15562127.	Does not include incidence of disease in analyses.
Philippou E, McGowan BM, Brynes AE, Dornhorst A, Leeds AR, Frost GS. The effect of a 12-week low glycaemic index diet on heart disease risk factors and 24-hour glycaemic response in healthy middle-aged volunteers at risk of heart disease: A pilot study. *Eur J Clin Nutr.* 2008 Jan; 62(1): 145-149. Epub 2007 Feb 21. PMID: 17311054.	Does not meet inclusion criteria for sample size.
Pi-Sunyer X. Glycemic index in early type 2 diabetes. *Am J Clin Nutr.* 2008 Jan; 87(1): 3-4. PMID: 18175729.	Publication is perspective.
Pittas AG, Roberts SB, Das SK, Gilhooly CH, Saltzman E, Golden J, Stark PC, Greenberg AS. The effects of the dietary glycemic load on type 2 diabetes risk factors during weight loss. *Obesity (Silver Spring).* 2006 Dec; 14(12): 2, 200-2, 209. PMID: 17189547.	Does not include incidence of disease in analyses.

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Qi L, Meigs JB, Liu S, Manson JE, Mantzoros C, Hu FB. Dietary fibers and glycemic load, obesity, and plasma adiponectin levels in women with type 2 diabetes. *Diabetes Care.* 2006 Jul; 29(7): 1, 501-1, 505. PMID: 16801569.	Participants diagnosed with type 2 diabetes.
Qi L, Rimm E, Liu S, Rifai N, Hu FB. Dietary glycemic index, glycemic load, cereal fiber, and plasma adiponectin concentration in diabetic men. *Diabetes Care.* 2005 May; 28(5): 1, 022-1, 028. PMID: 15855561.	Participants diagnosed with type 2 diabetes.
Rendell M, Vanderhoof J, Venn M, Shehan MA, Arndt E, Rao CS, Gill G, Newman RK, Newman CW. Effect of a barley breakfast cereal on blood glucose and insulin response in normal and diabetic patients. *Plant Foods Hum Nutr.* 2005 Jun; 60(2): 63-67. PMID: 16021833.	Does not include incidence of disease in analyses.
Riccardi G, Rivellese AA, Giacco R. Role of glycemic index and glycemic load in the healthy state, in prediabetes, and in diabetes. *Am J Clin Nutr.* 2008 Jan; 87(1): 269S-274S. Review. PMID: 18175767.	Study design is narrative review.
Roberts SB, Pittas AG. The role of glycemic index in type 2 diabetes. *Nutr Clin Care.* 2003 May-Sep; 6(2): 73-78. Review. PMID: 14692295.	Study design is narrative review.
Sahyoun NR, Anderson AL, Kanaya AM, Koh-Banerjee P, Kritchevsky SB, de Rekeneire N, Tylavsky FA, Schwartz AV, Lee JS, Harris TB. Dietary glycemic index and load, measures of glucose metabolism, and body fat distribution in older adults. *Am J Clin Nutr.* 2005 Sep; 82(3): 547-552. PMID: 16155266.	Does not include incidence of disease in analyses.
Shani M, Taylor TR, Vinker S, Lustman A, Erez R, Elhayany A, Lahad A. Characteristics of diabetics with poor glycemic control who achieve good control. *J Am Board Fam Med.* 2008 Nov-Dec; 21(6): 490-496. PMID: 18988715.	Participants diagnosed with type 2 diabetes.

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Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, Howard BV, Kirkman MS, Kosiborod M, Reaven P, Sherwin RS; American Diabetes Association; American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials: A position statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association. *J Am Coll Cardiol.* 2009 Jan 20; 53(3): 298-304. Review. PMID: 19147051.	Publication is position statement.
Slama G, Elgrably F, Kabir M, Rizkalla S. Low glycemic index foods should play a role in improving overall glycemic control in type-1 and type-2 diabetic patients and, more specifically, in correcting excessive postprandial hyperglycemia. *Nestle Nutr Workshop Ser Clin Perform Programme.* 2006; 11: 73-79; discussion, 79-81. Review. PMID: 16820732.	Study design is narrative review.
Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med.* 2000 Jul 6; 343(1): 16-22. PMID: 10882764.	Does not include glycemic index or load in analyses (part of composite dietary score).
Tapola N, Karvonen H, Niskanen L, Mikola M, Sarkkinen E. Glycemic responses of oat bran products in type 2 diabetic patients. *Nutr Metab Cardiovasc Dis.* 2005 Aug; 15(4): 255-261. PMID: 16054549.	Participants diagnosed with type 2 diabetes.
Terry J, Terry P. [Glycemic index--relevant in the treatment of overweight and diabetes]*Lakartidningen.* 2006 Feb 15-21; 103(7): 466-470; discussion 471-473. Swedish. PMID: 16535876.	Study not published in English.
Thomas D, Elliott EJ. Low glycaemic index, or low glycaemic load, diets for diabetes mellitus.*Cochrane Database Syst Rev.* 2009 Jan 21; (1): CD006296. Review. PMID: 19160276.	Participants diagnosed with diabetes.

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Thomas DE, Elliott EJ, Baur L. Low glycaemic index or low glycaemic load diets for overweight and obesity. *Cochrane Database Syst Rev.* 2007 Jul 18; (3): CD005105. Review. PMID: 17636786.	Study design is systematic review.
Tokuyama Y, Ishizuka T, Matsui K, Egashira T, Kanatsuka A. Predictors of glycemic control in Japanese subjects with type 2 diabetes mellitus. *Metabolism.* 2008 Apr; 57(4): 453-457. PMID: 18328344.	Participants diagnosed with type 2 diabetes.
Ukleja A, Kunachowicz H, Pachocka L. The use of glycaemic index in the prevention of cardiovascular diseases. *Rocz Panstw Zakl Hig.* 2007; 58(1): 145-151. Review. PMID: 17711103.	Study design is narrative review.
Whiting PH, Kalansooriya A, Holbrook I, Haddad F, Jennings PE. The relationship between chronic glycaemic control and oxidative stress in type 2 diabetes mellitus. *Br J Biomed Sci.* 2008; 65(2): 71-74. PMID: 19055108.	Participants diagnosed with type 2 diabetes.
Willett W, Manson J, Liu S. Glycemic index, glycemic load, and risk of type 2 diabetes. *Am J Clin Nutr.* 2002 Jul; 76(1): 274S-280S. Review. PMID: 12081851.	Study design is review.
Wilson T, Meyers SL, Singh AP, Limburg PJ, Vorsa N. Favorable glycemic response of type 2 diabetics to low-calorie cranberry juice. *J Food Sci.* 2008 Nov; 73(9): H241-H245. PMID: 19021808.	Participants diagnosed with type 2 diabetes.
Wolever TM, Gibbs AL, Mehling C, Chiasson JL, Connelly PW, Josse RG, Leiter LA, Maheux P, Rabasa-Lhoret R, Rodger NW, Ryan EA. The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-year controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: No effect on glycated hemoglobin but reduction in C-reactive protein. *Am J Clin Nutr.* 2008 Jan; 87(1): 114-125. PMID: 18175744.	Participants diagnosed with type 2 diabetes.

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Wolever TM, Mehling C, Chiasson JL, Josse RG, Leiter LA, Maheux P, Rabasa-Lhoret R, Rodger NW, Ryan EA. Low glycaemic index diet and disposition index in type 2 diabetes (the Canadian trial of carbohydrates in diabetes): a randomised controlled trial. *Diabetologia.* 2008 Sep; 51(9): 1, 607-1, 615. Epub 2008 Jul 22. PMID: 18648764.	Participants diagnosed with type 2 diabetes.

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CHAPTER 6. LIQUIDS VERSUS SOLID FOODS

WHAT IS THE IMPACT OF LIQUIDS VS. SOLID FOODS ON ENERGY INTAKE AND BODY WEIGHT?

Conclusion statement

A limited body of evidence shows conflicting results about whether liquid and solid foods differ in their effects on energy intake and body weight, except that liquids in the form of soup may lead to decreased energy intake and body weight.

Grade

Limited

Evidence summary overview

No consistent relationships have been reported between the form of a food and energy intake and body weight. This review included 12 studies with no consistent experimental designs. One study examined liquid calories to solid calories in the PREMIER trial (Chen, 2009). Six of the studies were crossover trials that investigated the impact of a preload before breakfast (Stull, 2008) or lunch (Almiron-Roig, 2004; Flood-Obbagy, 2009; Mattes, 2009; Mourao, 2007; Tsuchiya, 2006) on ad libitum intake of a meal. An additional crossover trial (Moorhead, 2006) examined the intake of carrots in various forms with a meal rather than as a preload. DiMeglio et al, (2000) conducted a longer term crossover trial that included two, four-week interventions with daily consumption of liquid (caffeine-free soda) or solid (jelly beans) food. Finally, three studies (Rolls, 2005; Flood, 2007; Bertrais, 2001) examined soup as the liquid form.

No standard protocol has been established to answer this question, and information on food form and consumption of liquid is not collected in prospective cohort trials. Most of the available evidence to answer this question is from preload studies, in which meals are controlled for total calories and macronutrient content, and then satiety is measured for three hours after the meal. Subsequent food intake is then measured by consumption of a buffet lunch and food intake for 24 hours may then be calculated.

In the one prospective study, Chen et al, (2009) examined beverage consumption in the PREMIER study at baseline, six months and 18 months. Analyses considered changes in volume, calorie intake and percentage of calories from beverages both overall and from seven categories [sugar-sweetened beverages (SSB); diet drinks; milk; 100% juices; coffee and tea with sugar; coffee and tea without sugar or with artificial sweeteners; and alcoholic beverages]. A reduction of 100kcal per day in liquid calorie intake was associated with an approximate 0.25kg weight loss at six and 18 months. In comparison, a reduction in solid calorie intake by 100kcal per day was associated with a less than 0.1kg weight loss at six and 18 months. Reductions in liquid calorie intake had a stronger effect on weight loss than did a reduction in solid calorie intake, but the difference was statistically significant only at six months. A significant dose-response trend between change in body weight and change in liquid calorie intake was observed at six and 18 months.

Consumption of solid food compared to juice in a controlled caloric load may decrease energy intake at a subsequent meal. Flood-Obbagy and Rolls (2009) examined how

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consuming preloads of apples in different forms (apple, applesauce and apple juice with and without added fiber) influenced energy intake of a meal. Study participants consumed fewer calories at lunch after consuming apples compared to equal calories as applesauce, apple juice or apple juice with added fiber. In a similar study, whole carrots were associated with less calorie intake for the remainder of the day compared to carrot juice or a carrot juice cocktail that contained all the nutrients in carrots (Moorhead, 2006).

Mourao et al, (2007) investigated the independent effect of food form on appetite and energy intake in lean and obese adults using high carbohydrate (CHO), fat or protein (PRO) food stimuli. Treatments were matched beverage and solid food forms: High CHO (watermelon and watermelon juice); high PRO (cheese and milk); high fat (coconut meat and coconut milk). Participants consumed the entire test food as part of an ad libitum meal. Regardless of the predominant energy source, the beverage form elicited a weaker compensatory dietary response than the matched solid food form. The authors concluded that inclusion of a caloric beverage in a lunch meal led to greater daily energy intake compared to customary intake or days where a solid version of the same food was ingested. This occurred regardless of the primary energy source, and there was no clear indication that the lean and obese differ in this regard.

Stull et al, (2008) assessed the effect of liquid vs. solid meal replacements on appetite and subsequent food intake in healthy older adults. After an overnight fast, participants consumed meal replacement products as either a liquid or as a solid (bar) followed by ad libitum oatmeal. Participants consumed more calories from oatmeal after the liquid vs. solid meal replacement product.

Other studies suggest that food form may affect food intake, although inconsistent study designs make it difficult to compare results. DiMeglio and Mattes (2000) examined the differential effects of matched liquid (soda) and solid (jelly beans) CHO loads on diet and body weight. Participants were assigned to one of two dietary load conditions (solid: 450kcal serving of jelly beans; liquid: 450kcal serving of caffeine-free soda) for four weeks, followed by a four-week washout period and subsequent participation in the other condition for four weeks. During the solid load condition, participants compensated for some of the energy in the test foods by reducing free-feeding intake such that the overall compensation score was 118%. However, when the liquid load was included in the diet, no compensation was observed, resulting in a compensation score of -17%. The authors concluded that liquid CHO promotes positive energy balance, whereas a comparable solid CHO elicits dietary compensation; further, body weight and body mass index (BMI) increased only with the liquid load.

In contrast, both Mattes and Campbell (2009) and Almiron-Roig et al, (2004) found no differences in subsequent food intake when they compared solid food to liquids in studies well controlled for macronutrients and calories. Mattes and Campbell (2009) assessed the effects of apple food form (apple, applesauce, apple juice) and timing of eating events (meal or snack) on appetite and daily energy intake. There were no treatment effects on daily energy intake.

Almiron-Roig et al, (2004) compared the impact on energy intakes of equal-energy preloads (300kcal) of regular cola or fat-free cookies presented either two hours or 20 minutes before a tray lunch. Liquid or solid form had no impact on energy intakes during the test meal. Similarly, physical form had no effect when the sum of the energy

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intake of breakfast, preload and lunch was considered.

In another crossover trial (Tsuchiya, 2006) participants consumed 200kcal preloads: Semi-solid peach yogurt with peach pieces, peach yogurt homogenized to liquid form, peach syrup and water, or a milk-based peach and apricot beverage followed by an ad libitum lunch. No significant (NS) differences in energy intakes were detected across the four conditions, either for lunch alone or for total energy consumed from breakfast, preload and lunch.

Liquids in soup may have different effects as studies find that daily soup consumers have lower daily energy intake than those who consume little soup (Bertrais, 2001), and soup pre-loads reduce food intake at a subsequent meal (Flood, 2007). Rolls et al, (2005) tested the effect on weight loss of a diet incorporating one or two servings per day of foods equal in energy but differing in energy density. Participants followed an energy-restricted diet in a one-year trial (six-month weight loss and six-month weight maintenance); participants were randomized to one of four intervention groups. Participants were instructed to consume daily: One serving of soup, two servings of soup, or two servings of dry snack foods. Participants in the fourth group were not provided with any specific food to consume (comparison group). There were no significant differences in reported energy intake among the intervention groups at any time-points. All four groups showed significant weight loss at six months that was well maintained at 12 months. The magnitude of weight loss, however, differed by group. At one year, weight loss in the comparison (8.1±1.1kg) and two-soup (7.2±0.9kg) groups was significantly greater than that in the two-snack group (4.8±0.7kg); weight loss in the one-soup group (6.1±1.1kg) did not differ significantly from other groups. The authors concluded that on an energy-restricted diet, consuming two servings of low energy-dense soup daily led to 50% greater weight loss than consuming the same amount of energy as high energy-dense snack food.

When macronutrient content of a liquid food and a solid food is balanced, there are few data that food form affects energy intake. These studies are difficult to design and conduct as the form of the food cannot be blinded (i.e., participants know that they are eating apples or drinking apple juice). In the acute studies of food intake, efforts are made to control variables, including the time allowed to consume the test food, but it is difficult to generalize these results to the eating environment of real life.

Food structure may play a role in food intake. Whole foods, such as apples and carrots, play a role in satiety and decrease food intake at a subsequent meal. When a non-viscous fiber was added to apple juice, the fiber-enriched apple juice was not as effective as the apple in reducing food intake at a subsequent meal. Thus, factors besides the fiber in whole foods may affect energy intake, including food structure and chewing.

The data with soup as a preload are often in conflict with other data on liquid calories. In a one-year weight loss trial, consumption of two servings of soup per day led to greater weight loss than consuming the same amount of energy from two snack foods. Soup preload significantly reduced test meal and total meal energy intake in one study. Thus, the studies with soup as a liquid calorie source suggest that specific liquid calories can be an aid to weight loss and that liquid calories from soup result in reduced intake at a subsequent meal.

Evidence summary paragraphs

Liquid=Beverage

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Chen et al, 2009 (positive quality), a prospective cohort study conducted in the US, examined how changes in beverage consumption affect weight change among adults. Participants were 810 adults (62% female; age 50.0±8.9 years; BMI=33.1±5.8kg/m^2) from the PREMIER study. Dietary intake was estimated by the average of two multiple pass 24-hour recalls conducted at baseline, six and 18 months to determine changes in volume, kcal intake, and percentage of calories from beverages both overall and from seven categories (SSB; diet drinks; milk; 100% juices; coffee and tea with sugar; coffee and tea without sugar or with artificial sweeteners; and alcoholic beverages). Weight and height were measured at each time-point. A reduction of 100kcal per day in liquid calorie intake was associated with a 0.25kg weight loss (95% CI: 0.11, 0.39; P<0.001) at six months and of 0.24kg (95% CI: 0.06, 0.41; P=0.008) at 18 months; a reduction in solid calorie intake by 100kcal per day was associated with a 0.06kg weight loss (95% CI: 0.002, 0.14; P=0.04) at six months and 0.09kg (95% CI: 0.005, 0.16; P=0.003) at 18 months. Reductions in liquid calorie intake had a stronger effect on weight loss than did a reduction in solid calorie intake, but the difference was statistically significant only at six months (P=0.006). Similarly, a reduction in the percentage of liquid calories from total calories by 1% was associated with a weight loss of 0.04kg (95% CI: 0.01, 0.06; P=0.005) at six months and of 0.02kg (95% CI: -0.01, 0.06; P=0.02) at 18 months. When changes in consumption of liquid calories were divided into tertiles, a significant dose-response trend between change in body weight and change in liquid calorie intake was observed for both the six-month change (P=0.01) and the 18 month change (P<0.001). The authors concluded that their data support recommendations to limit liquid calorie intake among adults.

DiMeglio and Mattes, 2000 (positive quality), a randomized crossover clinical trial conducted in the US, studied the differential effects of matched liquid (soda) and solid (jelly beans) CHO loads on diet and body weight. Participants were 15 adults (53% female; age 22.8±2.73 years; BMI=21.9±2.2kg/m^2) who were assigned to one of two dietary load conditions (solid: 450kcal serving of jelly beans; liquid: 450kcal serving of caffeine-free soda) for four weeks, followed by a four-week washout period and subsequent participation in the other condition for four weeks. Dietary free-feeding energy intake was estimated by unannounced telephone 24-hour dietary recalls at baseline (three days) and six times during each treatment period and washout. Body composition was measured weekly. During the solid load condition, subjects compensated for the provided energy by reducing free-feeding intake such that the overall compensation score was 118%. However, when the liquid load was included in the diet, no compensation was observed; there was a slight increase in free-feeding intake such that the failure to compensate resulted in a score of -17%. Daily energy intake with the liquid load was significantly greater than intake with the solid load (P<0.001). Consequently, body weight and BMI increased significantly only during the liquid period. Body weight at the end of the liquid load period was significantly higher than at the beginning (P<0.05), although there was no difference between the change in body weight in the two conditions. BMI also increased significantly over the liquid load period (P<0.05), but the change was not different from that with the solid load. The authors concluded that liquid CHO promotes positive energy balance, whereas a comparable solid CHO elicits precise dietary compensation; further, increased consumption of energy-yielding fluids may promote positive energy balance.

Mourao et al, 2007 (neutral quality), a crossover dietary challenge, investigated the independent effect of food form on appetite and energy intake in lean and obese adults using high CHO, fat or PRO food stimuli. Treatments were matched beverage and

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solid food forms: High CHO (watermelon and watermelon juice); high PRO (cheese and milk); high fat (coconut meat and coconut milk). Participants were 120 lean (N=60; 18-23kg/m^2) and obese (N=60; 30-35kg/m^2) adults(18-50 years old) with stable body weight. Forty different participants (N=20 lean and 20 obese) were tested with each of the food systems. Each participant came to the lab on three test days (control, beverage, and solid). The lean participants were provided 125kcal of test food and the obese participants were provided 225kcal of test food. Participants ate their breakfast followed by a three-hour fast before reporting to the lab for lunch. Participants were instructed to consume the entire test food as part of an ad libitum meal. Food records were kept each testing day to determine energy intake. Regardless of the predominant energy source, the beverage form elicited a weaker compensatory dietary response than the matched solid food form. Thus, total daily energy intake was significantly higher by 12.4, 19 and 15% on days the beverage forms of the high-CHO, -fat and -PROn foods were ingested, respectively. Differences between lean and obese participants were small and not systematic. The authors concluded that inclusion of a caloric beverage in a lunch meal led to greater daily energy intake compared to customary intake or days, where a solid version of the same food was ingested. This occurred regardless of the primary energy source, and there was no clear indication that the lean and obese differ in this regard.

Mattes and Campbell, 2009 (positive quality), a randomized crossover study conducted in the US, assessed the effects of food form (solid, semi-solid, or beverage) and timing of eating events (meal or snack) on appetite and daily energy intake. Participants were 20 normal weight (50% male; BMI=22.6±1.8kg/m^2; age 21.6±2.1 years) and 20 obese (50% male; BMI=32.3±1.5kg/m^2; age 25.6±5.9 years) adults. On six occasions, participants reported to the laboratory for a fixed portion mid-day meal. In addition, participants consumed 300kcal loads of a solid (apple), semi-solid (applesauce) and beverage (apple juice) at the meal or two hours later (snack). Diet recalls were collected the next day. The form of the food load had NS effect on energy intake at the first eating occasion of >100kcal after ingestion of the experimental meal and the load whether consumed with the meal or two hours after. There were no treatment effects on daily energy intake. There were NS differences between lean participants and those with obesity for daily energy intake. Although the authors noted different appetitive findings for the different food forms, these appetitive effects did not translate into differences in energy intake.

Flood-Obbagy and Rolls, 2009 (positive quality), a randomized crossover trial conducted in the US, examined how consuming preloads of apples in different forms prior to a meal (apple, applesauce, and apple juice with and without added fiber) influences satiety and energy intake at a meal. Once a week for five weeks, 58 adults (52% male) consumed one of four apple preloads (266g; 125kcal), or no preload (control), followed by a test meal consumed ad libitum 15 minutes later. All foods and beverages were weighed before and after being served to participants. Consuming apple significantly reduced total energy intake at lunch (preload and test meal) by 91±24kcal compared to consuming applesauce, by 152±36 compared to apple juice with fiber and by 178±27 compared to apple juice without fiber (all $P<0.02$). Lunch intake was significantly lower when applesauce was consumed compared to both types of apple juice ($P<0.05$); in the two juice conditions, however, total energy intakes at lunch did not differ significantly from each other. Compared to when no preload was consumed, subjects reduced total energy intake at lunch by 187±36kcal when apple was eaten, to 85±4% of intake in the control condition ($P<0.0001$). In addition, when

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applesauce was eaten as a preload, total energy intake at lunch was reduced by 96±29kcal compared to control (P<0.01). No significant difference in total energy intake at lunch was observed between the control (1,024±49kcal), apple juice with fiber (989±52kcal) and apple juice without fiber (1,015±51kcal) treatments. The authors concluded that consuming fruit before a meal can enhance satiety and reduce subsequent food intake, leading to a substantial reduction in total energy intake at the meal. In addition, the energy content of the apple juice both with and without fiber was compensated for by a reduction in subsequent intake; thus, drinking juice as a preload did not increase total meal energy intake.

Moorhead et al, 2006 (positive quality), a randomized crossover trial conducted in the United Kingdom, evaluated the effects of the fiber content and physical structure (gross anatomy and cell structure) of carrots on postprandial satiety and subsequent food intakes when consumed as part of a mixed meal. Thirty-six women (age: 33±7.03 years; BMI: 24.4±4.03kg/m^2) consumed a standardized breakfast and test lunches on three occasions, four weeks apart. The test lunches (3,329kJ) comprised boiled rice (200g) with sweet and sour sauce (200g) that included chicken (200g) and carrots (200g) in three conditions: Whole carrots (suspended in sauce), blended carrots (in sauce) or carrot nutrients (in sauce). All meals had the same energy, macronutrient, sodium, potassium, calcium and water contents, and the same weight and volume. Participants returned to the lab later in the day for an ad libitum afternoon meal that was weighed to determine intake. Participants then completed food diaries to estimate intake the remainder of the day. All subjected consumed the complete test lunches. There were significant differences between the three conditions for energy intake at the afternoon ad libitum meal (whole=1,669 (489) kJ; blended=2,247 (904) kJ; nutrients=2,881 (778); P<0.05). Similarly, energy intake for the remainder of the day was significantly lower for the remainder of the day for the whole and blended conditions compared to the carrot nutrient condition. The authors concluded that whole or blended carrots, eaten as part of a mixed lunch meal, result in significantly increased satiety and decreased subsequent intakes.

Stull et al, 2008 (neutral quality), a randomized crossover study conducted in the US, assessed the effect of liquid vs. solid meal replacements on appetite and subsequent food intake in healthy older adults. Participants were 24 adults(50% female; BMI=26.0±0.8kg/m^2; age=62±2 years) who completed two days of testing in random order and separated by one week. After an overnight fast, the subjects consumed meal replacement products as either a beverage (liquid) or a bar (solid). The meal replacement products provided 25% of each subject's daily estimated energy needs with comparable macronutrient compositions. At minute 120, each subject consumed cooked oatmeal ad libitum. The oatmeal bowl was weighed before and after eating to quantify amount consumed. On average, subjects consumed 13.4% more oatmeal after the liquid vs. solid meal replacement product (338±33 vs. 298±32kcal; P=0.006). The authors concluded that older adults consumed more food at the next eating occasion after consuming a liquid vs. solid meal replacement product.

Almiron-Roig et al, 2004 (neutral quality) compared the relative impact on satiety and energy intakes of the physical form of foods vs. the timing of consumption in a study with a within-subject design conducted in the US. Participants were 32 adults (50% female) aged 18 to 35 years. Average BMI for the men and women were 22.5±2.4 and 21.9±2.4kg/m^2, respectively. Participants consumed equal-energy preloads (300kcal) of regular cola (24-ounce) or fat-free raspberry cookies (three-ounce) on two

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occasions each for a total of four separate test sessions that were spaced at least a week apart. The order of presentation of the four preloads was counterbalanced across sessions. The preloads were presented either two hour or 20 minutes before a tray lunch. The same lunch foods were offered on all four testing occasions. All lunch foods were pre-weighed and plate waste was collected and weighed to determine food intake. Participants were also asked to record all the foods and beverages that they had consumed for breakfast that morning. Liquid or solid form had no impact on energy intakes [$F(1,30)=0.04$; $P>0.05$] during the test meal. Similarly, when the sum of the energy intake of breakfast, preload and lunch was considered, physical form had no effect [$F(1,30)=0.99$; $P>0.05$]. The authors concluded that energy intakes at lunch following the consumption of equal-energy amounts of cola or cookies were NS different.

Tsuchiya et al, 2006 (positive quality), a crossover study conducted in the US, compared the satiating power of semi-solid and liquid yogurts with fruit beverages and dairy fruit drinks. Participants (N=32; 50% female; BMI=22.9±1.9kg/m^2; age=27.1±4.7 years) consumed a 200kcal preload stimulus on four separate occasions separated by at least a week. The preloads were: Semi-solid peach yogurt with peach pieces, peach yogurt homogenized to liquid form, peach syrup and water or a milk-based peach and apricot beverage. A light breakfast was provided on arrival at the laboratory. The preload was provided 90 minutes later, and ad libitum lunch was provided 90 minutes after that. All foods were weighed when served and plate waste was collected and weighed. Mean energy intake (±SE) across the four conditions was 806±43kcal. No significant differences in energy intakes were detected across the four conditions, either for lunch alone or for total energy consumed from breakfast, preload, and lunch. Analysis of pooled dietary intake data for all subjects indicated that when yogurts were compared to the two beverages, energy intakes at lunch were lower (790±46 vs. 823±50kcal), but differences were NS. The authors concluded that lower hunger and higher fullness ratings after yogurt consumption were observed but did not lead to energy compensation at the next meal.

Liquid=Soup

Rolls et al, 2005 (neutral quality), a randomized controlled trial conducted in the US, tested the effect on weight loss of a diet incorporating one or two servings per day of foods equal in energy but differing in energy density. Two-hundred participants (77% female; BMI approximately 31kg/m^2; age approximately 44 years) followed an energy-restricted diet in a one-year trial (six-month weight loss and six-month weight maintenance); subjects were randomized to one of four intervention groups. Subjects in three of the groups were given supplies of commercially available food that was low in energy (100kcal per serving) and fat (less than 4g per serving). Subjects in these groups were instructed to consume daily: One serving of soup (one-soup group), two servings of soup (two-soup group), or two servings of dry snack foods (two-snack group). Subjects in the fourth group were not provided with any specific food to consume (comparison group). Three-day diet records were completed at baseline and one, two, six and 12 months. Height and weight were measured by study personnel. One hundred forty-seven participants (74%) completed the one-year trial. Reported energy intake decreased significantly from baseline to six months and increased slightly at 12 months ($P<0.005$). There were NS differences in reported energy intake among the intervention groups at any time-points. All four groups showed significant weight loss at six months that was well-maintained at 12 months. The magnitude of

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weight loss, however, differed by group (P<0.006). At one year, weight loss in the comparison (8.1±1.1kg) and two-soup (7.2±0.9kg) groups was significantly greater than that in the two-snack group (4.8±0.7kg); weight loss in the one-soup group (6.1±1.1kg) did not differ significantly from other groups. The authors concluded that on an energy-restricted diet, consuming two servings of low energy-dense soup daily led to 50% greater weight loss than consuming the same amount of energy as high energy-dense snack food.

Flood and Rolls, 2007 (positive quality), a randomized crossover trial conducted in the US, examined the effects of consuming different forms of a low-energy dense soup on subsequent test meal intake and total energy intake at the meal. Participants were 60 normal weight adults (50% female; age 20-46 years) who went to the laboratory for lunch once a week for five weeks. Each week subjects participated in one of five test sessions, the order of which was randomly assigned: No preload or one of four soup preloads (females: 350ml; males 475ml) with the same energy density (1.4kJper gram), but prepared differently (broth and vegetables served separately, chunky vegetable soup, chunky-pureed vegetable soup or pureed vegetable soup). A test meal was consumed ad libitum 15 minutes after the soup was served. Results showed that consuming soup significantly reduced test meal intake (P<0.0001) and total meal energy intake (preload and test meal; P<0.0001) compared to having no soup. When soup was consumed, subjects reduced meal energy intake by 20% (134±25kcal). The type of soup had NS effect on test meal intake or total meal energy intake. The authors concluded that consuming a preload of low-energy-dense soup, in a variety of forms, is one strategy for moderating energy intake in adults.

Bertrais et al, 2001 (neutral quality), a cross-sectional study conducted in France, assessed the impact of soup consumption on nutrient intake and nutritional indicators in adults who were participants in the SU.VI.MAX cohort. Dietary intake data was analyzed for a sub-sample of men (N=2,188; age 45 to 60 years) and women (N=2,849; age 35 to 60 years), who completed twelve 24-hour diet records over a two-year period (N=60,444 total records); analysis utilized average intakes for the total records for each subject. Height and weight were measured by study personnel. Respondents were divided into three groups based on soup consumption every six days:

1. Occasional/non-consumers (zero to two times)
2. Regular consumers (three to four times)
3. Heavy consumers (five to six times).

Mean energy intake was lower in heavy consumers than in occasional/non-consumers, but the difference was significant only for women (1,784±37kcal vs. 1,831±12kcal, respectively; P=0.02). 92% of soups were consumed at dinner. Soup consumers presented lower energy intake at dinner than occasional/non-consumers (P≤10-6 for men and women). In men, energy intakes at dinner for heavy and occasional/non-consumers were 756±22 and 909±8kcal, respectively. In women, energy intakes at dinner for heavy and occasional/non-consumers were 548±3 and 655±6kcal, respectively. In men, a higher frequency of BMI>27kg/m^2 was found in occasional/non-consumers of soup; conversely, a higher frequency of BMI between 23 and 27kg/m^2 was found in regular consumers of soup and a higher frequency of BMI<23kg/m^2 was found in heavy consumers. For women, an association was found between occasional/non-consumers and BMI>25kg/m^2 and between heavy consumers and BMI<22kg/m^2. The authors concluded that consumption of soup may be beneficial

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in weight reduction programs.

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Overview table

Study	Study Design	Liquid	Solid	Outcome	Results
Chen, 2009 Positive Quality	Prospective cohort study(PREMIER): Intake data the average of two 24-hour recalls conducted at zero, six and 18 months.	Liquid calories (beverages).	Solid calories.	(1) Body weight Δ (2) Weight loss.	Liquid: (+) body weight Δ ↓ in liquid calorie intake had stronger effect on weight loss than ↓ in solid calorie intake.
DiMeglio, 2000 Positive Quality	Randomized crossover trial with two, four-week interventions with daily consumption of test foods.	Caffeine-free soda.	Jelly beans.	(1) Daily energy intake (2) Body weight.	Daily energy intake higher with liquid load than solid load. Body weight and BMI significantly ↑ only during liquid load.
Mourao, 2007 Neutral Quality	Crossover dietary challenge with matched preloads followed by ad lib lunch	Watermelon juice. Milk. Coconut milk.	Watermelon. Cheese. Coconut meat.	Daily energy intake.	Daily energy intake was ↑ on days the liquid forms were ingested regardless of primary energy source.

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Mattes, 2009 Positive Quality	Randomized crossover trial with apple preload followed by ad lib lunch.	Apple juice.	Apple. Applesauce.	Daily energy intake.	Ø between food form and daily energy intake.
Flood-Obbagy, 2009 Positive Quality	Randomized crossover trial with no preload or apple preloads followed by ad lib lunch.	Apple juice with added fiber. Apple juice without added fiber.	Apple. Applesauce.	Energy intake of: (1) preload and test meal.	Apple and applesauce: ↓ total meal energy intake Juice (with or without added fiber): Did not ↑ total meal energy intake compared with no preload.
Moorhead, 2006 Positive Quality	Randomized crossover trial with standardized breakfast and test lunches followed by ad lib meal later in the day.	Carrot nutrients (formulated to give same energy, major nutrients, and portion weight).	Carrots. Blended carrots.	Energy intake of: (1) ad lib meal (2) remainder of day.	Whole and blended carrots result in significantly ↓ subsequent intakes.
Stull, 2008 Neutral Quality	Randomized crossover trial with meal replacement preload followed by ad lib breakfast.	Meal replacement beverage.	Meal replacement bar.	Energy intake of: (1) test meal.	Energy intake ↑ after the liquid vs. solid meal replacement product.

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Almiron-Roig, 2004 Neutral Quality	Crossover trial with preload followed by ad lib lunch.	Regular cola.	Fat-free cookies.	Energy intake of: (1) test meal (2) breakfast + preload plus test meal.	Ø on energy intakes during test meal or B+P+TM.
Tsuchiya, 2006 Positive Quality	Crossover trial with peach preload followed by ad lib lunch.	Peach yogurt in liquid form. Peach syrup and water. Milk-based peach beverage.	Semisolid peach yogurt with peach pieces.	Energy intake of: (1) test meal (2) breakfast + preload plus test meal.	Ø on energy intakes during test meal or B+P+TM.
Rolls, 2005 Neutral Quality	RCT: one-year weight loss / maintenance trial.	One serving soup per day. Two servings soup per day.	Two snack foods per Control.	(1) Daily energy intake (2) Weight loss.	No difference in daily energy intake Consuming two servings soup per day led to ↑ weight loss than consuming same amount of energy from two snack foods per day.

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Flood, 2007 Positive Quality	Randomized crossover trial with no preload or soup preload followed by ad lib lunch.	Soup (four versions).	No soup.	Energy intake of: (1) Test meal (2) Preload and test meal.	Soup preload significantly ↓ test meal and total meal energy intake.
Bertrais, 2001 Neutral Quality	Cross-sectional study (SU.VI.MAX Cohort): Average of 12, 24-hour diet records from 5,037 participants.	Regular soup consumers. Heavy soup consumers.	Occasional/ non-consumers of soup.	(1) Daily energy intake (2) Dinner energy intake (3) BMI.	Heavy soup consumers: (-) Daily energy intake (women), (-) Energy intake at dinner, (-) BMI.

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Search plan and results

Inclusion criteria

- January 2000 to December 2009
- Human subjects
- English language
- International
- *Sample size*: Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate*: Less than 40%; preference for smaller dropout rates
- *Ages*: Children, two to 18 years; adults, 19 and older
- *Populations*: Healthy, those with elevated chronic disease risk.

Exclusion criteria

- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (Websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed

((Liquid* OR solid*) AND ("Food and Beverages"[Mesh] OR (food[mh] AND beverages[mh]))) AND (“Total caloric consumption” OR “energy compensation” OR “dietary compensation” OR (“energy intake”[mh]))

(“food form” OR “fluid calories” OR soup* OR “energy drinks” OR “liquid calories” OR “solid foods”) AND (“Total caloric consumption” OR "energy compensation” OR “dietary compensation” OR (“energy intake”[majr]))

("Food and Beverages"[Mesh] OR (food[mh] AND beverages[mh]) OR “food form” OR “fluid calories” OR soup* OR “energy drinks” OR “ liquid calories” OR “solid foods”) AND ("body weight"[mh] OR adiposity[mh] OR "Body Mass Index"[mh] OR "Overweight"[mh] OR "Obesity"[mh] OR "Weight Gain"[mh] OR "Waist-Hip Ratio"[Mesh])

Liquid* AND solid* AND ("Food and Beverages"[Mesh] OR (food[mh] AND beverages[mh])) AND ("body weight"[mh] OR adiposity[mh] OR "Body Mass Index"[mh] OR "Overweight"[mh] OR "Obesity"[mh] OR "Weight Gain"[mh] OR "Waist-Hip Ratio"[Mesh])

Date searched: 12/10/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 339
- Total articles identified to review from electronic databases: 34
- Articles identified via handsearch or other means: 2
- Number of Primary Articles Identified: 12

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- Number of Review Articles Identified: 0
- Total Number of Articles Identified: 12
- Number of Articles Reviewed but Excluded: 24

Included articles (References)

1. Almiron-Roig E, Flores SY, Drewnowski A. No difference in satiety or in subsequent energy intakes between a beverage and a solid food. *Physiol Behav.* 2004 Sep 30; 82(4): 671-677. PMID: 15327915. (Hand search)
2. Bertrais S, Galan P, Renault N, Zarebska M, Preziosi P, Hercberg S. Consumption of soup and nutritional intake in French adults: Consequences for nutritional status. *J Hum Nutr Diet.* 2001 Apr; 14(2): 121-128. PMID: 11330261.
3. Chen L, Appel LJ, Loria C, Lin PH, Champagne CM, Elmer PJ, Ard JD, Mitchell D, Batch BC, Svetkey LP, Caballero B. Reduction in consumption of sugar-sweetened beverages is associated with weight loss: the PREMIER trial. *Am J Clin Nutr.* 2009 May; 89(5): 1, 299-1, 306. Epub 2009 Apr 1. PMID: 19339405; PMCID: PMC2676995.
4. DiMeglio DP, Mattes RD. Liquid vs. solid carbohydrate: Effects on food intake and body weight. *Int J Obes Relat Metab Disord.* 2000 Jun; 24(6): 794-800. PMID: 10878689.
5. Flood JE, Rolls BJ. Soup preloads in a variety of forms reduce meal energy intake. *Appetite.* 2007 Nov; 49(3): 626-634. Epub 2007 Apr 14. PMID: 17574705; PMCID: PMC2128765.
6. Flood-Obbagy JE, Rolls BJ. The effect of fruit in different forms on energy intake and satiety at a meal. *Appetite.* 2009 Apr; 52(2): 416-422. Epub 2008 Dec 6. PMID: 19110020; PMCID: PMC2664987.
7. Mattes RD, Campbell WW. Effects of food form and timing of ingestion on appetite and energy intake in lean young adults and in young adults with obesity. *J Am Diet Assoc.* 2009 Mar; 109(3): 430-437. PMID: 19248858; PMCID: PMC2680008.
8. Moorhead SA, Welch RW, Barbara M, Livingstone E, McCourt M, Burns AA, Dunne A. The effects of the fibre content and physical structure of carrots on satiety and subsequent intakes when eaten as part of a mixed meal. *Br J Nutr.* 2006; 96(3): 587-595. PMID: 16925866. (Hand search)
9. Mourao DM, Bressan J, Campbell WW, Mattes RD. Effects of food form on appetite and energy intake in lean and obese young adults. *Int J Obes (Lond).* 2007 Nov; 31(11): 1, 688-1, 695. Epub 2007 Jun 19. PMID: 17579632.
10. Rolls BJ, Roe LS, Beach AM, Kris-Etherton PM. Provision of foods differing in energy density affects long-term weight loss. *Obes Res.* 2005 Jun; 13(6): 1, 052-1, 060. PMID: 15976148.
11. Stull AJ, Apolzan JW, Thalacker-Mercer AE, Iglay HB, Campbell WW. Liquid and solid meal replacement products differentially affect postprandial appetite and food intake in older adults. *J Am Diet Assoc.* 2008 Jul; 108(7): 1, 226-1, 230. PMID: 18589034; PMCID: PMC2556245.
12. Tsuchiya A, Almiron-Roig E, Lluch A, Guyonnet D, Drewnowski A. Higher satiety ratings following yogurt consumption relative to fruit drink or dairy fruit drink. *J Am Diet Assoc.* 2006 Apr; 106(4): 550-557. PMID: 16567151.

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Excluded articles

Articles	Reason for Exclusion
Almiron-Roig E, Chen Y, Drewnowski A. Liquid calories and the failure of satiety: How good is the evidence? *Obes Rev.* 2003 Nov; 4(4): 201-212. Review. PMID: 14649371.	Study design is narrative review.
Bachman CM, Baranowski T, Nicklas TA. Is there an association between sweetened beverages and adiposity? *Nutr Rev.* 2006 Apr; 64(4): 153-174. Review. PMID: 16673752.	Study design is narrative review.
Ballistreri MC, Corradi-Webster CM. Consumption of energy drinks among physical education students. *Rev Lat Am Enfermagem.* 2008 Jul-Aug; 16 Spec No: 558-564. PMID: 18709275.	Does not answer question; does not examine liquids vs. solids.
Bell EA, Roe LS, Rolls BJ. Sensory-specific satiety is affected more by volume than by energy content of a liquid food. *Physiol Behav.* 2003 Apr; 78(4-5): 593-600. PMID: 12782213.	Does not answer question; does not examine liquids vs. solids; does not include energy intake or body weight in analyses.
Briefel RR, Wilson A, Gleason PM. Consumption of low-nutrient, energy-dense foods and beverages at school, home, and other locations among school lunch participants and nonparticipants. *J Am Diet Assoc.* 2009 Feb; 109(2 Suppl): S79-S90. PMID: 19166676.	Does not answer question; does not examine liquids vs. solids.
Burger KS, Kern M, Coleman KJ. Characteristics of self-selected portion size in young adults. *J Am Diet Assoc.* 2007 Apr; 107(4): 611-618. PMID: 17383267.	Does not answer question; does not examine liquids vs. solids.
Dennis EA, Flack KD, Davy BM. Beverage consumption and adult weight management: A review. *Eat Behav.* 2009 Dec; 10(4): 237-246. Epub 2009 Jul 16. Review. PMID: 19778754.	Does not answer question; does not examine liquids vs. solids.
Drewnowski A, Bellisle F. Liquid calories, sugar, and body weight. *Am J Clin Nutr.* 2007 Mar; 85(3): 651-661. Review. Erratum in: *Am J Clin Nutr.* 2007 Jun; 85(6): 1, 668. PMID: 17344485.	Study design is narrative review.

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Ello-Martin JA, Ledikwe JH, Rolls BJ. The influence of food portion size and energy density on energy intake: implications for weight management. *Am J Clin Nutr.* 2005 Jul; 82(1 Suppl): 236S-241S. Review. PMID: 16002828.	Does not answer question; does not examine liquids vs. solids.
Frecka JM, Hollis JH, Mattes RD. Effects of appetite, BMI, food form and flavor on mastication: almonds as a test food. *Eur J Clin Nutr.* 2008 Oct; 62(10): 1, 231-1, 238. Epub 2007 Jul 18. PMID: 17637602.	Does not answer question; does not examine liquids vs. solids.
Harrington S. The role of sugar-sweetened beverage consumption in adolescent obesity: A review of the literature. *J Sch Nurs.* 2008 Feb; 24(1): 3-12. Review. PMID: 18220450.	Does not answer question; does not examine liquids vs. solids.
Johnson L, Mander AP, Jones LR, Emmett PM, Jebb SA. Is sugar-sweetened beverage consumption associated with increased fatness in children? *Nutrition.* 2007 Jul-Aug; 23(7-8): 557-563. PMID: 17616342.	Does not answer question; does not examine liquids vs. solids.
Lecheminant JD, Gibson CA, Sullivan DK, Hall S, Washburn R, Vernon MC, Curry C, Stewart E, Westman EC, Donnelly JE. Comparison of a low carbohydrate and low fat diet for weight maintenance in overweight or obese adults enrolled in a clinical weight management program. *Nutr J.* 2007 Nov 1; 6: 36. PMID: 17976244; PMCID: PMC2228297.	Does not answer question; does not examine liquids vs. solids.
Mattes R. Fluid calories and energy balance: the good, the bad, and the uncertain. *Physiol Behav.* 2006 Aug 30; 89(1): 66-70. Epub 2006 Mar 6. Review. PMID: 16516935.	Study design is narrative review.
Mattes RD. Food palatability, rheology, and meal patterning. *JPEN J Parenter Enteral Nutr.* 2008 Sep-Oct; 32(5): 572-574. PMID: 18753396.	Does not answer question; does not examine liquids vs. solids.
Mattes RD, Rothacker D. Beverage viscosity is inversely related to postprandial hunger in humans. *Physiol Behav.* 2001 Nov-Dec; 74(4-5): 551-557. PMID: 11790415.	Does not answer question; does not examine liquids vs. solids; examines beverage viscosity.

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Norton GN, Anderson AS, Hetherington MM. Volume and variety: relative effects on food intake. *Physiol Behav.* 2006 Apr 15; 87(4): 714-722. Epub 2006 Mar 3. PMID: 16516251.	Does not answer question; does not examine liquids vs. solids.
O'Connor TM, Yang SJ, Nicklas TA. Beverage intake among preschool children and its effect on weight status. *Pediatrics.* 2006 Oct; 118(4): e1, 010-e1, 018. PMID: 17015497.	Does not answer question; does not examine liquids vs. solids.
Rolls BJ, Drewnowski A, Ledikwe JH. Changing the energy density of the diet as a strategy for weight management. *J Am Diet Assoc.* 2005 May; 105(5 Suppl 1): S98-S103. Review. PMID: 15867904.	Study design is narrative review.
Rothacker DQ, Watemberg S. Short-term hunger intensity changes following ingestion of a meal replacement bar for weight control. *Int J Food Sci Nutr.* 2004 May; 55(3): 223-226. PMID: 15223599.	Does not answer question; does not examine liquids vs. solids; examines meal replacement bar.
Rush E, Schulz S, Obolonkin V, Simmons D, Plank L. Are energy drinks contributing to the obesity epidemic? *Asia Pac J Clin Nutr.* 2006; 15(2): 242-244. PMID: 16672210.	Does not answer question; does not examine liquids vs. solids.
Tieken SM, Leidy HJ, Stull AJ, Mattes RD, Schuster RA, Campbell WW. Effects of solid versus liquid meal-replacement products of similar energy content on hunger, satiety, and appetite-regulating hormones in older adults. *Horm Metab Res.* 2007 May; 39(5): 389-394. PMID: 17533583; PMCID: PMC2197163.	Sample size less than inclusion criteria.
West DS, Bursac Z, Quimby D, Prewitt TE, Spatz T, Nash C, Mays G, Eddings K. Self-reported sugar-sweetened beverage intake among college students. *Obesity (Silver Spring).* 2006 Oct; 14(10): 1, 825-1, 831. PMID: 17062813.	Does not answer question; does not examine liquids vs. solids.
Zijlstra N, Mars M, de Wijk RA, Westerterp-Plantenga MS, de Graaf C. The effect of viscosity on ad libitum food intake. *Int J Obes (Lond).* 2008 Apr; 32(4): 676-683. Epub 2007 Dec 11. PMID: 18071342.	Does not include energy intake or body weight in analyses.

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CHAPTER 7. SUGAR-SWEETENED BEVERAGES AND NON-CALORIC SWEETENERS – ENERGY INTAKE

IN ADULTS, WHAT IS THE ASSOCIATION BETWEEN INTAKE OF SUGAR-SWEETENED BEVERAGES AND ENERGY INTAKE?

Conclusion statement

Limited evidence shows that intake of sugar-sweetened beverages is linked to higher energy intake in adults.

Grade

Limited

Evidence summary overview

To answer this question the Committee reviewed one meta-analysis (Vartanian, 2007) and four trials (Flood, 2006; Reid, 2007; Soenen, 2007, Stookey et al, 2007) published since 1990. Vartanian et al (2007) conducted a meta-analysis that examined the association between soft drink consumption and various health outcomes, including energy intake. It should be noted that this analysis included some unpublished data as well as cross-sectional studies. However, they conducted separate analyses based on study design and outcomes. Of the 88 studies in the review, three longitudinal studies and 11 experimental studies examined the relationship between soft drink consumption and energy intake in adults. Although effect size was small, the authors concluded that there was a clear positive association between soft drink intake and energy intake.

Two additional primary studies also support a relationship between the intake of sugar-sweetened beverages (SSB) and increased energy intake. Flood et al (2006) examined the impact of beverage type (cola, diet cola or water) and size (12 or 18 fluid ounces) on intake at an ad libitum lunch. Energy intake from food consumed at lunch did not differ across conditions. However, when the energy from beverages was added to the energy consumed from food, mean total energy intake at lunch was greater when regular cola was served as compared to the other beverages, regardless of portion size.

Reid et al (2007) compared the effects of supplementary soft drinks sweetened with sucrose or aspartame added to the diet over four weeks on dietary intake in normal-weight women. Participants consumed four 250ml bottles of drink per day. Sucrose supplements provided 430kcal per day and aspartame supplements provided less than 20kcal per day. For those consuming the sucrose drink, daily energy intake was higher during the intervention phase than at baseline; women consuming the SSB consumed about 200kcal more energy each day.

Stookey et al (2007) compared four weight loss diets and predicted that replacing sweetened caloric beverages with water would save 200kcal per day over 12 months. Although weight loss might be expected due to lower energy intake, change in body weight was not analyzed.

Soenen and Westerterp-Platenga (2007) examined the satiating effects of high fructose corn syrup (HFCS) and sucrose in comparison with milk and a diet drink. In

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this trial, participants completed four test sessions that included an ad libitum meal served after one of four beverages: one containing sucrose, one HFCS, one milk and one a diet drink. All four drinks were isovolumetric (800ml). The energy drinks were isocaloric. Test meal energy intake was lower after consumption of pre-loads containing sucrose or HFCS or milk (with no differences between the energy-containing pre-loads) compared to the diet drink pre-load. Total energy intake (pre-load + meal) with the energy-containing pre-loads was significantly higher than total energy intake with the diet drink pre-load. During the meal, energy intake from the beverage was partly compensated for. However, compensation for energy intake from the pre-loads containing sucrose, HFCS or milk did not differ significantly and ranged from 30% to 45%. This study indicated that although energy intake was higher following the drinks sweetened with HFCS and sucrose compared to a diet drink pre-load, energy intakes were not different than the milk pre-load, indicating that the added sugar did not have a unique effect on energy intake.

Evidence summary paragraphs

Vartanian et al, 2007 (positive quality), a systematic review and meta-analysis, examined the association between soft drink consumption and nutrition and health outcomes. MEDLINE and PsycINFO were searched to find articles that examined the association between soft drink consumption and nutrition and health outcomes. Key words used included “soft drink,” “soda” and “sweetened beverage” along with four primary outcomes (energy intake, body weight, milk intake and calcium intake) and two secondary outcomes (nutrition and health). Additional articles were identified by searching each article’s reference section and the Web of Science database. Finally, authors were contacted to request unpublished or in-press work. Eighty-eight studies were included in the meta-analysis; approximately 30 comparisons were available for soft drinks and energy intake or body weight in adults. Analysis of primary outcomes revealed a significant degree of heterogeneity of effect sizes, and thus, studies were separated according to research design. Average energy intake effect sizes for adults:

- Overall: R=0.28 (95% CI: 0.27, 0.30; P<0.0056; N=19)
- Cross-sectional: R=0.28 (95% CI: 0.26, 0.30; P<0.0056; N=2)
- Longitudinal: R=0.29 (95% CI: 0.27, 0.31; P<0.0056; N=3)
- Experimental (short): R=0.22 (95% CI: 0.15, 0.29; NS; N=11).

The authors concluded that they found clear associations of soft drink intake with increased energy intake and body weight. Further, they stated that recommendations to reduce population soft drink consumption are strongly supported by the available science.

Reid et al, 2007 (positive quality) compared the effects of supplementary soft drinks added to the diet over four weeks on dietary intake, mood and body mass index (BMI) in normal-weight women (N=133; age 20 to 55 years; BMI 17 to 24.9kg/m^2). The study took place over five weeks, including one week of baseline data collection followed by four weeks of drink supplementation. Drinks contained either sucrose or aspartame. Participants were either informed that they were receiving sugary drinks or ‘diet’ drinks, meaning that half were correctly informed about the drink content and half misinformed. In addition, participants were recruited according to whether they were or were not currently watching their weight. This resulted in a 2 x 2 x 2 design (sucrose vs. aspartame, drinks labeled sugar vs. labeled aspartame or diet, watcher vs. non-watcher). Subjects received four 250ml bottles of drink per day in uniform bottles with

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the labeling manipulated. Each week of the four-week intervention, participants were given one week's supply of 28 test drinks and were instructed to drink the agreed amount each day at the specified times (11.00, 14.00, 18.00 and 20.00 hours). Sucrose supplements provided 1,800kJ per day and aspartame supplements provided 67kJ per day. Food intake was measured with a seven-day diary during each week of the five-week study. Height and weight were measured by study personnel. There were no significant effects of restraint (watching or non-watching) status on any of the experimental analyses. For this reason, results were presented without 'watching' as a factor. For those consuming the sucrose drink, energy intake was higher at week one: (t (67df) = 6.44; $P<0.001$) and at week four than at baseline (t (67df) = 3.82; $P<0.001$) and week one and week four did not differ (t (67df) = 1.81; $P=0.075$). Women in the sucrose group consumed about 800kJ more energy per day; the supplements contained 1,800kJ. Mean body weight at baseline was 61.35±8.37kg. There was a marginal effect of drink on body weight (F (10•20, 1.86) = 4.509; $P<0.05$), with more women who received the sucrose drink gaining some weight during the study and more women receiving aspartame losing weight. There was a non-significant trend for those receiving sucrose to gain weight. The authors concluded that compensation was only partial for added sucrose, so were sucrose to be added to the diet, some weight gain might result in normal-weight individuals.

Flood et al, 2006 (positive quality), a randomized crossover trial, examined the impact of increasing beverage portion size on beverage and food intake. A component of the study design was to compare beverage type (cola, diet cola or water). Participants were 33 adults (55% female; age 19 to 30 years) who consumed lunch in the laboratory once a week for six weeks, for a total of six test sessions. On each test day, a standard breakfast was served in order to ensure a consistent level of hunger across sessions. At each lunch, the same foods were served, but the beverage served was varied in type (cola, diet cola or water) and portion size (12 or 18 fl oz). The regular soda provided 150 and 225kcal for the small and large servings, respectively. The order of experimental conditions was randomized across subjects. At all meals, subjects could eat ad libitum from the amount of food and beverage that was served. All foods and beverages were weighed prior to being served to subjects, and reweighed after the subjects had finished eating, to determine the amount of food and beverage consumed. Energy intake from food consumed at lunch did not differ significantly across conditions. However, when the energy from beverages was added to the energy consumed from food, mean total energy intake at lunch was significantly greater when regular cola was served, regardless of portion size ($P<0.001$). Therefore, even though subjects consumed more energy from the caloric beverage than the non-caloric beverages, they did not compensate for this additional energy by reducing food intake. The authors concluded that when a caloric beverage was consumed with a meal, food intake was not reduced and energy from the beverage added on to energy from food, resulting in a significant increase in total energy consumed at a meal; further, replacing caloric beverages with low-calorie or non-caloric beverages can be an effective strategy for decreasing energy intake.

Soenen and Westerterp-Platenga, 2007 (positive quality) examined the satiating effects of HFCS and sucrose in comparison with milk and a diet drink. Participants were 40 adults (50% female; BMI 22.4±2.1kg/m^2). The four beverages were as follows: A beverage containing sucrose, one containing HFCS, one containing milk and a diet drink. All four drinks were isovolumetric (800 ml). The energy drinks were isoenergetic and provided 1.5mJ. The diet drink had an energy content of 0.2mJ. A within-subjects

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design was used, with each subject returning for four separate test days one or more weeks apart. An ad libitum meal (granola cereal and yogurt) was served 50 minutes after participants completed the pre-load; all foods were pre-weighed at the time of serving, and plate waste was collected and weighed. Test meal energy intake was significantly lower after consumption of pre-loads containing sucrose or HFCS or the milk pre-load (with no differences between the energy-containing pre-loads) than after the diet pre-load ($P<0.05$). Total energy intake (pre-load + meal) with the energy-containing pre-loads was significantly higher than total energy intake with the diet pre-load ($P<0.01$). Therefore, during the meal, energy intake was only partly compensated for. Compensation for energy intake from the pre-loads containing sucrose, HFCS, or milk did not differ significantly and ranged from 30% to 45%. The authors concluded that there were no differences in energy balance consequences after HFCS, sucrose, or milk pre-loads.

Stookey et al, 2007 (positive-quality) evaluated change in beverage pattern, specifically, drinking water as an alternative to sweetened caloric beverages (SCBs), in a secondary analysis of data from the Stanford A-TO-Z intervention. The Stanford A-TO-Z study was a clinical weight loss trial that randomized overweight pre-menopausal women to four weight loss diets: Dr. Atkins' New Diet Revolution, The Zone: A Dietary Roadmap, The LEARN Program for Weight Management 2000, or Eat More, Weigh Less by Dr. Dean Ornish. Participants included in analyses were 118 overweight women (25 to 50 years) who regularly consumed SCBs (12oz or more a day) at baseline. At baseline and two, six and 12 months, mean daily beverage intake (SCBs, drinking water, non-caloric diet beverages and nutritious caloric beverages), food composition (macronutrient, water and fiber content) and total energy intake were estimated using three 24-hour diet recalls. Beverage intake was expressed in relative terms (percentage of beverages). In fixed-effects models that controlled for total beverage intake, non-caloric and nutritious caloric beverage intake (percentage of beverages), food composition and energy expenditure [metabolic equivalent (MET)], replacing SCBs with drinking water was associated with significant decreases in total energy intake that were sustained over time. The caloric deficit attributable to replacing SCBs with water was not negated by compensatory increases in other food or beverages. Replacing all SCBs with drinking water was associated with a predicted mean decrease in total energy of 200kcal per day over 12 months. The authors concluded that replacing SCBs with drinking water can help lower total energy intake in overweight consumers of SCBs motivated to diet.

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Overview table

Study	Meta-Analysis	Authors Conclusion
*Vartanian, 2007 Class: M Positive Quality	Meta-analysis examined the association between soft drink consumption and nutrition and health outcomes [88 original studies [energy intake: three longitudinal and 11 experimental studies with adults)].	(+) Clear association of soft drink intake with ↑ energy intake observed.

*Review included cross-sectional studies.

Study	Design: Trials	Sugar-Sweetened Beverage (SSB)	Comparison	Time	Support a Positive Relationship Between SSB and Energy Intake?
Reid, 2007 Class: A Positive Quality	Parallel-arm trial with four soft drinks added to daily diet.	Regular soft drink.	Diet soft drink.	Four weeks	Yes
Flood, 2006 Class: A Positive Quality	Randomized crossover trial with ad libitum beverage and lunch.	Cola	• Diet cola • Water	One day (test meal)	Yes
Soenen, 2007 Class: A Positive Quality	Crossover trial with pre-load followed by test meal.	• Sucrose beverage • HFCS beverage	• Milk • Diet drink	One day (test meal)	No (higher energy intake with added sugar, but same energy intake as with milk drink)

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Stookey, 2007 Class: B Positive Quality	Secondary analysis of data from Stanford A-TO-Z intervention examining drinking water as alternative to sweetened-caloric beverages (SCB).	SCB.	Water	Two, six and 12 months	Yes

Search plan and results

Inclusion criteria

- January 1990 to December 2009 (systematic review search updated February 2010)
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Adults 19 years and older
- *Populations:* Healthy, those with elevated chronic disease risk.

Exclusion criteria

- Cross-sectional studies
- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed

  ("Body Weight"[Mesh] OR "overweight"[Mesh] OR obesity[mh] OR adiposity[mh]) AND (added sugar* OR sugar based* or sugar sweetened* or HFCS or high fructose corn syrup* or corn syrup* OR candy OR “dietary sucrose"[Mesh] OR “Liquid sugars” OR Soda pop*) AND ("Energy

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Intake"[Mesh] OR “Total caloric consumption” OR “energy compensation” OR “dietary compensation” OR “caloric intake OR ("Body Weight"[Mesh] OR "overweight"[Mesh] OR obesity[mh] OR adiposity[mh]) AND (“Carbonated beverages”[mh] OR Soft drink* OR Sugar-sweetened beverage* OR Sweetened drink*)

Updated search for systematic reviews/meta-analyses (02/03/10)

(added sugar* OR sugar based* OR sugar sweetened* OR HFCS OR high fructose corn syrup* OR corn syrup* OR candy OR "dietary sucrose"[Mesh] OR "Liquid sugars" OR Soda pop* OR "Carbonated beverages"[mh] OR Soft drink* OR Sugar-sweetened beverage* OR Sweetened drink*) AND (systematic[sb] OR Meta-Analysis[ptyp])

Date searched: 12/23/2009, Updated 02/03/2010

Summary of articles identified to review

- Total hits from all electronic database searches: 497
- Total articles identified to review from electronic databases: 79
- Articles identified via handsearch or other means: 1
- Number of Primary Articles Identified: 10
- Number of Review Articles Identified: 4
- Total Number of Articles Identified: 14
- Number of Articles Reviewed but Excluded: 66

Included articles (References)

In adults, what is the association between the intake of sugar-sweetened beverages and energy intake?

Systematic Reviews / Meta-Analyses:

1. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: A systematic review and meta-analysis. Am J Public Health. 2007 Apr; 97 (4): 667-675. Epub 2007 Feb 28. Review. PMID: 17329656; PMCID: PMC1829363.

Primary Citations:

1. Flood JE, Roe LS, Rolls BJ. The effect of increased beverage portion size on energy intake at a meal. *J Am Diet Assoc.* 2006 Dec; 106 (12): 1, 984-1, 990; discussion 1990-1991. PMID: 17126628. (Hand search)
2. Reid M, Hammersley R, Hill AJ, Skidmore P. Long-term dietary compensation for added sugar: effects of supplementary sucrose drinks over a four-week period. *Br J Nutr.* 2007 Jan; 97 (1): 193-203. PMID: 17217576.
3. Soenen S, Westerterp-Plantenga MS. No differences in satiety or energy intake after high-fructose corn syrup, sucrose or milk preloads. *Am J Clin Nutr.* 2007 Dec; 86 (6): 1, 586-1, 594. Erratum in: *Am J Clin Nutr.* 2008 Apr; 87 (4): 1, 071. PMID: 18065574.
4. Stookey JD, Constant F, Gardner CD, Popkin BM. Replacing sweetened caloric beverages with drinking water is associated with lower energy intake. *Obesity* (Silver Spring). 2007 Dec; 15 (12): 3, 013-3, 022. PMID: 18198310.

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In adults, what is the association between the intake of sugar-sweetened beverages and body weight?

Systematic Reviews / Meta-Analyses:

1. Gibson S. Sugar-sweetened soft drinks and obesity: a systematic review of the evidence from observational studies and interventions. *Nutr Res Rev.* 2008 Dec; 21 (2): 134-147. Review. PMID: 19087367.
2. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: A systematic review. *Am J Clin Nutr*. 2006 Aug; 84 (2): 274-288. Review. PMID: 16895873.
3. Ruxton CH, Gardner EJ, McNulty HM. Is sugar consumption detrimental to health? A review of the evidence 1995-2006. *Crit Rev Food Sci Nutr*. 2010 Jan; 50 (1): 1-19. PMID: 20047137.
4. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. *Am J Public Health.* 2007 Apr; 97 (4): 667-675. Epub 2007 Feb 28. Review. PMID: 17329656; PMCID: PMC1829363.

Primary Citations:

Trials

1. Raben A, Macdonald I, Astrup A. Replacement of dietary fat by sucrose or starch: effects on 14-day ad libitum energy intake, energy expenditure and body weight in formerly obese and never-obese subjects. *Int J Obes Relat Metab Disord.* 1997 Oct; 21 (10): 846-859. PMID: 9347402.
2. Reid M, Hammersley R, Hill AJ, Skidmore P. Long-term dietary compensation for added sugar: Effects of supplementary sucrose drinks over a four-week period. *Br J Nutr.* 2007 Jan; 97 (1): 193-203. PMID: 17217576.
3. Stanhope KL, Schwarz JM, Keim NL, Griffen SC, Bremer AA, Graham JL, Hatcher B, Cox CL, Dyachenko A, Zhang W, McGahan JP, Seibert A, Krauss RM, Chiu S, Schaefer EJ, Ai M, Otokozawa S, Nakajima K, Nakano T, Beysen C, Hellerstein MK, Berglund L, Havel PJ. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight or obese humans. *J Clin Invest.* 2009 May; 119 (5): 1, 322-1, 334. doi: 10.1172/JCI37385. Epub 2009 Apr 20. PMID: 19381015; PMCID: PMC2673878.
4. Surwit RS, Feinglos MN, McCaskill CC, Clay SL, Babyak MA, Brownlow BS, Plaisted CS, Lin PH. Metabolic and behavioral effects of a high-sucrose diet during weight loss. *Am J Clin Nutr.* 1997 Apr; 65 (4): 908-915. PMID: 9094871.

Prospective Observational

1. Chen L, Appel LJ, Loria C, Lin PH, Champagne CM, Elmer PJ, Ard JD, Mitchell D, Batch BC, Svetkey LP, Caballero B. Reduction in consumption of sugar-sweetened beverages is associated with weight loss: The PREMIER trial. *Am J Clin Nutr.* 2009 May; 89 (5): 1, 299-1, 306. Epub 2009 Apr 1. PMID: 19339405; PMCID: PMC2676995.
2. Dhingra R, Sullivan L, Jacques PF, Wang TJ, Fox CS, Meigs JB, D'Agostino RB, Gaziano JM, Vasan RS. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation.* 2007 Jul 31; 116 (5): 480-488. Epub 2007 Jul 23. Erratum in: *Circulation*. 2007 Dec 4; 116 (23): e557. PMID: 17646581.

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3. Palmer JR, Boggs DA, Krishnan S, Hu FB, Singer M, Rosenberg L. Sugar-sweetened beverages and incidence of type 2 diabetes mellitus in African American women. *Arch Intern Med.* 2008 Jul 28; 168 (14): 1, 487-1, 492. PMID: 18663160; PMCID: PMC2708080.

Excluded articles

Article	Reason for Exclusion
Babey SH, Jones M, Yu H, Goldstein H. Bubbling over: soda consumption and its link to obesity in California. *Policy Brief UCLA Cent Health Policy Res*. 2009 Sep; (PB2009-5): 1-8. PMID: 19768858.	Article is policy brief.
Barkeling B, Andersson I, Lindroos AK, Birkhed D, Rössner S. Intake of sweet foods and counts of cariogenic microorganisms in obese and normal-weight women. *Eur J Clin Nutr.* 2001 Oct; 55 (10): 850-855. PMID: 11593346.	Study design is cross-sectional.
Barkeling B, Linné Y, Lindroos AK, Birkhed D, Rooth P, Rössner S. Intake of sweet foods and counts of cariogenic microorganisms in relation to body mass index and psychometric variables in women. *Int J Obes Relat Metab Disord.* 2002 Sep; 26(9): 1, 239-1, 244. PMID: 12187402.	Study design is cross-sectional.
Barquera S, Hernandez-Barrera L, Tolentino ML, Espinosa J, Ng SW, Rivera JA, Popkin BM. Energy intake from beverages is increasing among Mexican adolescents and adults. *J Nutr*. 2008 Dec; 138(12): 2, 454-2, 461. PMID: 19022972.	Does not include energy intake or body weight in analyses.
Bergen D, Yeh MC. Effects of energy-content labels and motivational posters on sales of sugar-sweetened beverages: Stimulating sales of diet drinks among adults study. *J Am Diet Assoc*. 2006 Nov; 106(11): 1, 866-1, 869. PMID: 17081839.	Does not answer question: Examines the impact of labels and posters on beverage sales.
Bes-Rastrollo M, Sánchez-Villegas A, Gómez-Gracia E, Martínez JA, Pajares RM, Martínez-González MA. Predictors of weight gain in a Mediterranean cohort: The Seguimiento Universidad de Navarra Study 1. *Am J Clin Nutr.* 2006 Feb; 83 (2): 362-370; quiz 394-395. PMID: 16469996.	Included in Malik (2006), Vartanian (2007), and Gibson (2008) systematic reviews.

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Bleich SN, Wang YC, Wang Y, Gortmaker SL. Increasing consumption of sugar-sweetened beverages among US adults: 1988-1994 to 1999-2004. *Am J Clin Nutr*. 2009 Jan; 89(1): 372-381. Epub 2008 Dec 3. PMID: 19056548.	Does not include energy intake or body weight in analyses.
Bowman SA, Vinyard BT. Fast food consumption of US adults: Impact on energy and nutrient intakes and overweight status. *J Am Coll Nutr.* 2004 Apr; 23(2): 163-168. PMID: 15047683.	Does not include the consumption of added sugars in analyses.
Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr.* 2004 Apr; 79 (4): 537-543. Review. Erratum in: *Am J Clin Nutr.* 2004 Oct; 80(4): 1, 090. PMID: 15051594.	Article is a commentary.
Brown CM, Dulloo AG, Montani JP. Sugary drinks in the pathogenesis of obesity and cardiovascular diseases. *Int J Obes* (Lond). 2008 Dec; 32 Suppl 6: S28-S34. Review. PMID: 19079277.	Study design is narrative review.
Chacko E, McDuff I, Jackson R. Replacing sugar-based soft drinks with sugar-free alternatives could slow the progress of the obesity epidemic: Have your Coke and drink it too. *N Z Med J*. 2003 Oct 24; 116(1, 184): U649. PMID: 14583807.	Article is a commentary.
Charlton KE, Kolbe-Alexander TL, Nel JH. Micronutrient dilution associated with added sugar intake in elderly black South African women. *Eur J Clin Nutr*. 2005 Sep; 59(9): 1, 030-1, 042. PMID: 16015273.	Study population not from a developed country as defined by the Human Development Index (2009).
Claesson AL, Holm G, Ernersson A, Lindström T, Nystrom FH. Two weeks of overfeeding with candy, but not peanuts, increases insulin levels and body weight. *Scand J Clin Lab Invest.* 2009; 69 (5): 598-605. PMID: 19396658.	Does not include sugar-sweetened beverages in analyses.
Crowe TC, Fontaine HL, Gibbons CJ, Cameron-Smith D, Swinburn BA. Energy density of foods and beverages in the Australian food supply: Influence of macronutrients and comparison to dietary intake. *Eur J Clin Nutr.* 2004 Nov; 58 (11): 1, 485-1, 491. PMID: 15173855.	Does not include energy intake or body weight in analyses.

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Dennis EA, Flack KD, Davy BM. Beverage consumption and adult weight management: A review. *Eat Behav.* 2009 Dec; 10(4): 237-246. Epub 2009 Jul 16. Review. PMID: 19778754.	Study design is narrative review.
Duffey KJ, Popkin BM. High-fructose corn syrup: Is this what's for dinner? *Am J Clin Nutr.* 2008 Dec; 88 (6): 1, 722S-1, 732S. PubMed PMID: 19064537; PubMed Central PMCID: PMC2746720.	Does not include energy intake or body weight in analyses.
Epstein LH, Gordy CC, Raynor HA, Beddome M, Kilanowski CK, Paluch R. Increasing fruit and vegetable intake and decreasing fat and sugar intake in families at risk for childhood obesity. *Obes Res.* 2001 Mar; 9 (3): 171-178. PMID: 11323442.	Does not answer question: examined behavioral weight-control programs.
Forshee RA, Storey ML, Allison DB, Glinsmann WH, Hein GL, Lineback DR, Miller SA, Nicklas TA, Weaver GA, White JS. A critical examination of the evidence relating high fructose corn syrup and weight gain. *Crit Rev Food Sci Nutr.* 2007; 47 (6): 561-582. Review. PMID: 17653981.	Study design is narrative review.
Fowler SP, Williams K, Resendez RG, Hunt KJ, Hazuda HP, Stern MP. Fueling the obesity epidemic? Artificially sweetened beverage use and long-term weight gain. *Obesity* (Silver Spring). 2008 Aug; 16(8): 1, 894-1, 900. Epub 2008 Jun 5. PMID: 18535548.	Does not include sugar-sweetened beverages in analyses.
Frazier CR, Mason P, Zhuang X, Beeler JA. Sucrose exposure in early life alters adult motivation and weight gain. *PLoS One*. 2008 Sep 17; 3(9): e3, 221. PMID: 18797507; PMCID: PMC2529404.	Study tested animals.
Gatenby SJ, Aaron JI, Jack VA, Mela DJ. Extended use of foods modified in fat and sugar content: nutritional implications in a free-living female population. *Am J Clin Nutr.* 1997 Jun; 65 (6): 1, 867-1, 873. PMID: 9174485.	Does not answer question: examined reduced-sugar and reduced-fat products.
Gibson SA. Are high-fat, high-sugar foods and diets conducive to obesity? *Int J Food Sci Nutr*. 1996 Sep; 47(5): 405-415. PMID: 8889626.	Study design is cross-sectional.

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Gibson SA. Dietary sugars intake and micronutrient adequacy: A systematic review of the evidence. *Nutr Res Rev.* 2007 Dec; 20(2): 121-131. PMID: 19079865.	Does not include energy intake or body weight in analyses.
Guerrero RT, Paulino YC, Novotny R, Murphy SP. Diet and obesity among Chamorro and Filipino adults on Guam. *Asia Pac J Clin Nutr.* 2008; 17(2): 216-222. PMID: 18586639; PMCID: PMC2762033.	Study population not from a developed country.
Hudson SM, Dixon JB, O'Brien PE. Sweet eating is not a predictor of outcome after Lap-Band placement. Can we finally bury the myth? *Obes Surg.* 2002 Dec; 12(6): 789-794. PMID: 12568183.	Participants had Lap-Band surgery.
Huffman L, West DS. Readiness to change sugar sweetened beverage intake among college students. *Eat Behav.* 2007 Jan; 8 (1): 10-14. Epub 2006 May 30. PMID: 17174846.	Does not include energy intake or body weight in analyses.
Joyce T, McCarthy SN, Gibney MJ. Relationship between energy from added sugars and frequency of added sugars intake in Irish children, teenagers and adults. *Br J Nutr*. 2008 May; 99 (5): 1, 117-1, 126. Epub 2007 Dec 21. PMID: 18096092.	Does not include energy intake or body weight in analyses.
Julis RA, Mattes RD. Influence of sweetened chewing gum on appetite, meal patterning and energy intake. *Appetite*. 2007 Mar; 48(2): 167-175. Epub 2006 Oct 13. PMID: 17050036.	Does not include sugar-sweetened beverages in analyses.
Kasim-Karakas SE, Almario RU, Cunningham W. Effects of protein versus simple sugar intake on weight loss in polycystic ovary syndrome (according to the National Institutes of Health criteria). *Fertil Steril.* 2009 Jul; 92(1): 262-270. Epub 2008 Aug 8. PubMed PMID: 18691705.	Participants diagnosed with polycystic ovary syndrome.
Krahn D, Grossman J, Henk H, Mussey M, Crosby R, Gosnell B. Sweet intake, sweet-liking, urges to eat and weight change: Relationship to alcohol dependence and abstinence. *Addict Behav*. 2006 Apr; 31 (4): 622-631. Epub 2005 Jun 29. PMID: 15990241.	Participants diagnosed with alcohol dependence.

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Kvaavik E, Andersen LF, Klepp KI. The stability of soft drinks intake from adolescence to adult age and the association between long-term consumption of soft drinks and lifestyle factors and body weight. *Public Health Nutr.* 2005 Apr; 8(2): 149-157. PMID: 15877908.	Included in Malik (2006), Gibson (2008), and Vartanian (2007) systematic reviews.
Leth T, Jensen U, Fagt S, Andersen R. Estimated intake of intense sweeteners from non-alcoholic beverages in Denmark, 2005. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess.* 2008 Jun; 25 (6): 662-668. PMID: 18484294.	Does not include sugar-sweetened beverages or energy intake/body weight in analyses.
Lewis CJ, Park YK, Dexter PB, Yetley EA. Nutrient intakes and body weights of persons consuming high and moderate levels of added sugars. *J Am Diet Assoc.* 1992 Jun; 92 (6): 708-713. PMID: 1607567.	Study design is cross-sectional.
Liebman M, Pelican S, Moore SA, Holmes B, Wardlaw MK, Melcher LM, Liddil AC, Paul LC, Dunnagan T, Haynes GW. Dietary intake, eating behavior, and physical activity-related determinants of high body mass index in rural communities in Wyoming, Montana and Idaho. *Int J Obes Relat Metab Disord*. 2003 Jun; 27 (6): 684-692. PMID: 12833112.	Included in Malik (2006), Vartanian (2007), and Gibson (2008) systematic reviews.
Livesey G, Taylor R. Fructose consumption and consequences for glycation, plasma triacylglycerol, and body weight: Meta-analyses and meta-regression models of intervention studies. *Am J Clin Nutr.* 2008 Nov; 88 (5): 1, 419-1, 437. PMID: 18996880.	Does not answer question: examined relationship between fructose consumption and health outcomes.
Macdiarmid JI, Vail A, Cade JE, Blundell JE. The sugar-fat relationship revisited: Differences in consumption between men and women of varying BMI. *Int J Obes Relat Metab Disord.* 1998 Nov; 22(11): 1, 053-1, 061. PMID: 9822942.	Study design is cross-sectional.
Melanson KJ, Zukley L, Lowndes J, Nguyen V, Angelopoulos TJ, Rippe JM. Effects of high-fructose corn syrup and sucrose consumption on circulating glucose, insulin, leptin, and ghrelin and on appetite in normal-weight women. *Nutrition.* 2007 Feb; 23 (2): 103-112. PMID: 17234503.	Does not include body weight as an outcome.

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Miller WC, Niederpruem MG, Wallace JP, Lindeman AK. Dietary fat, sugar and fiber predict body fat content. *J Am Diet Assoc.* 1994 Jun; 94(6): 612-615. PMID: 8195547.	Study design is cross-sectional.
Parnell W, Wilson N, Alexander D, Wohlers M, Williden M, Mann J, Gray A. Exploring the relationship between sugars and obesity. *Public Health Nutr.* 2008 Aug; 11 (8): 860-866. Epub 2007 Sep 21. PMID: 17888201.	Study design is cross-sectional.
Pivonka EE, Grunewald KK. Aspartame- or sugar-sweetened beverages: Effects on mood in young women. *J Am Diet Assoc*. 1990 Feb; 90 (2): 250-254. PMID: 2303661.	Does not include body weight as an outcome.
Promdee L, Trakulthong J, Kangwantrakul W. Sucrose consumption in Thai undergraduate students. *Asia Pac J Clin Nutr.* 2007; 16 Suppl 1: 22-26. PMID: 17392071.	Study population not from a developed country as defined by the Human Development Index (2009).
Quatromoni PA, Pencina M, Cobain MR, Jacques PF, D'Agostino RB. Dietary quality predicts adult weight gain: Findings from the Framingham Offspring Study. *Obesity* (Silver Spring). 2006 Aug; 14 (8): 1, 383-1, 391. PMID: 16988081.	Does not answer question: Examined diet quality and weight gain.
Quílez J, Bulló M, Salas-Salvadó J. Improved postprandial response and feeling of satiety after consumption of low-calorie muffins with maltitol and high-amylose corn starch. *J Food Sci.* 2007 Aug; 72 (6): S407-S411. PMID: 17995698.	Does not answer question: Did not examine relationship between sugar-sweetened beverages and body weight.
Raben A, Vasilaras TH, Møller AC, Astrup A. Sucrose compared with artificial sweeteners: Different effects on ad libitum food intake and body weight after 10 weeks of supplementation in overweight subjects. *Am J Clin Nutr*. 2002 Oct; 76(4): 721-729. PMID: 12324283.	Included in Malik (2006), Gibson (2008), Ruxton (2010) and Vartanian (2007) systematic reviews.
Rehm CD, Matte TD, Van Wye G, Young C, Frieden TR. Demographic and behavioral factors associated with daily sugar-sweetened soda consumption in New York City adults. *J Urban Health.* 2008 May; 85 (3): 375-385. Epub 2008 Mar 18. PMID: 18347992; PMCID: PMC2329746.	Study design is cross-sectional.

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Rennie KL, Livingstone MB. Associations between dietary added sugar intake and micronutrient intake: A systematic review. *Br J Nutr.* 2007 May; 97(5): 832-841. Review. PMID: 17408523.	Does not include energy intake or body weight in analyses.
Reyna NY, Cano C, Bermúdez VJ, Medina MT, Souki AJ, Ambard M, Nuñez M, Ferrer MA, Inglett GE. Sweeteners and beta-glucans improve metabolic and anthropometrics variables in well controlled type 2 diabetic patients. *Am J Ther.* 2003 Nov-Dec; 10 (6): 438-443. PMID: 14624282.	Participants diagnosed with type 2 diabetes.
Ritchie LD, Spector P, Stevens MJ, Schmidt MM, Schreiber GB, Striegel-Moore RH, Wang MC, Crawford PB. Dietary patterns in adolescence are related to adiposity in young adulthood in black and white females. *J Nutr.* 2007 Feb; 137 (2): 399-406. PMID: 17237318.	Does not include added sugars intake, specifically, in analyses. Examined dietary patterns.
Rodearmel SJ, Wyatt HR, Stroebele N, Smith SM, Ogden LG, Hill JO. Small changes in dietary sugar and physical activity as an approach to preventing excessive weight gain: The America on the Move family study. *Pediatrics*. 2007 Oct; 120 (4): e869-e879. PMID: 17908743.	Does not answer question: Examines an intervention program (America on the Move) and does not directly assess the relationship between added sugars on body weight.
Rush E, Schulz S, Obolonkin V, Simmons D, Plank L. Are energy drinks contributing to the obesity epidemic? *Asia Pac J Clin Nutr.* 2006; 15(2): 242-244. PMID: 16672210.	Does not include energy intake or body weight as an outcome.
Schiffman SS, Graham BG, Sattely-Miller EA, Peterson-Dancy M. Elevated and sustained desire for sweet taste in African-Americans: A potential factor in the development of obesity. *Nutrition.* 2000 Oct; 16 (10): 886-893. PMID: 11054593.	Does not answer question: Examines oral habituation to sweet taste.
Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, Hu FB. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA.* 2004 Aug 25; 292 (8): 927-934. PMID: 15328324.	Included in Malik (2006), Gibson (2008), and Vartanian (2007) systematic reviews.

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Shubair MM, McColl RS, Hanning RM. Mediterranean dietary components and body mass index in adults: The peel nutrition and heart health survey. *Chronic Dis Can.* 2005 Spring-Summer; 26 (2-3): 43-51. PMID: 16251009.	Does not include added sugars intake, specifically, in analyses. Examined dietary patterns.
Sørensen LB, Raben A, Stender S, Astrup A. Effect of sucrose on inflammatory markers in overweight humans. *Am J Clin Nutr*. 2005 Aug; 82(2): 421-427. PMID: 16087988.	Included in Malik (2006).
Stanhope KL, Griffen SC, Bair BR, Swarbrick MM, Keim NL, Havel PJ. 24-hour endocrine and metabolic profiles following consumption of high-fructose corn syrup-, sucrose-, fructose- and glucose-sweetened beverages with meals. *Am J Clin Nutr*. 2008 May; 87 (5): 1, 194-1, 203. PMID: 18469239.	Does not answer question: examines postprandial hormone response to various beverages.
Sun SZ, Empie MW. Lack of findings for the association between obesity risk and usual sugar-sweetened beverage consumption in adults: A primary analysis of databases of CSFII-1989-1991, CSFII-1994-1998, NHANES III and combined NHANES 1999-2002. *Food Chem Toxicol.* 2007 Aug; 45 (8): 1, 523-1, 536. Epub 2007 Feb 17. PMID: 17383789.	Included in Gibson (2008) systematic review.
Tordoff MG, Alleva AM. Effect of drinking soda sweetened with aspartame or high-fructose corn syrup on food intake and body weight. *Am J Clin Nutr*. 1990 Jun; 51 (6): 963-969. PMID: 2349932.	Included in Malik (2006) and Vartanian (2007) systematic reviews.
Vågstrand K, Karin Lindroos A, Birkhed D, Linné Y. Associations between salivary bacteria and reported sugar intake and their relationship with body mass index in women and their adolescent children. *Public Health Nutr.* 2008 Apr; 11(4): 341-348. Epub 2007 Jul 3. PMID: 17605840.	Study design is cross-sectional.
Vos MB, Kimmons JE, Gillespie C, Welsh J, Blanck HM. Dietary fructose consumption among US children and adults: The Third National Health and Nutrition Examination Survey. *Medscape J Med.* 2008 Jul 9; 10 (7): 160. PMID: 18769702; PMCID: PMC2525476.	Does not include energy intake or body weight in analyses.

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Wansink B, Painter JE, Lee YK. The office candy dish: Proximity's influence on estimated and actual consumption. *Int J Obes* (Lond). 2006 May; 30 (5): 871-875. PMID: 16418755.	Does not answer question: Does not examine relationship between added sugars and body weight.
West DS, Bursac Z, Quimby D, Prewitt TE, Spatz T, Nash C, Mays G, Eddings K. Self-reported sugar-sweetened beverage intake among college students. *Obesity* (Silver Spring). 2006 Oct; 14 (10): 1, 825-1, 831. PMID: 17062813.	Does not include energy intake or body weight in analyses.
West JA, de Looy AE. Weight loss in overweight subjects following low-sucrose or sucrose-containing diets. *Int J Obes Relat Metab Disord.* 2001 Aug; 25 (8): 1, 122-1, 128. PMID: 11477496.	Dropout rate higher than inclusion criteria.
White JS. Misconceptions about high-fructose corn syrup: Is it uniquely responsible for obesity, reactive dicarbonyl compounds, and advanced glycation endproducts? *J Nutr.* 2009 Jun; 139 (6): 1, 219S-1, 227S. Epub 2009 Apr 22. PMID: 19386820.	Study design is narrative review.
Wolff E, Dansinger ML. Soft drinks and weight gain: How strong is the link? Meds*cape J Med.* 2008; 10 (8): 189. Epub 2008 Aug 12. Review. PMID: 18924641; PMCID: PMC2562148.	Study design is narrative review.
Yamada M, Murakami K, Sasaki S, Takahashi Y, Okubo H. Soft drink intake is associated with diet quality even among young Japanese women with low soft drink intake. *J Am Diet Assoc.* 2008 Dec; 108 (12): 1, 997-2, 004. PMID: 19027402.	Does not include energy intake or body weight as an outcome.
Ziemer DC, Berkowitz KJ, Panayioto RM, El-Kebbi IM, Musey VC, Anderson LA, Wanko NS, Fowke ML, Brazier CW, Dunbar VG, Slocum W, Bacha GM, Gallina DL, Cook CB, Phillips LS. A simple meal plan emphasizing healthy food choices is as effective as an exchange-based meal plan for urban African Americans with type 2 diabetes. *Diabetes Care.* 2003 Jun; 26 (6): 1, 719-1, 724. PMID: 12766100.	Participants diagnosed with type 2 diabetes.

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CHAPTER 8. SUGAR-SWEETENED BEVERAGES AND NON-CALORIC SWEETENERS – BODY WEIGHT

IN ADULTS, WHAT IS THE ASSOCIATION BETWEEN INTAKE OF SUGAR-SWEETENED BEVERAGES AND BODY WEIGHT?

Conclusion statement

A moderate body of epidemiologic evidence suggests that greater consumption of sugar-sweetened beverages is associated with increased body weight in adults.

A moderate body of evidence suggests that under isocaloric controlled conditions, added sugars, including sugar-sweetened beverages, are no more likely to cause weight gain than any other source of energy.

Grade

Moderate

Evidence summary overview

The Committee addressed this question by reviewing four systematic reviews (Gibson, 2008; Malik, 2006; Ruxton, 2010; Vartanian; 2007), four randomized controlled trials (RCTs) (Raben, 1997; Reid, 2007; Stanhope, 2009; Surwit, 1997) and three prospective observational studies (Chen, 2009; Dhingra, 2007; Palmer, 2008).

The studies included in the systematic reviews did not use consistent methods to evaluate added sugars. Typical search terms were soft drinks, sugar-sweetened beverages (SSB), liquid sugar and soda. The systematic reviews used different criteria to review the literature and three reviews (Gibson, 2008; Malik, 2006; Vartanian, 2007) included cross-sectional studies, as there were limited prospective studies on the topic. Malik et al, (2006), attempted a meta-analysis, but the degree of heterogeneity among study designs made a more qualitative assessment necessary. Vartanian et al, (2007) attempted to separate out the effects in different study designs. Studies with experimental designs (five studies) showed no association with added sugar intake for body weight for adults. Significant relationships were found in longitudinal studies (three studies) for a relationship between added sugar intake and body weight, although the effect size was small. Similarly, Malik et al, (2006) concluded that epidemiologic and experimental data indicated a greater consumption of SSB is associated with weight gain and obesity. In contrast, Gibson (2008) reviewed six longitudinal and one intervention study with adults and concluded that SSB are a source of energy, but that little evidence showed that they are any more obesogenic than any other source of energy. In a recent review, Ruxton et al, (2010) concluded that recent evidence does not suggest a positive association between body mass index (BMI) and sugar intake. However, some studies, specifically on sweetened beverages, highlight a potential concern in the relation to obesity risk. The methods used for these systematic reviews varied and may explain the discrepancies in results.

The four trials included in the Nutrition Evidence Library (NEL) systematic review varied greatly in design. In general, when calorie intake was controlled, there were no differences in weight gain when participants consumed diets with a higher percent of calories from added sugars, compared to diets with a lower percent of intake from added sugars (Raben, 1997; Stanhope, 2009; Surwit, 1997).

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When energy intake was not controlled, Reid et al, (2007) found a non-significant (NS) trend for weight gain among normal-weight women consuming four regular soft drinks per day, compared to those consuming diet soft drinks. In a trial by Stanhope et al, (2009) that included 25% of energy from beverages sweetened with glucose or fructose, weight gain was observed when participants consumed self-selected diets in an outpatient setting.

The Committee also reviewed three prospective studies. Lower consumption of soft drinks was linked to weight loss in the PREMIER study (Chen, 2009). A reduction in SSB intake of one serving per day was associated with a weight loss of approximately 0.5kg at six months and 18 months, and a significant dose-response trend between change in body weight and change in SSB intake also was observed. Over a mean follow-up of four years in the Framingham Heart Study (Dhingra, 2007), consumption of one or more soft drinks per day was associated with increased odds of developing obesity and increased waist circumference (WC) compared to drinking none.

Palmer et al, (2008) included sugar-sweetened soft drinks and fruit drinks in their analysis of type 2 diabetes (T2D) in a prospective cohort study of African-American women. Subjects gained weight during the study, but the lowest mean weight gain occurred among those who decreased their consumption of soft drinks.

Thus, there are mixed results on this topic. Randomized controlled trials report that added sugars are not different from other calories in increasing energy intake or body weight. Prospective studies report some relationship with SSB and weight gain, but it is not possible to determine if these relationships are merely linked to additional calories, as opposed to added sugars per se. The systematic reviews in this area are also inconsistent, probably based on different measures used to determine added sugars intake or intake of SSB.

Evidence summary paragraphs

Gibson, 2008 (neutral quality), a systematic review, examined the evidence from epidemiological studies and interventions regarding the association between sugar-containing drinks and body weight and obesity. Database searches up to July 2008 of Medline, Cochrane Reviews and Google scholar were conducted to examine the association of sugar-sweetened soft drinks (SSD) with body weight, BMI or adiposity in adults or children. Search terms were ‘soft drinks’/‘sugar-sweetened beverages’/‘-soda’/‘liquid sugars’ with ‘weight’/‘body weight’/‘obesity’/‘adiposity’. In addition, a hand search of cross-references was conducted. Sugar-sweetened soft drinks were defined as all cold beverages containing added sugars, whether carbonated or still, including soda pop and fruit squash and drinks with a fruit component less than 100% pure fruit juice; hot beverages and diet drinks were not included. Forty-four original studies (23 cross-sectional, 17 prospective, four intervention) were included. Eleven of these studies were conducted with adults. In addition, six review articles were considered.

For the 11 studies with adults:

- Three cross-sectional studies showed a significant positive association between SSD and obesity; one cross-sectional study showed no association between SSD and BMI
- Three longitudinal studies showed a positive association between SSD and BMI in at least one subgroup; one longitudinal study showed a positive, but non-

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significant, association with BMI; two longitudinal studies showed no association with BMI
- One intervention study showed a positive association with body weight.

Most studies suggest that the effect of SSD is small except in susceptible individuals or at high levels of intake. Of the six reviews, two concluded that the evidence was strong, one that an association was probable, while three described it as inconclusive, equivocal or near zero. Gibson concluded that SSD are by nature a source of energy but there is little evidence from epidemiological studies that they are more obesogenic than any other source of energy. Further, the author noted that despite the large number of studies on this topic, the inconsistencies of definition, design, statistical treatment and interpretation make it difficult to draw definitive conclusions as to whether SSB are significantly implicated in weight gain.

Malik et al, 2006 (neutral quality), a systematic review, examined cross-sectional, prospective cohort, and experimental studies to determine whether an association exists between intake of SSB and weight gain and obesity. English-language MEDLINE publications from 1966 through May 2005 examining the relation between SSB and the risk of weight gain, obesity or both were examined. Key words such as “soda,” “soda pop” and “sugar-sweetened beverage” hedged with “weight gain,” “overweight” and “obesity” were used in the primary search strategy, as well as in a subsequent search using MeSH terms. Additional published reports were obtained by cross-matching references of selected articles. Sugar-sweetened beverages included soft drinks, soda, fruitades, fruit drinks, sports drinks, sweetened iced tea, squashes and lemonade. Thirty original studies (15 cross-sectional, 10 prospective and five experimental), including nine adult comparisons, were included in the review. A meta-analysis was attempted, but the degree of heterogeneity among study designs, particularly with respect to the age groups of participants and to outcome assessment, was prohibitive and therefore, a more qualitative assessment was used.

For the nine comparisons with adults:

- Two cross-sectional analyses showed a positive association
- Two prospective cohorts showed a positive association, one showed a non-significant positive association and one found no association
- Three experimental studies showed a positive association.

Findings from large cross-sectional studies, in conjunction with those from well-powered prospective cohort studies with long periods of follow-up, show a positive association between greater intakes of SSB and weight gain and obesity in both children and adults. Findings from short-term feeding trials in adults also support an induction of positive energy balance and weight gain by intake of sugar-sweetened sodas, but these trials are few. The authors concluded that epidemiologic and experimental evidence indicates that a greater consumption of SSB is associated with weight gain and obesity. Further, although more research is needed, sufficient evidence exists for public health strategies to discourage consumption of sugary drinks as part of a healthy lifestyle.

Ruxton et al, 2010 (neutral quality), a systematic review, considered whether current intakes of added sugars are harmful to health and evaluated published literature from 1995-2006. The Cochrane Library and MEDLINE were searched for epidemiologic studies, clinical trials, meta-analyses and systematic reviews. The search terms were “sugar (sucrose)” and various outcomes including “obesity” and “body weight.” The

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search was limited to English-language, human studies of sugar and sugar-containing foods and beverages. Dates of publication were restricted to January 1995 to March 2006. This process was supplemented with a hand-search and a check of reference lists from pertinent reviews. All studies were ranked separately by two reviewers with the higher ranking prevailing in the case of disagreement. Eight studies were included in the review of SSB and obesity. Of these, three were considered primary studies and were included in the review, while five were tertiary and not considered in conclusions. The authors concluded that results from high quality obesity studies did not suggest a positive association between BMI and sugar intake. However, some studies, specifically on sweetened beverages, highlighted a potential concern in relation to obesity risk, although these were limited by methodological issues.

Vartanian et al, 2007 (positive quality), a systematic review and meta-analysis, examined the association between soft drink consumption and nutrition and health outcomes. MEDLINE and PsycINFO were searched to find articles that examined the association between soft drink consumption and nutrition and health outcomes. Key words used included “soft drink,” “soda” and “sweetened beverage” along with four primary outcomes (energy intake, body weight, milk intake and calcium intake) and two secondary outcomes (nutrition and health). Additional articles were identified by searching each article’s reference section and the Web of Science database. Finally, authors were contacted to request unpublished or in-press work. Eighty-eight studies were included in the meta-analysis; approximately 30 comparisons were available for soft drinks and energy intake or body weight in adults. Analysis of primary outcomes revealed a significant degree of heterogeneity of effect sizes, and thus, studies were separated according to research design.

Average body weight effect sizes for adults:

- Overall: r=0.11 (95% CI: 0.10, 0.12; P<0.0056; N=11)
- Cross-sectional: r=0.06 (95% CI: 0.05, 0.08; P<0.0056; N=5)
- Longitudinal: r=0.14 (95% CI: 0.13, 0.16; P<0.0056; N=3)
- Experimental (long): r=0.15 (95% CI: 0.05, 0.24; NS; N=5).

The authors concluded that they found clear associations of soft drink intake with increased energy intake and body weight. Further, they stated that recommendations to reduce population soft drink consumption are strongly supported by the available science.

Chen et al, 2009 (positive quality), a prospective cohort study conducted in the US, examined how changes in beverage consumption affect weight change among adults. Participants were 810 adults (62% female; age 50.0±8.9 years; BMI=33.1±5.8kg/m^2) from the PREMIER study. Dietary intake was estimated by the average of two multiple pass 24-hour recalls conducted at baseline, six and 18 months to determine changes in volume, kcal intake and percentage of calories from beverages both overall and from seven categories (SSB; diet drinks; milk; 100% juices; coffee and tea with sugar; coffee and tea without sugar or with artificial sweeteners; and alcoholic beverages). Weight and height were measured at each time point. Of the individual beverages, only intake of SSB was significantly associated with weight change. A reduction in SSB intake of one serving per day was associated with a weight loss of 0.49kg (95% CI: 0.11, 0.82; P=0.006) at six months and of 0.65kg (95% CI: 0.22, 1.09; P=0.003) at 18 months. Participants were divided into tertiles based on their six- or 18-month change in consumption of SSBs. At both six and 18 months, participants in the first

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tertile had a greater mean weight loss than did those in the second (six-month change: 0.7kg; P=0.006; 18-month change: 1.6 kg; P<0.001) and third (six-month change: 2.4kg; P<0.001; 18-month change: 3.6kg; P<0.001) tertiles. A significant dose-response trend between change in body weight and change in SSB intake was observed at both six months (P<0.001) and 18 months (P<0.001). The authors concluded that their data support recommendations to limit liquid calorie intake among adults and to reduce SSB consumption as a means to accomplish weight loss or avoid excess weight gain.

Dhingra et al, 2007 (positive-quality) related the incidence of metabolic syndrome and its components to soft drink consumption in participants in the Framingham Heart Study (6,039 person-observations, 3,470 in women; mean age 52.9 years). Information on daily consumption of soft drinks was collected via a physician-administered questionnaire at each study visit from the fourth (1987-1991) through the sixth (1995-1998) examination cycles. Participants reported the average number of 12-ounce servings of soft drinks consumed per day in the year preceding the examination. The examination questionnaire did not elicit information regarding consumption of regular vs. diet soft drinks; however, such information was available from the self-administered food frequency questionnaire (FFQ) completed by participants at the fifth (1992-1995) and sixth examination cycles. Individuals were categorized as consuming less than one, one, at least one or at least two soft drinks per day. Analyses on components of metabolic syndrome were done with soft drink intake, including regular and diet. Anthropometrics were measured by study personnel. Over a mean follow-up of four years, consumption of at least one soft drink (including regular and diet) per day was associated with increased odds of developing obesity (multivariable adjusted OR=1.31; 95% CI: 1.02, 1.68) and increased waist circumference (multivariable adjusted OR=1.30; 95% CI: 1.09 to 1.56) compared to drinking none. The authors concluded that, in middle-aged adults, soft drink consumption is associated with a higher prevalence and incidence of multiple metabolic risk factors.

Palmer et al, 2008 (positive-quality) examined the association between consumption of SSB, weight gain and incidence of type 2 diabetes (T2D) in a prospective cohort study of 43,960 African American women (age 21 to 69 years) in the US. Food and beverage intake were obtained through a modified, 68-item Block FFQ. Three items were targeted for this article: “Regular soft drinks (not diet soda),” “orange juice or grapefruit juice” and “other fruit juices, fortified fruit drinks, Kool-Aid”. Data from questionnaires were used to assess the relation of changes in consumption patterns to changes in weight for the six years from 1995 to 2001. Participants were classified into five mutually-exclusive categories: Those who consumed no more than one drink per week in 1995 and had not changed their intake; those who consumed no more than one drink per week in 1995 and increased to at least one drinks per day; those who consumed at least one drink per day in 1995 and did not change; those who consumed at least one per day in 1995 and reduced their intake to no more than one drink per week in 2001; and those who did not fit into any of the previous categories. Height and weight were self-reported. The majority of participants gained weight during the six-year interval. In multivariate models that included terms for change in other risk factors, the greatest weight gain was seen in those who increased their consumption of soft drinks (mean weight gain, 6.8kg). The lowest mean weight gain (4.1kg) occurred among those who decreased their consumption of soft drinks (P<0.001 for the comparison of those with the greatest and lowest mean weight gains). Weight loss

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in the six-year interval was most common (24%) among women who decreased their intake of SSD and least common (16%) among those who increased consumption or were already consuming one or more soft drinks per day and did not cut back. The association between changes in consumption and weight gain was weaker for sweetened fruit drinks. The authors concluded that reducing consumption of soft drinks is a concrete step that women may find easier to achieve than other approaches to weight loss.

Reid et al, 2007 (positive quality) compared the effects of supplementary soft drinks added to the diet over four weeks on dietary intake, mood and BMI in normal-weight women (N=133; age 20 to 55 years; BMI 17 to 24.9kg/m^2). The study took place over five weeks including one week of baseline data collection followed by four weeks of drink supplementation. Drinks contained either sucrose or aspartame. Participants were either informed that they were receiving sugary drinks or 'diet' drinks, meaning that half were correctly informed about the drink content and half misinformed. In addition, participants were recruited according to whether they were or were not currently watching their weight. This resulted in a 2 x 2 x 2 design (sucrose vs. aspartame, drinks labeled sugar vs. labeled aspartame or diet, watcher vs. non-watcher). Subjects received four 250ml bottles of drink per day in uniform bottles with the labeling manipulated. Each week of the four-week intervention, participants were given one week's supply of 28 test drinks and were instructed to drink the agreed amount each day at the specified times (11.00, 14.00, 18.00 and 20.00 hours). Sucrose supplements provided 1,800kJ per day and aspartame supplements provided 67kJ per day. Food intake was measured with a seven-day diary during each week of the five-week study. Height and weight were measured by study personnel. There were no significant effects of restraint (watching/non-watching) status on any of the experimental analyses. For this reason, results were presented without 'watching' as a factor. For those consuming the sucrose drink, energy intake was higher at week one (t (67 df)=6.44; $P<0.001$) and at week four than at baseline (t (67 df)=3.82; $P<0.001$) and week one and week four did not differ (t (67 df)=1.81; $P=0.075$). Women in the sucrose group consumed about 800kJ more energy per day; the supplements contained 1,800kJ. Mean body weight at baseline was 61.35±8.37kg. There was a marginal effect of drink on body weight ($F(10•20, 1.86)=4.509$; $P<0.05$), with more women who received the sucrose drink gaining some weight during the study and more women receiving aspartame losing weight. There was a non-significant trend for those receiving sucrose to gain weight. The authors concluded that compensation was only partial for added sucrose so were sucrose to be added to the diet, some weight gain might result in normal-weight individuals.

Stanhope et al, 2009 (neutral quality) assessed the effects of the consumption of glucose- or fructose-sweetened beverages providing 25% of energy requirements for 10 weeks among overweight and obese adults (N=32; 50% female; age 40 to 72 years; BMI 25-35kg/m^2). This was a double-blinded parallel arm study that used matched subjects and consisted of three phases:

1. A two-week inpatient baseline period during which subjects consumed an energy-balanced diet
2. An eight-week outpatient intervention period during which subjects consumed either fructose- or glucose-sweetened beverages providing 25% of daily energy requirements along with their usual ad libitum diet
3. A two-week inpatient intervention period during which subjects consumed

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fructose- or glucose-sweetened beverages providing 25% of daily energy requirements with an energy-balanced diet.

Sugars were provided to the subjects as three daily servings of glucose- or fructose-sweetened beverages flavored with an unsweetened drink mix (Kool-Aid; Kraft). During the outpatient intervention, subjects were instructed to drink three servings per day, one with each meal and not to consume other sugar-containing beverages including fruit juice during the study protocol. Body weight was stable during the two-week inpatient periods at both the beginning and end of the study. However, during the eight-week outpatient intervention period, when the subjects consumed 25% of daily energy requirement as glucose- or fructose-sweetened beverages along with ad libitum self-selected diets, both groups exhibited similar significant increases in body weight. Percent changes in body weight after consumption of glucose- or fructose-sweetened beverages for 10 weeks were +1.8±0.5 ($P<0.01$) and +1.4±0.3 ($P<0.001$), respectively. A variety of outcomes were considered in this study. In an energy-balanced inpatient setting in which participants consumed 25% of energy as glucose- or fructose-sweetened beverages, body weight remained stable; however, when these beverages were consumed in an outpatient setting along with usual dietary intake, body weight increased.

Raben et al,1997 (neutral quality) investigated ad libitum energy intake, changes in body weight, 24-hour energy expenditure and sympathoadrenal activity when replacing dietary fat with sucrose or starch during a 14-day period. Participants were 20 healthy, normal-weight women (nine post-obese [PO] and 11 controls [C], closely matched for age, weight, height, fat mass and fat-free mass). Each subject completed three 14-day dietary periods, a sucrose-rich (sucrose), a starch-rich (starch) and a fat-rich (fat). The order of the periods differed, but subjects in the PO and C groups were 'paired' (except for two controls) so that the diet order was similar in the two groups. The dietary periods were separated by two to six weeks. Participants were supplied ad libitum amounts of the experimental diets to be consumed at home. The subjects collected the food twice a week and returned all leftovers for weighing and recording. The planned macronutrient composition of the sucrose and starch diet was similar with 59% carbohydrate (CHO), 28% fat and 13% protein, while the fat diet contributed 45-50% fat, 37-42% CHO and 13% protein. Sucrose contributed 23% energy on the sucrose diet and 2% on the starch and fat diets. Body weight was measured on days one and 15 of each treatment. On the fat, starch and sucrose diet the actual intake of CHO averaged 40.8, 59.1 and 58.6% ($P<0.0001$), of sucrose 2.2, 2.6 and 23.2% ($P<0.0001$), of fat 46.1, 28.0 and 28.6% ($P<0.0001$) and of protein 13.1, 13.4, and 13.2% ($P<0.05$), respectively. Average 14-day energy intake for all subjects was lowest on the starch diet (9.1±0.4MJ per day) compared with both the sucrose (10.3±0.4MJ per day) and fat diet (10.2±0.4MJ per day) ($P<0.05$). Compared to a change of 0.0kg, total body weight decreased on the starch diet by 0.7±0.2kg ($P<0.05$), but was unchanged on the fat (-0.3±0.3kg) and sucrose diet (0.2±0.2kg). The changes were significantly different between the starch and sucrose diets ($P<0.05$). The authors concluded that the present study showed that a starch-rich diet resulted in a significantly lower energy intake and a small but significant reduction in body weight after 14-day ad libitum intake in both previously obese and normal weight subjects; in contrast, no significant (NS) changes in either of these parameters were observed on the sucrose-rich diet.

Surwit et al, 1997 (positive quality) studied the comparative effects of high- and low-

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sucrose, low-fat, hypoenergetic diets on a variety of metabolic and behavioral indexes in a six-week weight-loss program. Participants were assigned to a high-sucrose diet (N=20; age 40.6±8.2 years; BMI 35.93±4.8kg/m^2) or low-sucrose diet (N=22; age 40.3±7.3 years; BMI). Both diets contained approximately 4,606kJ energy per day with 11% of energy as fat, 19% as protein and 71% as CHO. The high-sucrose diet contained 43% of the total daily energy intake as sucrose; the low-sucrose diet contained 4% of the total daily energy intake as sucrose. The trial was conducted as a controlled feeding study in which subjects were provided with all meals and snacks for the six-week period. Subjects also received a list of beverages and seasonings that could be consumed freely. Weekday dinners were served in a communal dining room; all other meals were precooked and packaged as “take-out meals.” Mixed-design analysis of variance showed a main effect of time ($P<0.001$), with both diet groups showing decreases in weight. Group-by-time interactions were non-significant, indicating that the groups did not differ in the magnitude of this decrease over the duration of the study, ie, there were no treatment effects. The authors concluded that a high sucrose content in a hypoenergetic, low-fat diet did not adversely affect weight loss compared to a low-sucrose diet.

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Overview table

Trials Examining Relationship between Added Sugars and Body Weight in Energy-Balanced Setting

Study	Design: Trials	Added Sugars	Comparison	Time	Support a positive relationship between added sugars and body weight in an energy-balanced setting?
Raben, 1997 Neutral Quality	Crossover case-control study with three diets (sucrose-, starch-, fat-rich) in normal weight adults	Sucrose-rich diet: 23% energy from sucrose	Starch- and fat-rich diets: Both with 2% energy from sucrose	14 days for each treatment	No
Stanhope, 2009 Neutral Quality	Parallel-arm study with glucose- or fructose-sweetened beverages including both outpatient and inpatient phases	Beverages sweetened with glucose or fructose provided 25% of energy intake		10 wk	Inpatient energy-balanced diet: No
Surwit, 1997 Positive Quality	Controlled feeding study with high vs. low sucrose weight-loss (hypoenergetic) programs	High-sucrose diet: 43% energy from sucrose	Low-sucrose diet: 4% energy from sucrose	Six weeks	No

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Systematic Reviews Examining Relationship between *Sugar-Sweetened Beverages* and Body Weight

Study	Systematic Review / Meta-Analysis	Authors Conclusion
**Gibson, 2008* Neutral Quality	Systematic review of sugar-sweetened soft drinks (SSD) and body weight, BMI or adiposity (44 original studies [six *longitudinal and one intervention study with adults*]; six review articles)	(?) SSD are a source of energy, but there is little evidence that they are more obesogenic than any other source of energy
**Malik, 2006* Neutral Quality	Systematic review of SSB and body weight, obesity or both (30 original studies [four *prospective cohorts and three intervention studies with adults*])	(+) Epidemiologic and experimental evidence indicates that a greater consumption of SSB is associated with weight gain and obesity
Ruxton, 2010 Neutral Quality	Systematic review of sugar consumption and health (eight studies in the section on SSB and obesity [three *intervention studies included in review-one with adults*])	(?) The possibility that considerable intakes of SSB contribute to obesity risk cannot be discounted
**Vartanian, 2007* Positive Quality	Meta-analysis examined the association between soft drink consumption and nutrition and health outcomes (88 original studies [three *longitudinal and five experimental studies with adults*])	(+) Clear association of soft drink intake with ↑ body weight observed

*These reviews included cross-sectional studies.

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Prospective Observational Studies Examining Relationship between *Sugar-Sweetened Beverages* and Body Weight

Study	Design: Prospective Observational	Sugar-sweetened Beverages	Comparison	Time	Support a positive relationship between SSB and weight gain?
Palmer, 2008 Positive Quality	Prospective cohort of African American women in the US examining change in soft drink intake over time	At least one soft drink per day	No more than one soft drink per day	Six years	Yes
Dhingra, 2007 Positive Quality	Prospective cohort (Framingham Heart Study) examining soft drink intake and obesity	• One soft drink per day • More than one soft drink per day • At least two soft drinks per day	Less than one soft drink per day	Four years	Yes
Chen, 2009 Positive Quality	Prospective cohort (PREMIER) examining Δs in beverage consumption and weight Δ	SSB	Diet drinks, milk, 100% juice, coffee/tea, alcoholic beverages	Six- and 18-months	Yes

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Trials Examining Relationship between *Sugar-Sweetened Beverages* and Body Weight

Study	Design: Trials	Sugar-sweetened Beverages	Comparison	Time	Support a positive relationship between SSB and weight gain?
Stanhope, 2009 Neutral Quality	Parallel-arm study with glucose- or fructose-sweetened beverages including both outpatient and inpatient phases	Beverages sweetened with glucose or fructose provided 25% of energy intake		10 weeks	Outpatient self-selected diets: Yes
Reid, 2007 Positive Quality	Parallel-arm trial with four soft drinks added to daily diet	Regular soft drink	Diet soft drink	Four weeks	No (NS trend for weight gain)

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Search plan and results

Inclusion criteria

- January 1990 to December 2009 (systematic review search updated February 2010)
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20%; preference for smaller dropout rates
- *Ages:* Adults 19 years and older
- *Populations:* Healthy, those with elevated chronic disease risk.

Exclusion criteria

- Cross-sectional studies
- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed

  ("Body Weight"[Mesh] OR "overweight"[Mesh] OR obesity[mh] OR adiposity[mh]) AND (added sugar* OR sugar based* or sugar sweetened* or HFCS or high fructose corn syrup* or corn syrup* OR candy OR “dietary sucrose"[Mesh] OR “Liquid sugars” OR Soda pop*) AND ("Energy Intake"[Mesh] OR “Total caloric consumption” OR “energy compensation” OR “dietary compensation” OR “caloric intake OR

  ("Body Weight"[Mesh] OR "overweight"[Mesh] OR obesity[mh] OR adiposity[mh]) AND (“Carbonated beverages”[mh] OR Soft drink* OR Sugar-sweetened beverage* OR Sweetened drink*)

  Updated search for systematic reviews/meta-analyses (02/03/10)

  (added sugar* OR sugar based* OR sugar sweetened* OR HFCS OR high fructose corn syrup* OR corn syrup* OR candy OR "dietary sucrose"[Mesh] OR "Liquid sugars" OR Soda pop* OR "Carbonated beverages"[mh] OR Soft drink* OR Sugar-sweetened beverage* OR Sweetened drink*) AND (systematic[sb] OR Meta-Analysis[ptyp])

Date searched: 12/23/2009, Updated 02/03/2010

Summary of articles identified to review

- Total hits from all electronic database searches: 497
- Total articles identified to review from electronic databases: 79

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- Articles identified via handsearch or other means: 1
- Number of Primary Articles Identified: 10
- Number of Review Articles Identified: 4
- Total Number of Articles Identified: 14
- Number of Articles Reviewed but Excluded: 66

Included articles (References)

In adults, what is the association between the intake of sugar-sweetened beverages and energy intake?

Systematic Reviews / Meta-Analyses:

1. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: A systematic review and meta-analysis. *Am J Public Health.* 2007 Apr; 97 (4): 667-675. Epub 2007 Feb 28. Review. PMID: 17329656; PMCID: PMC1829363.

Primary Citations:

1. Flood JE, Roe LS, Rolls BJ. The effect of increased beverage portion size on energy intake at a meal. *J Am Diet Assoc.* 2006 Dec; 106 (12): 1, 984-1, 990; discussion 1990-1991. PMID: 17126628. (Hand search)
2. Reid M, Hammersley R, Hill AJ, Skidmore P. Long-term dietary compensation for added sugar: effects of supplementary sucrose drinks over a four-week period. *Br J Nutr.* 2007 Jan; 97 (1): 193-203. PMID: 17217576.
3. Soenen S, Westerterp-Plantenga MS. No differences in satiety or energy intake after high-fructose corn syrup, sucrose or milk preloads. *Am J Clin Nutr.* 2007 Dec; 86 (6): 1, 586-1, 594. Erratum in: *Am J Clin Nutr.* 2008 Apr; 87 (4): 1, 071. PMID: 18065574.
4. Stookey JD, Constant F, Gardner CD, Popkin BM. Replacing sweetened caloric beverages with drinking water is associated with lower energy intake. *Obesity* (Silver Spring). 2007 Dec; 15 (12): 3, 013-3, 022. PMID: 18198310.

In adults, what is the association between the intake of sugar-sweetened beverages and body weight?

Systematic Reviews / Meta-Analyses:

1. Gibson S. Sugar-sweetened soft drinks and obesity: a systematic review of the evidence from observational studies and interventions. *Nutr Res Rev.* 2008 Dec; 21 (2): 134-147. Review. PMID: 19087367.
2. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: A systematic review. *Am J Clin Nutr*. 2006 Aug; 84 (2): 274-288. Review. PMID: 16895873.
3. Ruxton CH, Gardner EJ, McNulty HM. Is sugar consumption detrimental to health? A review of the evidence 1995-2006. *Crit Rev Food Sci Nutr*. 2010 Jan; 50 (1): 1-19. PMID: 20047137.
4. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. *Am J Public Health.* 2007 Apr; 97 (4): 667-675. Epub 2007 Feb 28. Review. PMID: 17329656; PMCID: PMC1829363.

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Primary Citations:

Trials

1. Raben A, Macdonald I, Astrup A. Replacement of dietary fat by sucrose or starch: effects on 14-day ad libitum energy intake, energy expenditure and body weight in formerly obese and never-obese subjects. *Int J Obes Relat Metab Disord.* 1997 Oct; 21 (10): 846-859. PMID: 9347402.
2. Reid M, Hammersley R, Hill AJ, Skidmore P. Long-term dietary compensation for added sugar: Effects of supplementary sucrose drinks over a four-week period. *Br J Nutr.* 2007 Jan; 97 (1): 193-203. PMID: 17217576.
3. Stanhope KL, Schwarz JM, Keim NL, Griffen SC, Bremer AA, Graham JL, Hatcher B, Cox CL, Dyachenko A, Zhang W, McGahan JP, Seibert A, Krauss RM, Chiu S, Schaefer EJ, Ai M, Otokozawa S, Nakajima K, Nakano T, Beysen C, Hellerstein MK, Berglund L, Havel PJ. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight or obese humans. *J Clin Invest.* 2009 May; 119 (5): 1, 322-1, 334. doi: 10.1172/JCI37385. Epub 2009 Apr 20. PMID: 19381015; PMCID: PMC2673878.
4. Surwit RS, Feinglos MN, McCaskill CC, Clay SL, Babyak MA, Brownlow BS, Plaisted CS, Lin PH. Metabolic and behavioral effects of a high-sucrose diet during weight loss. *Am J Clin Nutr.* 1997 Apr; 65 (4): 908-915. PMID: 9094871.

Prospective Observational

1. Chen L, Appel LJ, Loria C, Lin PH, Champagne CM, Elmer PJ, Ard JD, Mitchell D, Batch BC, Svetkey LP, Caballero B. Reduction in consumption of sugar-sweetened beverages is associated with weight loss: The PREMIER trial. *Am J Clin Nutr.* 2009 May; 89 (5): 1, 299-1, 306. Epub 2009 Apr 1. PMID: 19339405; PMCID: PMC2676995.
2. Dhingra R, Sullivan L, Jacques PF, Wang TJ, Fox CS, Meigs JB, D'Agostino RB, Gaziano JM, Vasan RS. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation.* 2007 Jul 31; 116 (5): 480-488. Epub 2007 Jul 23. Erratum in: *Circulation*. 2007 Dec 4; 116 (23): e557. PMID: 17646581.
3. Palmer JR, Boggs DA, Krishnan S, Hu FB, Singer M, Rosenberg L. Sugar-sweetened beverages and incidence of type 2 diabetes mellitus in African American women. *Arch Intern Med.* 2008 Jul 28; 168 (14): 1, 487-1, 492. PMID: 18663160; PMCID: PMC2708080.

Excluded articles

Article	Reason for Exclusion
Babey SH, Jones M, Yu H, Goldstein H. Bubbling over: soda consumption and its link to obesity in California. *Policy Brief UCLA Cent Health Policy Res*. 2009 Sep; (PB2009-5): 1-8. PMID: 19768858.	Article is policy brief.

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Barkeling B, Andersson I, Lindroos AK, Birkhed D, Rössner S. Intake of sweet foods and counts of cariogenic microorganisms in obese and normal-weight women. *Eur J Clin Nutr.* 2001 Oct; 55 (10): 850-855. PMID: 11593346.	Study design is cross-sectional.
Barkeling B, Linné Y, Lindroos AK, Birkhed D, Rooth P, Rössner S. Intake of sweet foods and counts of cariogenic microorganisms in relation to body mass index and psychometric variables in women. *Int J Obes Relat Metab Disord.* 2002 Sep; 26(9): 1, 239-1, 244. PMID: 12187402.	Study design is cross-sectional.
Barquera S, Hernandez-Barrera L, Tolentino ML, Espinosa J, Ng SW, Rivera JA, Popkin BM. Energy intake from beverages is increasing among Mexican adolescents and adults. *J Nutr*. 2008 Dec; 138(12): 2, 454-2, 461. PMID: 19022972.	Does not include energy intake or body weight in analyses.
Bergen D, Yeh MC. Effects of energy-content labels and motivational posters on sales of sugar-sweetened beverages: Stimulating sales of diet drinks among adults study. *J Am Diet Assoc*. 2006 Nov; 106(11): 1, 866-1, 869. PMID: 17081839.	Does not answer question: Examines the impact of labels and posters on beverage sales.
Bes-Rastrollo M, Sánchez-Villegas A, Gómez-Gracia E, Martínez JA, Pajares RM, Martínez-González MA. Predictors of weight gain in a Mediterranean cohort: The Seguimiento Universidad de Navarra Study 1. *Am J Clin Nutr.* 2006 Feb; 83 (2): 362-370; quiz 394-395. PMID: 16469996.	Included in Malik (2006), Vartanian (2007), and Gibson (2008) systematic reviews.
Bleich SN, Wang YC, Wang Y, Gortmaker SL. Increasing consumption of sugar-sweetened beverages among US adults: 1988-1994 to 1999-2004. *Am J Clin Nutr*. 2009 Jan; 89(1): 372-381. Epub 2008 Dec 3. PMID: 19056548.	Does not include energy intake or body weight in analyses.
Bowman SA, Vinyard BT. Fast food consumption of US adults: Impact on energy and nutrient intakes and overweight status. *J Am Coll Nutr.* 2004 Apr; 23(2): 163-168. PMID: 15047683.	Does not include the consumption of added sugars in analyses.

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Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr.* 2004 Apr; 79 (4): 537-543. Review. Erratum in: *Am J Clin Nutr.* 2004 Oct; 80(4): 1, 090. PMID: 15051594.	Article is a commentary.
Brown CM, Dulloo AG, Montani JP. Sugary drinks in the pathogenesis of obesity and cardiovascular diseases. *Int J Obes* (Lond). 2008 Dec; 32 Suppl 6: S28-S34. Review. PMID: 19079277.	Study design is narrative review.
Chacko E, McDuff I, Jackson R. Replacing sugar-based soft drinks with sugar-free alternatives could slow the progress of the obesity epidemic: Have your Coke and drink it too. *N Z Med J*. 2003 Oct 24; 116(1, 184): U649. PMID: 14583807.	Article is a commentary.
Charlton KE, Kolbe-Alexander TL, Nel JH. Micronutrient dilution associated with added sugar intake in elderly black South African women. *Eur J Clin Nutr*. 2005 Sep; 59(9): 1, 030-1, 042. PMID: 16015273.	Study population not from a developed country as defined by the Human Development Index (2009).
Claesson AL, Holm G, Ernersson A, Lindström T, Nystrom FH. Two weeks of overfeeding with candy, but not peanuts, increases insulin levels and body weight. *Scand J Clin Lab Invest.* 2009; 69 (5): 598-605. PMID: 19396658.	Does not include sugar-sweetened beverages in analyses.
Crowe TC, Fontaine HL, Gibbons CJ, Cameron-Smith D, Swinburn BA. Energy density of foods and beverages in the Australian food supply: Influence of macronutrients and comparison to dietary intake. *Eur J Clin Nutr.* 2004 Nov; 58 (11): 1, 485-1, 491. PMID: 15173855.	Does not include energy intake or body weight in analyses.
Dennis EA, Flack KD, Davy BM. Beverage consumption and adult weight management: A review. *Eat Behav.* 2009 Dec; 10(4): 237-246. Epub 2009 Jul 16. Review. PMID: 19778754.	Study design is narrative review.
Duffey KJ, Popkin BM. High-fructose corn syrup: Is this what's for dinner? *Am J Clin Nutr.* 2008 Dec; 88 (6): 1, 722S-1, 732S. PubMed PMID: 19064537; PubMed Central PMCID: PMC2746720.	Does not include energy intake or body weight in analyses.

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Epstein LH, Gordy CC, Raynor HA, Beddome M, Kilanowski CK, Paluch R. Increasing fruit and vegetable intake and decreasing fat and sugar intake in families at risk for childhood obesity. *Obes Res.* 2001 Mar; 9 (3): 171-178. PMID: 11323442.	Does not answer question: examined behavioral weight-control programs.
Forshee RA, Storey ML, Allison DB, Glinsmann WH, Hein GL, Lineback DR, Miller SA, Nicklas TA, Weaver GA, White JS. A critical examination of the evidence relating high fructose corn syrup and weight gain. *Crit Rev Food Sci Nutr.* 2007; 47 (6): 561-582. Review. PMID: 17653981.	Study design is narrative review.
Fowler SP, Williams K, Resendez RG, Hunt KJ, Hazuda HP, Stern MP. Fueling the obesity epidemic? Artificially sweetened beverage use and long-term weight gain. *Obesity* (Silver Spring). 2008 Aug; 16(8): 1, 894-1, 900. Epub 2008 Jun 5. PMID: 18535548.	Does not include sugar-sweetened beverages in analyses.
Frazier CR, Mason P, Zhuang X, Beeler JA. Sucrose exposure in early life alters adult motivation and weight gain. *PLoS One*. 2008 Sep 17; 3(9): e3, 221. PMID: 18797507; PMCID: PMC2529404.	Study tested animals.
Gatenby SJ, Aaron JI, Jack VA, Mela DJ. Extended use of foods modified in fat and sugar content: nutritional implications in a free-living female population. *Am J Clin Nutr.* 1997 Jun; 65 (6): 1, 867-1, 873. PMID: 9174485.	Does not answer question: examined reduced-sugar and reduced-fat products.
Gibson SA. Are high-fat, high-sugar foods and diets conducive to obesity? *Int J Food Sci Nutr*. 1996 Sep; 47(5): 405-415. PMID: 8889626.	Study design is cross-sectional.
Gibson SA. Dietary sugars intake and micronutrient adequacy: A systematic review of the evidence. *Nutr Res Rev.* 2007 Dec; 20(2): 121-131. PMID: 19079865.	Does not include energy intake or body weight in analyses.
Guerrero RT, Paulino YC, Novotny R, Murphy SP. Diet and obesity among Chamorro and Filipino adults on Guam. *Asia Pac J Clin Nutr.* 2008; 17(2): 216-222. PMID: 18586639; PMCID: PMC2762033.	Study population not from a developed country.

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Hudson SM, Dixon JB, O'Brien PE. Sweet eating is not a predictor of outcome after Lap-Band placement. Can we finally bury the myth? *Obes Surg.* 2002 Dec; 12(6): 789-794. PMID: 12568183.	Participants had Lap-Band surgery.
Huffman L, West DS. Readiness to change sugar sweetened beverage intake among college students. *Eat Behav.* 2007 Jan; 8 (1): 10-14. Epub 2006 May 30. PMID: 17174846.	Does not include energy intake or body weight in analyses.
Joyce T, McCarthy SN, Gibney MJ. Relationship between energy from added sugars and frequency of added sugars intake in Irish children, teenagers and adults. *Br J Nutr*. 2008 May; 99 (5): 1, 117-1, 126. Epub 2007 Dec 21. PMID: 18096092.	Does not include energy intake or body weight in analyses.
Julis RA, Mattes RD. Influence of sweetened chewing gum on appetite, meal patterning and energy intake. *Appetite*. 2007 Mar; 48(2): 167-175. Epub 2006 Oct 13. PMID: 17050036.	Does not include sugar-sweetened beverages in analyses.
Kasim-Karakas SE, Almario RU, Cunningham W. Effects of protein versus simple sugar intake on weight loss in polycystic ovary syndrome (according to the National Institutes of Health criteria). *Fertil Steril.* 2009 Jul; 92(1): 262-270. Epub 2008 Aug 8. PubMed PMID: 18691705.	Participants diagnosed with polycystic ovary syndrome.
Krahn D, Grossman J, Henk H, Mussey M, Crosby R, Gosnell B. Sweet intake, sweet-liking, urges to eat and weight change: Relationship to alcohol dependence and abstinence. *Addict Behav*. 2006 Apr; 31 (4): 622-631. Epub 2005 Jun 29. PMID: 15990241.	Participants diagnosed with alcohol dependence.
Kvaavik E, Andersen LF, Klepp KI. The stability of soft drinks intake from adolescence to adult age and the association between long-term consumption of soft drinks and lifestyle factors and body weight. *Public Health Nutr.* 2005 Apr; 8(2): 149-157. PMID: 15877908.	Included in Malik (2006), Gibson (2008), and Vartanian (2007) systematic reviews.
Leth T, Jensen U, Fagt S, Andersen R. Estimated intake of intense sweeteners from non-alcoholic beverages in Denmark, 2005. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess.* 2008 Jun; 25 (6): 662-668. PMID: 18484294.	Does not include sugar-sweetened beverages or energy intake/body weight in analyses.

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Lewis CJ, Park YK, Dexter PB, Yetley EA. Nutrient intakes and body weights of persons consuming high and moderate levels of added sugars. *J Am Diet Assoc.* 1992 Jun; 92 (6): 708-713. PMID: 1607567.	Study design is cross-sectional.
Liebman M, Pelican S, Moore SA, Holmes B, Wardlaw MK, Melcher LM, Liddil AC, Paul LC, Dunnagan T, Haynes GW. Dietary intake, eating behavior, and physical activity-related determinants of high body mass index in rural communities in Wyoming, Montana and Idaho. *Int J Obes Relat Metab Disord*. 2003 Jun; 27 (6): 684-692. PMID: 12833112.	Included in Malik (2006), Vartanian (2007), and Gibson (2008) systematic reviews.
Livesey G, Taylor R. Fructose consumption and consequences for glycation, plasma triacylglycerol, and body weight: Meta-analyses and meta-regression models of intervention studies. *Am J Clin Nutr.* 2008 Nov; 88 (5): 1, 419-1, 437. PMID: 18996880.	Does not answer question: examined relationship between fructose consumption and health outcomes.
Macdiarmid JI, Vail A, Cade JE, Blundell JE. The sugar-fat relationship revisited: Differences in consumption between men and women of varying BMI. *Int J Obes Relat Metab Disord.* 1998 Nov; 22(11): 1, 053-1, 061. PMID: 9822942.	Study design is cross-sectional.
Melanson KJ, Zukley L, Lowndes J, Nguyen V, Angelopoulos TJ, Rippe JM. Effects of high-fructose corn syrup and sucrose consumption on circulating glucose, insulin, leptin, and ghrelin and on appetite in normal-weight women. *Nutrition.* 2007 Feb; 23 (2): 103-112. PMID: 17234503.	Does not include body weight as an outcome.
Miller WC, Niederpruem MG, Wallace JP, Lindeman AK. Dietary fat, sugar and fiber predict body fat content. *J Am Diet Assoc.* 1994 Jun; 94(6): 612-615. PMID: 8195547.	Study design is cross-sectional.
Parnell W, Wilson N, Alexander D, Wohlers M, Williden M, Mann J, Gray A. Exploring the relationship between sugars and obesity. *Public Health Nutr.* 2008 Aug; 11 (8): 860-866. Epub 2007 Sep 21. PMID: 17888201.	Study design is cross-sectional.

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Pivonka EE, Grunewald KK. Aspartame- or sugar-sweetened beverages: Effects on mood in young women. *J Am Diet Assoc*. 1990 Feb; 90 (2): 250-254. PMID: 2303661.	Does not include body weight as an outcome.
Promdee L, Trakulthong J, Kangwantrakul W. Sucrose consumption in Thai undergraduate students. *Asia Pac J Clin Nutr.* 2007; 16 Suppl 1: 22-26. PMID: 17392071.	Study population not from a developed country as defined by the Human Development Index (2009).
Quatromoni PA, Pencina M, Cobain MR, Jacques PF, D'Agostino RB. Dietary quality predicts adult weight gain: Findings from the Framingham Offspring Study. *Obesity* (Silver Spring). 2006 Aug; 14 (8): 1, 383-1, 391. PMID: 16988081.	Does not answer question: Examined diet quality and weight gain.
Quílez J, Bulló M, Salas-Salvadó J. Improved postprandial response and feeling of satiety after consumption of low-calorie muffins with maltitol and high-amylose corn starch. *J Food Sci.* 2007 Aug; 72 (6): S407-S411. PMID: 17995698.	Does not answer question: Did not examine relationship between sugar-sweetened beverages and body weight.
Raben A, Vasilaras TH, Møller AC, Astrup A. Sucrose compared with artificial sweeteners: Different effects on ad libitum food intake and body weight after 10 weeks of supplementation in overweight subjects. *Am J Clin Nutr*. 2002 Oct; 76(4): 721-729. PMID: 12324283.	Included in Malik (2006), Gibson (2008), Ruxton (2010) and Vartanian (2007) systematic reviews.
Rehm CD, Matte TD, Van Wye G, Young C, Frieden TR. Demographic and behavioral factors associated with daily sugar-sweetened soda consumption in New York City adults. *J Urban Health.* 2008 May; 85 (3): 375-385. Epub 2008 Mar 18. PMID: 18347992; PMCID: PMC2329746.	Study design is cross-sectional.
Rennie KL, Livingstone MB. Associations between dietary added sugar intake and micronutrient intake: A systematic review. *Br J Nutr.* 2007 May; 97(5): 832-841. Review. PMID: 17408523.	Does not include energy intake or body weight in analyses.
Reyna NY, Cano C, Bermúdez VJ, Medina MT, Souki AJ, Ambard M, Nuñez M, Ferrer MA, Inglett GE. Sweeteners and beta-glucans improve metabolic and anthropometrics variables in well controlled type 2 diabetic patients. *Am J Ther.* 2003 Nov-Dec; 10 (6): 438-443. PMID: 14624282.	Participants diagnosed with type 2 diabetes.

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Ritchie LD, Spector P, Stevens MJ, Schmidt MM, Schreiber GB, Striegel-Moore RH, Wang MC, Crawford PB. Dietary patterns in adolescence are related to adiposity in young adulthood in black and white females. *J Nutr.* 2007 Feb; 137 (2): 399-406. PMID: 17237318.	Does not include added sugars intake, specifically, in analyses. Examined dietary patterns.
Rodearmel SJ, Wyatt HR, Stroebele N, Smith SM, Ogden LG, Hill JO. Small changes in dietary sugar and physical activity as an approach to preventing excessive weight gain: The America on the Move family study. *Pediatrics*. 2007 Oct; 120 (4): e869-e879. PMID: 17908743.	Does not answer question: Examines an intervention program (America on the Move) and does not directly assess the relationship between added sugars on body weight.
Rush E, Schulz S, Obolonkin V, Simmons D, Plank L. Are energy drinks contributing to the obesity epidemic? *Asia Pac J Clin Nutr.* 2006; 15(2): 242-244. PMID: 16672210.	Does not include energy intake or body weight as an outcome.
Schiffman SS, Graham BG, Sattely-Miller EA, Peterson-Dancy M. Elevated and sustained desire for sweet taste in African-Americans: A potential factor in the development of obesity. *Nutrition.* 2000 Oct; 16 (10): 886-893. PMID: 11054593.	Does not answer question: Examines oral habituation to sweet taste.
Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, Hu FB. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA.* 2004 Aug 25; 292 (8): 927-934. PMID: 15328324.	Included in Malik (2006), Gibson (2008), and Vartanian (2007) systematic reviews.
Shubair MM, McColl RS, Hanning RM. Mediterranean dietary components and body mass index in adults: The peel nutrition and heart health survey. *Chronic Dis Can.* 2005 Spring-Summer; 26 (2-3): 43-51. PMID: 16251009.	Does not include added sugars intake, specifically, in analyses. Examined dietary patterns.
Sørensen LB, Raben A, Stender S, Astrup A. Effect of sucrose on inflammatory markers in overweight humans. *Am J Clin Nutr*. 2005 Aug; 82(2): 421-427. PMID: 16087988.	Included in Malik (2006).

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Stanhope KL, Griffen SC, Bair BR, Swarbrick MM, Keim NL, Havel PJ. 24-hour endocrine and metabolic profiles following consumption of high-fructose corn syrup-, sucrose-, fructose- and glucose-sweetened beverages with meals. *Am J Clin Nutr*. 2008 May; 87 (5): 1, 194-1, 203. PMID: 18469239.	Does not answer question: examines postprandial hormone response to various beverages.
Sun SZ, Empie MW. Lack of findings for the association between obesity risk and usual sugar-sweetened beverage consumption in adults: A primary analysis of databases of CSFII-1989-1991, CSFII-1994-1998, NHANES III and combined NHANES 1999-2002. *Food Chem Toxicol.* 2007 Aug; 45 (8): 1, 523-1, 536. Epub 2007 Feb 17. PMID: 17383789.	Included in Gibson (2008) systematic review.
Tordoff MG, Alleva AM. Effect of drinking soda sweetened with aspartame or high-fructose corn syrup on food intake and body weight. *Am J Clin Nutr*. 1990 Jun; 51 (6): 963-969. PMID: 2349932.	Included in Malik (2006) and Vartanian (2007) systematic reviews.
Vågstrand K, Karin Lindroos A, Birkhed D, Linné Y. Associations between salivary bacteria and reported sugar intake and their relationship with body mass index in women and their adolescent children. *Public Health Nutr.* 2008 Apr; 11(4): 341-348. Epub 2007 Jul 3. PMID: 17605840.	Study design is cross-sectional.
Vos MB, Kimmons JE, Gillespie C, Welsh J, Blanck HM. Dietary fructose consumption among US children and adults: The Third National Health and Nutrition Examination Survey. *Medscape J Med.* 2008 Jul 9; 10 (7): 160. PMID: 18769702; PMCID: PMC2525476.	Does not include energy intake or body weight in analyses.
Wansink B, Painter JE, Lee YK. The office candy dish: Proximity's influence on estimated and actual consumption. *Int J Obes* (Lond). 2006 May; 30 (5): 871-875. PMID: 16418755.	Does not answer question: Does not examine relationship between added sugars and body weight.
West DS, Bursac Z, Quimby D, Prewitt TE, Spatz T, Nash C, Mays G, Eddings K. Self-reported sugar-sweetened beverage intake among college students. *Obesity* (Silver Spring). 2006 Oct; 14 (10): 1, 825-1, 831. PMID: 17062813.	Does not include energy intake or body weight in analyses.

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West JA, de Looy AE. Weight loss in overweight subjects following low-sucrose or sucrose-containing diets. *Int J Obes Relat Metab Disord.* 2001 Aug; 25 (8): 1, 122-1, 128. PMID: 11477496.	Dropout rate higher than inclusion criteria.
White JS. Misconceptions about high-fructose corn syrup: Is it uniquely responsible for obesity, reactive dicarbonyl compounds, and advanced glycation endproducts? *J Nutr.* 2009 Jun; 139 (6): 1, 219S-1, 227S. Epub 2009 Apr 22. PMID: 19386820.	Study design is narrative review.
Wolff E, Dansinger ML. Soft drinks and weight gain: How strong is the link? Meds*cape J Med.* 2008; 10 (8): 189. Epub 2008 Aug 12. Review. PMID: 18924641; PMCID: PMC2562148.	Study design is narrative review.
Yamada M, Murakami K, Sasaki S, Takahashi Y, Okubo H. Soft drink intake is associated with diet quality even among young Japanese women with low soft drink intake. *J Am Diet Assoc.* 2008 Dec; 108 (12): 1, 997-2, 004. PMID: 19027402.	Does not include energy intake or body weight as an outcome.
Ziemer DC, Berkowitz KJ, Panayioto RM, El-Kebbi IM, Musey VC, Anderson LA, Wanko NS, Fowke ML, Brazier CW, Dunbar VG, Slocum W, Bacha GM, Gallina DL, Cook CB, Phillips LS. A simple meal plan emphasizing healthy food choices is as effective as an exchange-based meal plan for urban African Americans with type 2 diabetes. *Diabetes Care.* 2003 Jun; 26 (6): 1, 719-1, 724. PMID: 12766100.	Participants diagnosed with type 2 diabetes.

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CHAPTER 9. SUGAR-SWEETENED BEVERAGES AND NON-CALORIC SWEETENERS – ENERGY INTAKE AND BODY WEIGHT

HOW ARE NON-CALORIC SWEETENERS RELATED TO ENERGY INTAKE AND BODY WEIGHT?

Conclusion statement

Moderate evidence shows that using non-caloric sweeteners will affect energy intake only if they are substituted for higher calorie foods and beverages. A few observational studies reported that individuals who use non-caloric sweeteners are more likely to gain weight or be heavier. This does not mean that non-caloric sweeteners cause weight gain, rather that they are more likely to be consumed by overweight and obese individuals.

Grade

Moderate

Evidence summary overview

The Dietary Guidelines Advisory Committee (DGAC) answered this question using a partial Nutrition Evidence Library (NEL) review. The American Dietetic Association (ADA) Evidence Analysis Library (EAL) conducted a search from January 1985 through March 2006 on the question, “In adults, does using foods or beverages with non-nutritive sweeteners (saccharin, aspartame, acesulfame-K, sucralose, neotame) in a calorie-restricted or ad libitum diet affect energy balance?”

For adults, the conclusion was, “Using non-nutritive sweeteners in either a calorie-restricted or ad libitum diet will affect overall energy balance only if the non-nutritive sweeteners are substituted for higher calorie food and beverages (Grade II).” For children, they concluded, “Studies do not support that the use of non-nutritive sweeteners causes weight gain. If non-caloric beverages, including non-nutritive sweeteners, are substituted for sugar-sweetened beverages, there is a potential for energy savings in adolescents (Grade III).”

Additionally, ADA conducted a review of aspartame and body weight in 2008 that included articles reviewed in 2006. In this review, they asked the question, “In adults, does aspartame affect energy balance (weight)?” The conclusion was “Use of aspartame by individuals consuming a hypocaloric diet may be associated with increased weight loss. In some cases aspartame did not affect weight loss (Grade I).”

The ADA EAL review of non-nutritive sweeteners in both adults and children served as the foundation for this review. This conclusion also is based on review of one meta-analysis (de la Hunty et al, 2006), a randomized crossover study (Flood, 2007) and a prospective cohort study (Fowler et al, 2008) published since 2006.

The meta-analysis by de la Hunty et al (2006) supports a significant reduction in energy intakes with aspartame compared with all types of control diets except when aspartame was compared with non-sucrose controls such as water. For body weight, the analysis was conducted in three stages: 1) Used all weight outcomes including follow-up weights, (2) excluded studies in which the control group gained weight and (3) excluded follow-up periods. A significant reduction in weight was seen for all three

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analyses. The combined effect was approximately a 3% reduction in body weight. The authors concluded that using foods and drinks sweetened with aspartame instead of sucrose results in a significant reduction in both energy intakes and body weight. Further, using foods and drinks sweetened with aspartame instead of those sweetened with sucrose is an effective way to maintain and lose weight.

In a prospective cohort study, Fowler et al (2008) reported a significant positive dose-response relationship between baseline artificially sweetened beverage consumption and incidence of overweight/obesity, incidence of obesity and body mass index (BMI) change; however, this association does not establish causality.

Flood et al (2006) examined the impact of beverage type (cola, diet cola or water) and size (12 or 18 fluid ounces) on intake at an ad libitum lunch. Participants consumed significantly more energy at lunch when cola was provided vs. diet cola or water.

Evidence summary paragraphs

Meta-analysis

de la Hunty et al, 2006 (neutral quality), a meta-analysis, examined the effect of substituting sugar with either aspartame alone or aspartame in combination with other intense sweeteners on energy intake or body weight. Included studies were randomized controlled trials (RCTs) that examined the effect of substituting sugar with either aspartame alone or aspartame in combination with other intense sweeteners on energy intake (at least 24 hours) or body weight. A total of 16 studies were included and two meta-analyses were performed: 1) Energy intake as outcome (15 studies), and 2) body weight as outcome (nine studies). Interventions ranged from one day to 19 weeks (with follow-up for three years). Seven trials had interventions less than one week, and three had trials that lasted for 10 or 12 weeks. Most trials were with normal weight or overweight adults and three trials were with obese adults. Four trials used soft drinks as the only vehicle for aspartame; the other studies used a combination of commercially available foods and drinks sweetened with aspartame or a mixture of intense sweeteners. A significant reduction in energy intake was seen with aspartame compared with all types of control except when aspartame was compared with non-sucrose controls such as water. Parallel design studies that compared the effects of aspartame with sucrose had an overall effect size of 0.4 standardized difference (SD) which corresponded to a mean reduction of about 10% of energy intake. For body weight, the analysis was conducted in three stages: 1) Used all weight outcomes including follow-up weights, 2) excluded studies in which the control group gained weight and 3) excluded follow-up periods. A significant reduction in weight was seen for all three analyses. The combined effect figure was 0.2 SD, which corresponded to about a 3% reduction in body weight. The authors concluded that using foods and drinks sweetened with aspartame instead of sucrose results in small, but significant reductions in energy intakes and body weight. Further, using foods and drinks sweetened with aspartame instead of those sweetened with sucrose is an effective way to maintain and lose weight.

Primary Citations

Flood et al, 2006 (positive quality), a randomized crossover trial, examined the impact of increasing beverage portion size on beverage and food intake. A component of the study design was to compare beverage type (cola, diet cola or water). Participants were 33 adults (55% female; age 19 to 30 years) who consumed lunch in the laboratory once a week for six weeks, for a total of six test sessions. On each test day,

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a standard breakfast was served in order to ensure a consistent level of hunger across sessions. At each lunch, the same foods were served, but the beverage served was varied in type (cola, diet cola or water) and portion size (12 fl oz or 18 fl oz). The diet cola was sweetened with aspartame and provided 0kcal per serving. The order of experimental conditions was randomized across subjects. At all meals, subjects could eat ad libitum from the amount of food and beverage that was served. All foods and beverages were weighed prior to being served to subjects, and reweighed after the subjects had finished eating, to determine the amount of food and beverage consumed. Increasing beverage portion size significantly increased the weight of beverage consumed, regardless of the type of beverage served ($P<0.05$). Food intake at lunch did not differ significantly by either type or portion size of the beverage served. When the energy from the caloric beverage was added to the energy from food, total energy intake at lunch was increased significantly ($P<0.001$) compared with non-caloric beverages. Therefore, even though subjects consumed considerably more energy from the caloric beverage than the non-caloric beverages, they did not compensate for this additional energy by reducing food intake. The authors concluded that when a caloric beverage was consumed with a meal, food intake was not reduced and energy from the beverage added on to energy from food, resulting in a significant increase in total energy consumed at a meal; further, replacing caloric beverages with low-calorie or non-caloric beverages can be an effective strategy for decreasing energy intake.

Fowler et al, 2008 (neutral quality), a prospective cohort study, examined the relationship between artificially sweetened beverage (ASB) consumption and long-term weight gain in 3,371 adults (age 25 to 64 years) from the San Antonio Heart Study. Height, weight and ASB consumption were measured at baseline and seven to eight years later. At baseline, weekly consumption of soft drinks, coffee and tea were estimated. Participants reporting soft drink use were asked whether they usually drank sugar-free sodas, regular sodas or similar amounts of each; their AS soda dose was calculated accordingly. For abstainers, AS soda dose was set equal to zero. “Usual” sweeteners for coffee and tea were ascertained, and AS dosage calculated accordingly (or set equal to zero for abstainers). Participants were also asked whether they “usually” used sugar or sugar substitutes. A significant positive dose–response relationship emerged between baseline ASB consumption and all outcome measures (incidence of overweight/obesity, incidence of obesity and BMI change), adjusted for baseline BMI and demographic and behavioral characteristics. Consuming more than 21 ASBs per week (vs. none) was associated with almost-doubled risk of OW and OB (OR=1.93; P=0.007) among 1,250 baseline normal weight (NW) individuals and doubled risk of obesity (OR=2.03; P=0.0005) among 2,571 individuals with baseline BMI of less than 30kg/m^2. Compared with non-users (+1.01kg/m^2), ΔBMIs were significantly higher for ASB quartiles two to four: +1.46 (P=0.003), +1.50 (P=0.002), and +1.78kg/m^2 (P<0.0001), respectively. Overall, adjusted ΔBMIs were 47% greater among AS users than nonusers (+1.48kg/m^2 vs. +1.01kg/m^2, respectively, P<0.0001). The authors concluded that they observed a positive dose-response relationship between ASB consumption and long-term weight gain. Further, they noted that the association does not establish causality but additional research is needed to evaluate the possible impact of AS use on the risk of obesity.

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Overview table

Author, Year, Study Design, Class, Rating	Participants	Description of Study Methodology	Outcomes
de la Hunty A, Gibson S et al, 2006 Study Design: Meta-analysis or Systematic Review Class: M Neutral Quality	Meta-analysis with energy intake as outcome = 15 studies. Meta-analysis with body weight as outcome = nine studies.	Included studies were RCTs that examined the effect of substituting sugar with either aspartame alone or aspartame in combination with other intense sweeteners on energy intake (at least 24 hours) or body weight. A total of 16 studies were included.	Interventions ranged from one day to 19 weeks (with follow-up for three years). Seven trials had interventions <one week and three had trials that lasted for 10 or 12 weeks. Most trials were with normal weight or overweight adults and three trials were with obese adults. Four trials used soft drinks as the only vehicle for aspartame; the other studies used a combination of commercially available foods and drinks sweetened with aspartame or a mixture of intense sweeteners. A significant ↓ in energy intake was seen with aspartame compared with all types of control except when aspartame was compared with non-sucrose controls such as water. Parallel design studies that compared the effects of aspartame with sucrose had an overall effect size of 0.4 SD, which corresponded to a mean ↓ of about 10% of energy intake. For body weight, the analysis was conducted in three stages: 1) Used all weight outcomes including follow-up weights 2) Excluded studies in which the control group ↑ weight 3) Excluded follow-up periods. A significant ↓ in weight was seen for all three analyses. The combined effect figure was 0.2 SD, which corresponded to about a 3% ↓ in body weight.

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Flood JE, Roe LS et al, 2006 Study Design: Randomized Crossover Trial Class: A Positive Quality	Initial N=40 adults. Final N=33 adults (55% female). Age: 19 to 30 years. Location: United States.	Participants consumed lunch in the laboratory once a week for six weeks, for a total of six test sessions. On each test day, a standard breakfast was served in order to ensure a consistent level of hunger across sessions. At each lunch, the same foods were served, but the beverage served was varied in type (cola, diet cola or water) and portion size (12 fl oz or 18 fl oz). The diet cola was sweetened with aspartame and provided 0kcal per serving. The order of experimental conditions was randomized across subjects. At all meals, subjects could eat ad libitum from the amount of food and beverage that was served. All foods and beverages were weighed prior to being served to subjects and reweighed after the subjects had finished eating, to determine the amount of food and beverage consumed.	Increasing beverage portion size significantly ↑ the weight of beverage consumed, regardless of the type of beverage served ($P<0.05$). NS difference in food intake at lunch by either type or portion size of the beverage served. When the energy from the caloric beverage was added to the energy from food, total energy intake at lunch was ↑ significantly ($P<0.001$), compared with non-caloric beverages. Therefore, even though subjects consumed considerably more energy from the caloric beverage than the non-caloric beverages, they did not compensate for this additional energy by reducing food intake.

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Fowler SP, Williams K et al, 2008 Study Design: Prospective Cohort Study Class: B Neutral Quality	N=3,371 adults. Age: 25 to 64 years. San Antonio Heart Study. Location: United States.	Height, weight and artificially sweetened beverage (ASB) consumption were measured at baseline and seven to eight years later. At baseline, weekly consumption of soft drinks, coffee and tea were estimated. Participants reporting soft drink use were asked whether they usually drank sugar-free sodas, regular sodas or similar amounts of each; their AS soda dose was calculated accordingly. For abstainers, AS soda dose was set equal to zero. “Usual” sweeteners for coffee and tea were ascertained and AS dosage calculated accordingly (or set equal to zero for abstainers). Participants were also asked whether they “usually” used sugar or sugar substitutes.	A significant positive dose-response relationship emerged between baseline ASB consumption and all outcome measures (incidence of overweight/obesity, incidence of obesity and BMI change), adjusted for baseline BMI and demographic and behavioral characteristics. Consuming more than 21 ASBs per week (vs. none) was associated with almost-doubled risk of OW and OB (OR=1.93; P=0.007) among 1,250 baseline normal weight (NW) individuals, and doubled risk of obesity (OR=2.03; P=0.0005) among 2,571 individuals with baseline BMI <30kg/m^2. Compared with non-users (+1.01kg/m2), ΔBMIs were significantly higher for ASB quartiles two to four: +1.46 (P=0.003), +1.50 (P=0.002) and +1.78kg/m2 (P<0.0001), respectively. Overall, adjusted ΔBMIs were 47% greater among AS users than non-users (+1.48kg/m^2 vs. +1.01kg/m^2, respectively, P<0.0001).

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Search plan and results

Inclusion criteria

- March 2006 to January 2010
- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* Less than 20% for trials; preference for smaller dropout rates
- *Ages:* Children, two to 18 years; adults, 19 and older
- *Populations:* Healthy, those with elevated chronic disease risk.

Exclusion criteria

- Cross-sectional studies
- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (Websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed

  ("Body Weight"[Mesh] OR "overweight"[Mesh] OR obesity[mh] OR adiposity[mh] OR "Body Mass Index"[mh]) OR (“Total caloric consumption” OR “energy compensation” OR “dietary compensation” OR “caloric intake” OR appetite OR energy intake[mh]) AND

  ("Sweetening Agents"[MeSH] OR Non-caloric sweetener* OR low calorie sweeten* OR (artificial* sweeten*) OR “sugar free” OR saccharin OR aspartame OR acetosulfam OR sucralose OR trichlorosucrose OR neotame OR erythritol OR rebaudioside A OR rebiana OR diet soda* OR diet drink* OR intense sweeten*)

  Note: Acesulfame-K is an entry substance name under acetosulfam.

Date searched: 01/06/2010

Summary of articles identified to review

- Total hits from all electronic database searches: 105
- Total articles identified to review from electronic databases: 15
- Articles identified via handsearch or other means: 2
- Number of Primary Articles Identified: 2
- Number of Review Articles Identified: 1
- Total Number of Articles Identified: 3
- Number of Articles Reviewed but Excluded: 14

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Included articles (References)

1. de La Hunty A, Gibson S, Ashwell M. A review of the effectiveness of aspartame in helping with weight control. *Br Nutr Found Nutr Bull.* 2006; 31: 115–128. (Hand search)
2. Flood JE, Roe LS, Rolls BJ. The effect of increased beverage portion size on energy intake at a meal. *J Am Diet Assoc.* 2006 Dec; 106(12): 1, 984-1, 990; discussion 1, 990-1, 991. PMID: 17126628. (Hand search)
3. Fowler SP, Williams K, Resendez RG, Hunt KJ, Hazuda HP, Stern MP. Fueling the obesity epidemic? Artificially sweetened beverage use and long-term weight gain. *Obesity (Silver Spring).* 2008 Aug; 16(8): 1, 894-1, 900. Epub 2008 Jun 5. PMID: 18535548.

Excluded articles

Articles	Reason for Exclusion
Appleton KM, Blundell JE. Habitual high and low consumers of artificially-sweetened beverages: Effects of sweet taste and energy on short-term appetite. *Physiol Behav.* 2007 Oct 22; 92(3): 479-486. Epub 2007 Apr 27. PMID: 17540414.	Does not answer question; investigated the effects of sweet taste and energy on subsequent short-term appetite in female habitual high and low consumers of artificially sweetened beverages.
Bellisle F, Drewnowski A. Intense sweeteners, energy intake and the control of body weight. *Eur J Clin Nutr.* 2007 Jun; 61(6): 691-700. Epub 2007 Feb 7. Review. PMID: 17299484.	Study design is narrative review.
Bergen D, Yeh MC. Effects of energy-content labels and motivational posters on sales of sugar-sweetened beverages: stimulating sales of diet drinks among adults study. *J Am Diet Assoc.* 2006 Nov; 106(11): 1, 866-1, 869. PMID: 17081839.	Does not answer question; examined impact of labels and posters on beverage sales.
Blum JE, Davee AM, Beaudoin CM, Jenkins PL, Kaley LA, Wigand DA. Reduced availability of sugar-sweetened beverages and diet soda has a limited impact on beverage consumption patterns in Maine high school youth. *J Nutr Educ Behav.* 2008 Nov-Dec; 40(6): 341-347. PMID: 18984489.	Does not answer question; examined impact of reducing availability of SSBs in schools on beverage consumption.
Collins JK, Davis AR, Adams A, Manness N, Perkins-Veazie PM. Consumer acceptability of low-sugar watermelon sweetened with non-calorie sweetener by a Native American community. *Int J Food Sci Nutr.* 2006 Aug-Sep; 57(5-6): 363-368. PMID:	Does not answer question; examined acceptability of low sugar watermelon sweetened with artificial sweetener.

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17135026.	
Dhingra R, Sullivan L, Jacques PF, Wang TJ, Fox CS, Meigs JB, D'Agostino RB, Gaziano JM, Vasan RS. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation.* 2007 Jul 31; 116(5): 480-488. Epub 2007 Jul 23. Erratum in: *Circulation.* 2007 Dec 4; 116(23): e557. PMID: 17646581.	Does not include artificial sweeteners in analyses; considers soft drink intake.
Elfhag K, Tynelius P, Rasmussen F. Sugar-sweetened and artificially sweetened soft drinks in association to restrained, external and emotional eating. *Physiol Behav.* 2007 Jun 8; 91(2-3): 191-195. Epub 2007 Mar 2. PMID: 17434544.	Study design is cross-sectional.
Klein DA, Boudreau GS, Devlin MJ, Walsh BT. Artificial sweetener use among individuals with eating disorders. *Int J Eat Disord.* 2006 May; 39(4): 341-345. PMID: 16523474.	Does not answer question; examined use of artificial sweeteners by those with eating disorders.
Leth T, Jensen U, Fagt S, Andersen R. Estimated intake of intense sweeteners from non-alcoholic beverages in Denmark, 2005. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess.* 2008 Jun; 25(6): 662-668. PMID: 18484294.	Does not answer question; describes intake of intense sweeteners in Denmark.
Malinauskas BM, Raedeke TD, Aeby VG, Smith JL, Dallas MB. Dieting practices, weight perceptions, and body composition: A comparison of normal weight, overweight, and obese college females. *Nutr J.* 2006 Mar 31; 5: 11. PMID: 16579846; PMCID: PMC1456978.	Does not answer question; describes dieting practices of college females.
Mattes RD, Popkin BM. Nonnutritive sweetener consumption in humans: effects on appetite and food intake and their putative mechanisms. *Am J Clin Nutr.* 2009 Jan; 89(1): 1-14. Epub 2008 Dec 3. Review. PMID: 19056571; PMCID: PMC2650084.	Study design is narrative review.
O'Connor TM, Yang SJ, Nicklas TA. Beverage intake among preschool children and its effect on weight status. *Pediatrics.* 2006 Oct; 118(4): e1, 010-e1, 018. PMID: 17015497.	Study design is secondary analysis of cross-sectional study.
Renwick AG. The use of a sweetener substitution method to predict dietary exposures for the intense	Does not answer question; describes dietary intake of

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sweetener rebaudioside A. *Food Chem Toxicol.* 2008 Jul; 46 Suppl 7: S61-S69. Epub 2008 May 16. PMID: 18547702.	rebaudioside A.
Wang YC, Ludwig DS, Sonneville K, Gortmaker SL. Impact of change in sweetened caloric beverage consumption on energy intake among children and adolescents. *Arch Pediatr Adolesc Med.* 2009 Apr; 163(4): 336-343. PMID: 19349562.	Study design is secondary analysis of cross-sectional study.

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CHAPTER 10. VEGETABLES AND FRUITS – CARDIOVASCULAR DISEASE

IN ADULTS, WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF VEGETABLES AND FRUITS, NOT INCLUDING JUICE, AND CARDIOVASCULAR DISEASE?

Conclusion statement

Consistent evidence suggests at least a moderate inverse relationship between vegetable and fruit consumption with myocardial infarction and stroke, with significantly larger, positive effects noted above five servings of vegetables and fruits per day. Notwithstanding prior work on dietary patterns that emphasize vegetables and fruits, insufficient evidence published since 2004 is available to assess the independent relationship between vegetable and fruit intake and blood pressure or serum cholesterol.

Grade

Moderate

Evidence summary overview

Cardiovascular Disease

Evidence suggests at least a moderate inverse relationship between vegetable and fruit consumption with myocardial infarction (MI) and stroke, with significantly larger, positive effects noted above five servings of vegetables and fruits per day. This evidence is based on 12 reports including four meta-analyses (Dauchet, 2005; Dauchet, 2006; He, 2006; He, 2007) of US and European subjects; six prospective studies, four of which were conducted in the US (Genkinger, 2004; Hung, 2004; Joshipura, 2009; Tucker, 2005) and two in Japan (Nakamura, 2008; Takachi, 2008), and two international case-control studies (Galeone, 2009; Nikolic, 2008). Results varied by sex, with a significant decrease for men and women reported in all-cause cardiovascular death (Genkinger, 2004; Hung, 2004; Joshipura, 2009), for men only (Tucker, 2005), for men only in terms of vegetable intake (Nakamura, 2008), and for women only in terms of fruit intake (Nakamura, 2008). In addition, Takachi (2008) found significant results for higher fruit (but not vegetable) intake in men and women. Risk for cardiovascular disease (CVD) is highest at consumption levels below three servings per day, results are ambiguous at three to five servings of vegetables and fruits per day, and lowest risk is associated with consumption levels above five servings per day (Dauchet, 2006; He, 2007), suggesting a linear relationship between vegetable and fruit consumption and coronary heart disease (CHD). Overall, risk reduction for CHD was estimated to be as much as 4% and 11% for stroke alone for each serving of vegetables and fruits added per day (Dauchet, 2006).

Blood Pressure

Five studies investigating blood pressure and vegetable and fruit intake were identified in the Nutrition Evidence Library (NEL) search. These included the PREMIER prospective cohort study in the US (Wang, 2008), one prospective study in Spain (Nuñez-Cordoba, 2009); cross-sectional studies in Iran (Mirmiran, 2009),

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Japan (Utsugi, 2008) and India (Radhika, 2008). Two studies showed no association between total vegetable and fruit intake and blood pressure (BP) (Mirmiran, 2009) and hypertension (HTN) (Nuñez-Cordoba, 2009). Utsugi et al (2008) showed a significant positive relationship with vegetable and fruit consumption and lower risk of home-measured HTN. The Wang et al (2008) study showed vegetable and fruit consumption was inversely associated with both systolic blood pressure (SBP) and diastolic blood pressure(DBP) at six months, but not at 18 months.

The US results support the work reviewed in the 2005 Dietary Guidelines Advisory Committee (DGAC) report, but the international studies do not. The variation in results may be due to differences between these international population samples and typical American patterns in baseline consumption levels of vegetables and fruits, types of vegetables and fruits consumed and overall dietary patterns.

Blood Lipids

Blood lipids are traditionally used as an intermediate indicator or marker for CVD. The evidence testing the effect of vegetable and fruit intake on blood lipids is sparse, but suggests an associative trend between an increased consumption of vegetables and fruits with lower total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels. The evidence is based on three reports since 2004, including one limited trial (Kelley, 2006) and two cross-sectional studies (Mirmiran, 2009; Radhika, 2008). The trend is apparent for total and LDL-C, and persists even after adjustment for education, physical activity and fat intakes. However, significance occurs only when the highest levels of vegetable and fruit intake are compared to the lowest levels of intake and the mechanisms of action are unknown.

Evidence summary paragraphs

Cardiovascular Disease

Meta-analyses of Prospective Cohort Studies

Dauchet et al, 2006 (positive quality), a meta-analysis of nine prospective cohort studies (seven from the US and two from Finland), assessed the magnitude of the relation between fruit and vegetable consumption and the risk of CHD. The meta-analysis consisted of 91,379 men, 129,701 women and 5,007 CHD events. Risk of CHD was decreased by 4% (RR=0.96; 95% CI: 0.93, 0.99; P=0.0027) for each additional daily portion of fruit and vegetables and by 7% (RR=0.93; 95% CI: 0.89, 0.96; P<0.0001) for each additional daily portion of fruit. The association between vegetable intake and risk of CHD was heterogeneous (P=0.0043), more marked for cardiovascular mortality (RR=0.74; 95% CI: 0.75, 0.84; P<0.0001) than for fatal and non-fatal MI (RR=0.95; 95% CI: 0.92, 0.99; P=0.0058). The authors reported a beneficial association between fruit and vegetable intake and CHD risk; however, they noted that the strength of this association is uncertain, because of possible publication or selection bias. Note: Seven studies in common with He, 2007.

He et al, 2007 (positive quality), a meta-analysis assessed quantitatively the relation between fruit and vegetable intake and the incidence of CHD by using data from 13 prospective cohort studies (nine from the US and four from Europe). The data comprised a total of 278,459 individuals and 9,143 events over a median of 11 years of follow-up. Relative risk (RR) or hazard ratio (HR) was used as a measure of the relation between fruit and vegetable intake and CHD. Individuals with higher fruit

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and vegetable intake had a lower risk of CHD. Compared with individuals who had less than three servings per day of fruit and vegetables, the pooled RR of CHD was 0.93 (95% CI: 0.86, 1.00; P=0.06) for those with three to five servings per day and 0.83 (95% CI: 0.77, 0.89; P<0.0001) for those with more than five servings per day. Compared with individuals who had less than three servings per day of fruits and vegetables, the pooled RR of MI was 0.94 (95% CI: 0.80, 1.10; P=0.43) for those with three to five servings per day and 0.83 (95% CI: 0.70, 0.99; P=0.04) for those with more than five servings per day. Compared with those who had fruit and vegetable intake of less than three servings per day, individuals with more than five servings per day had a significantly lower risk of CHD irrespective of subjects' gender, duration of follow-up, and method of dietary assessment. However, this association was not significant (NS) in studies where dietary assessment was completed via interview. For individuals with fruit and vegetable intake of three to five serving a day, the association was only significant in some subgroups. The authors concluded that their results provide support for the recommendation to consume more than five servings per day of fruit and vegetables. Note: Seven studies in common with Dauchet, 2006.

Dauchet et al, 2005 (positive quality), a meta-analysis assessed the relationship between fruit consumption, vegetable consumption and both fruit and vegetable consumption and the risk of stroke. Analyses included seven prospective cohort studies (five from the US, one from Europe, and one from Japan) that studied the relationship between stroke and the consumption of fruit and vegetables, separately or combined. The risk of stroke was decreased by 11% (pooled RR=0.89; 95% CI: 0.85, 0.93) for each additional portion of fruit per day, by 5% (pooled RR=0.95; 95% CI: 0.92, 0.97) for fruits and vegetables, and by 3% (pooled RR=0.97; 95% CI: 0.92, 1.02; not significant) for vegetables. The associations for fruit as well as fruits and vegetables were linear, suggesting a dose response relationship. In contrast, there was NSevidence for a substantial reduction in stroke rates with vegetable consumption. Note: Six studies in common with He, 2006.

He et al, 2006 (positive quality), a meta-analysis assessed quantitatively the relation between fruit and vegetable intake and the incidence of stroke by using data from nine prospective cohort studies (five from the US, three from Europe and one from Japan). The data comprised a total of 257,551 men and women, 4,917 events and a median of 13 years of follow-up. The results showed that individuals with an increased fruit and vegetable intake have a reduced risk of stroke. Compared with individuals who had less than three servings per day of fruit and vegetables, the pooled RR of stroke was 0.89 (95% CI: 0.83, 0.97; P=0.005) for those with three to five servings per day and 0.74 (95% CI: 0.69, 0.79; P<0.0001) for those with more than five servings per day. Compared with individuals who had less than three servings per day of fruits and vegetables, those with more than five servings per day had a significantly reduced risk of stroke, irrespective of sex, duration of follow-up, method of dietary assessment, dietary instrument administration or stroke subtype. For individuals who had three to five servings per day, the association was significant only in some groups. This study showed that increased consumption of fruit and vegetables from less than three to more than five servings per day was related to a 26% reduction in the risk of stroke, whereas increasing the intake to three to five servings per day was associated with an 11% reduction in the risk of stroke. Note: Six studies in common with Dauchet, 2005.

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Prospective Cohort Studies

Genkinger et al, 2004 (positive quality), a prospective cohort study conducted in the US, assessed the relationship of fruit and vegetable and dietary vitamin C, vitamin E and beta-carotene intake with all-cause, CVD and cancer mortality in the community-based CLUE cohorts in Washington County, Maryland. 5,952 participants (63% female, 99% white) were included in the analysis and 378 CVD deaths occurred over 12 years of follow-up. Compared with those in the bottom quintile (median = 0.87 servings per day), participants in the highest quintile (median = 4.89 servings per day) of fruit and vegetable intake had a lower risk of all-cause mortality (HR=0.63; 95% CI: 0.51, 0.78; P for trend = 0.0004) and CVD mortality (HR = 0.76; 95% CI: 0.54, 1.06; P for trend = 0.15). Higher intake of cruciferous vegetables was associated with lower risk of CVD mortality (HR=0.89; 95% CI: 0.64, 1.25; P for trend = 0.51). A further analysis evaluated the association of mortality with the recommended daily consumption of five or more servings per day of fruits and vegetables. Only 9% of participants reported five or more servings per day of fruits and vegetables; no association was present for CVD mortality (HR=1.04; 95% CI: 0.76, 1.42).

Hung et al, 2004 (positive quality), a prospective cohort study examined the association between fruit and vegetable consumption and the risk of major chronic diseases in two large cohorts of men and women followed for more than a decade. The data was from participants in the Nurses' Health Study (NHS), who were nurses aged 30 to 55 years recruited in 1976, and participants in the Health Professionals' Follow-Up Study (HPFS), who were health professionals aged 40 to 75 years recruited in 1986. Additional mailed questionnaires were completed in 1986, 1990 and 1994 for the NHS and 1990 and 1994 for the HPFS. The analyses included 71,910 women and 37,725 men. Study end dates were May 31, 1998 for the NHS and January 31, 1998 for the HPFS. During follow-up, 1964 CVD events were ascertained in women, and 1670 CVD events in men. For CVD, the pooled RR in the continuous analysis was statistically significant. RR of CVD was 0.88 (95% CI: 0.81, 0.95) for an increment of five servings per day of total fruits and vegetables; 0.87 (95% CI: 0.80, 0.94) and 0.93 (95% CI: 0.86, 1.00) for increments of three servings per day of all fruits and all vegetables, respectively; and 0.89 (95% CI: 0.83, 0.96) and 0.94 (95% CI: 0.91, 0.98) for increments of one serving per day of green leafy vegetables and of vitamin C-rich fruits and vegetables, respectively. Higher fruit and vegetable intake showed a statistically significant inverse association with CVD disease (RR for eight or more vs. less than 1.5 servings a day was 0.70 (95% CI: 0.55, 0.89; P=0.0003).

Joshipura et al, 2009 (positive quality), a prospective cohort study, examined whether carbohydrate intake affects the association between fruits and vegetables and CVD using data from the Nurses' Health Study (NHS) and Health Professionals' Follow-Up Study (HPFS). Participants in the NHS were nurses aged 30 to 55 years recruited in 1976, while those in the HPFS were professionals aged 40 to 75 years recruited in 1986. Information on ischemic CVD (myocardial infarction and stroke) and fruit and vegetable intake were updated over time using the 1984 to 1998 questionnaires in the NHS and the 1986 to 1998 questionnaires in the HPFS. Participants were 70,870 NHS females and 38,918 HPFS males who were followed 16 and 14 years, respectively. A total of 2,040 incident cases of CVD were documented among men and 1,852 among women. Fruit intake was strongly related

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with carbohydrate (CHO) intake, but vegetables showed a weak correlation. Total fruit and vegetable intake was 7.6 servings per day among men in high CHO group compared with 4.4 servings per day for men in the low CHO group; among women the intake was 6.9 servings per day in the high CHO group compared with 4.1 servings per day in the low CHO group. Total fruits and vegetables showed a non-significant inverse association among men and women with low energy-adjusted carbohydrate intake, with a pooled RR for an increment of five servings per day of 0.81 (95% CI: 0.65, 1.01; P for trend = 0.06). When comparing extreme quintiles of fruits and vegetables, NS association was seen in the low CHO group (RR=0.73; 95% CI: 0.51, 1.04). Total fruit intake was associated with a lower risk of ischemic CVD only among participants with moderate CHO intake (RR=0.81 comparing extreme quintiles; 95% CI: 0.70, 0.94). No significant linear association was found in any of the CHO intake groups. The linear trend was significant for total vegetables in the low CHO group, with a pooled RR for three servings a day of 0.82 (95% CI: 0.68, 0.99; P for trend = 0.04). Compared with the group with both high fruit and vegetable (more than five servings per day) and high CHO intake (higher than 50% of energy from CHO), the low fruit and vegetable intake and high CHO group showed an increase in CVD for men (RR=1.21; 95% CI: 1.02, 1.42) but not women. After adjustment for CHO intake, there was a significant inverse association between high fruit and vegetable intake and ischemic CVD in men (RR=0.90; 95% CI : 0.82, 0.99) but not women; the association was significant when pooled across the two cohorts: RR=0.91 (95% CI : 0.85, 0.98).

Nakamura et al, 2008 (positive quality), a prospective cohort study, examined the association between baseline fruit and vegetable intake and CVD mortality in 29,079 Japanese men and women. Two hundred men and 184 women died from CVD during seven years of follow-up. Median intakes of fruit in the lowest and highest quartiles were 0.3 to 2.6 servings per day for men and 0.4 and 2.7 servings per day for women. Median intakes of vegetables in the lowest and highest quartiles were 2.2 and 7.1 servings per day for men and 2.5 and 7.4 servings per day for women. For women, when comparing extreme quartiles of vegetable intake (2.5 vs/ 7.4 servings per day), there was a significant inverse association with CVD mortality after adjusting for total energy, age and non-dietary and dietary covariates (HR=0.62; 95% CI: 0.36, 1.08; P for trend = 0.007). Fruit intake was NS associated with CVD deaths among women. For men, CVD death was not associated with fruit or vegetable intake.

Takachi et al, 2008 (positive quality), a prospective cohort study conducted in Japan, examined the association between fruit and vegetable consumption and risk of CVD. The Japan Public Health Center-based Prospective Study was conducted on two cohorts, one initiated in 1990 and one in 1993. During 1995 to 1998, a food-frequency questionnaire (FFQ) was administered in nine areas to 77,891 men and women. During 459,320 person-years of follow-up until the end of 2002, 1,386 CVD cases were identified. Total fruit and vegetable intake ranged from a median value of 186g per day in the lowest quartile to 733g per day in the highest quartile. Higher consumption of fruit, but not vegetables, was associated with significantly lower risk of CVD; multivariate HR for highest vs. lowest quartiles of intake were 0.81 (95% CI: 0.67, 0.97; P for trend = 0.01) for fruit. Total fruit and vegetable intake was NS associated with CVD risk. The only specific fruit or vegetable significantly inversely associated with CVD risk was citrus fruits (HR=0.80; 95% CI: 0.67, 0.95; P for trend = 0.02). Cardiovascular disease risk for women was significantly inversely

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associated with total fruit and vegetable consumption (multivariate HR of highest vs. lowest quartiles = 0.73, 95% CI: 0.56, 0.95; P for trend = 0.02) and with fruit consumption (HR=0.78, 95% CI: 0.60, 1.01; P for trend = 0.06), and a NS, inverse association with vegetable consumption (HR=0.81, 95 % CI: 0.63, 1.05; P for trend = 0.14). No association between fruit or vegetable consumption and risk of CVD was found for men.

Tucker et al, 2005 (positive quality), a prospective cohort study conducted in the US, examined associations between habitual fruit and vegetable intake and saturated fat intake, separately and in combination, and subsequent coronary heart disease and total mortality among men in the Baltimore Longitudinal Study of Aging (BLSA). Dietary data were collected by seven-day diet records during four time periods and completed diet records at biennial visits. A total of 501 men were included in the analysis. After adjustment for covariates, each serving of fruits and vegetables was associated with a 6% reduction in risk for total mortality (P<0.05) and a 21% reduction in CHD death (P<0.01). When examined separately, intake of fruit was associated inversely with total mortality (P<0.05) and intake of vegetables was inversely associated with CHD mortality (P<0.01), with a risk reduction of 40% per serving. When examined together, participants consuming more than five servings of fruits and vegetables per day and less than 12% of energy intake came from saturated fat were 31% less likely to die of any cause (P<0.05) and 76% less likely to die from CHD (P<0.001).

Case-Control Studies

Galeone et al, 2009 (neutral quality), a case-control study conducted in Italy, determined the relationship between allium vegetable intake (such as onions and garlic) and risk of acute MI in 760 patients (76% male; median age = 61 years) with a first episode of non-fatal acute MI and 682 controls (64% male; median age = 59 years) admitted to the same hospitals between 1995 and 2003. Compared with non-onion-consumers, the odds ratios (OR) of acute MIs for subsequent categories of onion intake were 0.90 (95% CI: 0.69, 1.21) for less than one portion of onion per week and 0.78 (95% CI: 0.56, 0.99) for more than one portion per week (P for trend = 0.05). For garlic consumers, the ORs were 0.84 (95% CI: 0.66, 1.09) for intermediate and 0.94 (95% CI: 0.68, 1.32) for high use, compared with low or no garlic use (P for trend = 0.50).

Nikolic et al, 2008 (neutral quality), a case-control study examined the relationship between vegetable and fruit intake and the risk of CHD using data from a case-control study conducted from 2001 to 2003 in Serbia. The subjects were selected randomly: 290 cases with a first event of acute coronary syndrome and 290 selected paired controls by sex, age and region. Participants in the lowest tertile of vegetable consumption had 4.04 (95% CI: 1.51, 11.41) times higher odds of CHD compared to participants in the upper tertile of consumption. The OR for the middle tertile of vegetable consumption compared to the upper tertile was 1.06 (95% CI: 0.69, 1.65). Participants who consumed between one serving of fruit a day and one serving a week had 1.78 (95% CI: 1.12, 2.87) times greater odds of CHD compared to those who consumed more than one serving per day. These findings support an inverse relation between vegetable and fruit intake and CHD.

Blood Pressure

Prospective Cohort Study

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Nuñez-Cordoba et al, 2009 (positive quality), a prospective cohort study in Spain, assessed the association between fruit and vegetable consumption and the risk of HTN. A total of 8,594 participants (mean age = 41.1 years; 62% female) from the Mediterranean Study (SUN cohort) were included in analyses. Dietary habits were assessed with a validated semi-quantitative FFQ (136 items). Hypertension was self-reported. Over a median of 49 months of follow-up, 426 cases of HTN were reported. No significant associations between servings per day of fruits [multivariate HR between highest (more than four servings a day) and lowest (one or less serving a day) quintiles = 0.85; 95% CI: 0.59, 1.22; P for trend = 0.70], vegetables [multivariate HR between highest (more than four servings a day) and lowest (one or less serving a day) quintiles = 0.87; 95% CI: 0.55, 1.39; P for trend = 0.61], or fruits and vegetables combined [multivariate HR between highest (five or more servings a day) and lowest (two or less servings a day) quartiles = 0.78; 95% CI: 0.55, 1.10; P for trend = 0.22] and HTN were observed.

Wang et al, 2008 (positive equality) examined the association of dietary protein intake with BP, and particularly, the independent relationship of animal and plant protein with BP over 18 months of follow-up. Additional analyses examined the relationship between fruit and vegetable intake and BP. Participants were 810 adults (62% female; age 25 to 79 years) from the PREMIER Trial (US). Blood pressure measurements were obtained by study personnel at baseline, six and 18 months. Two 24-hour recalls, one on a weekday and the other on a weekend day, were obtained at baseline, six and 18 months. Fruit and vegetable intake was inversely associated with both SBP and DBP cross-sectionally at six months (P=0.0003 and 0.0157, respectively). Furthermore, increased intake of fruits and vegetables was significantly associated with a lower risk of HTN at six but not at 18 months. Using multiple logistic regression analyses (including fruits and vegetables, dairy food, meat and fat), only fruit and vegetable intake was significantly and inversely associated with risk of HTN. For every extra serving of fruit or vegetable, the odds of having HTN decreased by about 23% (OR=0.77; 95% CI: 0.79, 0.97; P=0.0041). The authors concluded that other studies showing that regular consumption of fruits and vegetables, nuts/seeds, whole grains and soy products is likely to benefit BP.

Cross-Sectional Studies

Mirmiran et al, 2009 (positive quality), a cross-sectional study in Iran, evaluated the association of fruit and vegetable intake and CVD factors. Data (N=840; aged 18 to 74 years) from the Tehran Lipid and Glucose Study (TLGS) was used. Dietary intake was assessed using a semi-quantitative FFQ (168 items). Weight, height, medical history, physical activity and glucose and lipid concentrations were also measured. Mean consumption of fruit and vegetables was 5.6±3.4 servings per day. No significant differences were observed between BP of participants in category one (the lowest category) and those in category four of fruit and vegetable intake.

Radhika et al, 2008 (positive quality), a population-based cross-sectional study, evaluated the association of fruit and vegetable intake with cardiovascular risk factors such as obesity, HTN, fasting plasma glucose and dyslipidemia in urban Asian Indians living in southern India. A total of 983 adults were included in the analysis. Dietary intake was assessed with an interviewer-administered semi-quantitative FFQ. Intake of fruit and vegetables ranged from 141g per day in the

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lowest quartile to 418g per day in the highest quartile. After adjusting for potential confounders, the highest quartile of fruit and vegetable intake showed a significant inverse association with SBP (β=-2.6mmHg, 95% CI: -5.92, -1.02, P=0.027) when compared with the lowest quartile. In energy-, age- and sex-adjusted models, there was a significant inverse association with DBP, but this relationship became insignificant after adjustment for body mass index (BMI).

Utsugi et al, 2008 (neutral-quality), a cross-sectional analysis of the longitudinal Ohasama study in Japan, investigated the association of fruit and vegetable consumption with the risk of HTN diagnosed by home BP in 1,569 adults (aged 35+ years; 59% female). All participants measured their BP at home using a validated device. Dietary intake was assessed with a valid FFQ. The mean consumption of fruits and vegetables were 108 and 63g per day, respectively. The prevalence of home HTN was 39.4% for men and 29.3% for women. In the sex- and BMI adjusted analysis, the highest-tertile of fruit consumption showed a significant relationship with a lower risk for home HTN (the highest-tertile for fruit consumption: OR=0.65; P=0.011). After adjustment for known risk factors, these associations did not change. The highest vegetable consumption tertile also showed a significant positive association with lower risk of home HTN (OR=0.62, P=0.029).

Blood Lipids

Trial

Kelley et al, 2006 (neutral quality), a time series study conducted in the US, determined the effects of consuming 300g of Bing sweet cherries daily for 28 days on plasma lipids and markers of inflammation in 18 healthy adults (aged 50±1 years; 89% female). The subjects completed a 64-day study with three metabolic periods: Eight-day baseline period, 28-day cherry intervention period and 28-day post-intervention period. Participants were provided cherries in 300g portions. They were asked not to change their activity level or diet except to replace an equivalent amount of dietary carbohydrates with CHO from cherries. Plasma concentrations for TC, LDL-C and high-density lipoprotein cholesterol (HDL-C), and TC:HDL-C ratio did not differ on study days seven, 35 and 64. Plasma lipids concentrations were not affected by cherry consumption.

Cross-sectional Studies

Mirmiran et al, 2009 (positive-quality), a cross-sectional study in Iran, evaluated the association of fruit and vegetable intake and CVD factors. Data (N=840; aged 18 to 74 years) from the Tehran Lipid and Glucose Study (TLGS) was used. Dietary intake was assessed using a semi-quantitative FFQ (168 items). Weight, height, medical history, physical activity and glucose and lipid concentrations were also measured. Mean consumption of fruit and vegetables was 5.6±3.4 servings per day. Subjects in the upper category of fruit and vegetable intake had lower TC, LDL-C, TC to HDL-C, and LDL-C/HDL-C as compared with those in the lower category. No significant differences were observed between HDL-C in category 1 (the lowest category) and those in category 4 of fruit and vegetable intake. Adjusted OR for high LDL-C concentrations were 1.00, 0.88, 0.81 and 0.75 (P for trend < 0.01; adjusted for age, sex, keys score, BMI, energy intake, smoking status, dietary cholesterol and history of diabetes mellitus and coronary artery disease); this trend was not appreciably altered by additional adjustment for education; physical activity; and saturated fat, polyunsaturated fat and total fat intakes. The authors concluded

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that consumption of fruits and vegetables was associated with lower concentrations of TC and LDL-C.

Radhika et al, 2008 (positive quality), a population-based cross-sectional study, evaluated the association of fruit and vegetable intake with cardiovascular risk factors such as obesity, HTN, fasting plasma glucose and dyslipidemia in urban Asian Indians living in southern India. A total of 983 adults were included in the analysis. Dietary intake was assessed with an interviewer-administered semi-quantitative FFQ. Intake of fruit and vegetables ranged from 141g per day in the lowest quartile to 418g per day in the highest quartile. After adjusting for potential confounders, the highest quartile of fruit and vegetable intake showed a significant inverse association with TC (β=-50mg per L, 95% CI: -113.9, -13.6, P=0.017) and LDL-C (β=-55mg per L, 95% CI: -110.8, -11.1, P=0.039), when compared with the lowest quartile.

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Overview table

Cardiovascular Disease

Study	Study Type	Association: Pos, Neg, None
Dauchet et al, 2005 Positive Quality	Meta-analysis, nine prospective cohort studies.	CHD: (-) Vegetable and/or fruit, decreased risk for each additional daily portion.
He et al, 2007 Positive Quality	Meta-analysis, 13 prospective cohort studies.	CHD: (-) Vegetable and fruit, decreased risk for those with 5+ servings a day.
Dauchet et al, 2006 Positive Quality	Meta-analysis, seven prospective cohort studies.	Stroke: (-) Vegetable and fruit, (-) fruit, Ø vegetables, decreased risk for each additional daily portion.
He et al, 2006 Positive Quality	Meta-analysis, nine prospective cohort studies.	Stroke: (-) Vegetable and fruit, decreased risk for those with 5+ servings a day.
Genkinger et al, 2004 Positive Quality	Prospective cohort study CLUE Cohorts, US.	CVD mortality: (-) Vegetable and fruit, (-) cruciferous vegetables.
Hung et al, 2004 Positive Quality	Prospective cohort study Nurses' Health and Health Professionals' Follow Up Studies, US.	CVD: (-) Vegetable and/or fruit, (-) vitamin C-rich fruit, (-) green leafy vegetable.
Joshipura et al, 2009 Positive Quality	Prospective cohort study Nurses' Health and Health Professionals' Follow Up Studies, US.	CVD: (-) Vegetable, stronger relationship among those consuming low-CHO diet.
Nakamura et al, 2008 Positive Quality	Prospective cohort study Japan.	CVD mortality: (-) Vegetable (women), Ø vegetable (men), Ø fruit (men or women).

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Takachi et al, 2008 Positive Quality	Prospective cohort study Japan Public Health Center Study, Japan.	CVD: Ø Vegetable and fruit, (-) fruit, Ø vegetable (some sex differences).
Tucker et al, 2005 Positive Quality	Prospective cohort study Baltimore Longitudinal Study of Aging, US.	CHD mortality: (-) Vegetable and fruit, Ø fruit, (-) vegetable.
Galeone et al, 2009 Neutral Quality	Case-control study Italy.	Acute MI: (-) Allium vegetable intake.
Nikolic et al, 2008 Neutral Quality	Case-control study Serbia.	Acute CHD: (-) Vegetable, (-) fruit.

Blood Pressure

Study	Study Type	Association: Pos, Neg, None
Nuñez-Cordoba et al, 2009 Positive Quality	Prospective cohort study SUN Cohort, Spain.	HTN: Ø Vegetable, Ø fruit, Ø vegetable and fruit.
Wang et al, 2008 Positive Quality	Prospective cohort study PREMIER, US.	SBP and DBP (six months): (-) Vegetable and fruit HTN: (-) Vegetable and fruit at six months, but not 18 months.
Mirmiran et al, 2009 Positive Quality	Cross-sectional Iran.	BP: Ø Vegetable and fruit.
Radhika et al, 2008 Positive Quality	Cross-sectional India.	SBP: (-) Vegetable and fruit. DBP: Ø Vegetable and fruit.
Utsugi et al, 2008 Neutral Quality	Cross-sectional Japan.	HTN (self-measured): (-) Vegetable, (-) fruit

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Blood Lipids

Study	Study Type	Association: Pos, Neg, None
Kelley et al, 2006 Neutral Quality	Time series study, participants consumed cherries daily for 28 days with baseline and post-intervention periods.	TC: Ø; LDL-C: Ø; HDL-C: Ø.
Mirmiran et al, 2009 Positive Quality	Cross-sectional Iran.	TC: (-) Vegetable and fruit; LDL-C: (-) vegetable and fruit; HDL-c: Ø vegetable and fruit.
Radhika et al, 2008 Positive Quality	Cross-sectional India.	TC: (-) Vegetable and fruit; LDL-C: (-) vegetable and fruit; HDL-C not examined.

Search plan and results

Inclusion criteria

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

Exclusion criteria

- Studies that only consider cancer outcomes
- Studies that considered vegetables and fruits as part of a larger dietary pattern
- Medical treatment/therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

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- PubMed

  ("Fruit"[majr:NoExp] OR fruit OR "Vegetables"[majr]) AND ("Adiposity"[majr] OR "Overweight"[majr] OR "Obesity"[majr] OR "Weight Gain"[majr] OR "Body Weights and Measures"[Majr] OR "body mass index"[majr] OR "body composition"[majr] OR "energy intake"[majr] OR caloric intake*)

  ("Fruit"[majr:NoExp] OR "Vegetables"[majr]) AND ("Diabetes Mellitus, Type 2"[majr] OR "metabolic syndrome X"[majr] OR "hypertension"[majr] OR "dyslipidemias"[MeSH Terms] OR "cardiovascular diseases"[majr] OR "heart diseases"[majr] OR "chronic disease"[mh] OR "Neoplasms"[majr])

Date searched: 07/23/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 626
- Total articles identified to review from electronic databases: 143
- Articles identified via handsearch or other means: 1
- Number of Primary Articles Identified: 29
- Number of Review Articles Identified: 4
- Total Number of Articles Identified: 33
- Number of Articles Reviewed but Excluded: 111

Included articles (References)

In adults, what is the relationship between the intake of vegetables and fruits, not including juice and cardiovascular disease?

Systematic Reviews/Meta-analyses

1. Dauchet L, Amouyel P, Hercberg S, Dallongeville J. Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. *J Nutr.* 2006 Oct; 136 (10): 2, 588-2, 593. PMID: 16988131.
2. Dauchet L, Amouyel P, Dallongeville J. Fruit and vegetable consumption and risk of stroke: A meta-analysis of cohort studies. *Neurology*. 2005 Oct 25; 65 (8): 1, 193-1, 197. PMID: 16247045.
3. He FJ, Nowson CA, Lucas M, MacGregor GA. Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: Meta-analysis of cohort studies. *J Hum Hypertens.* 2007 Sep; 21 (9): 717-728. Epub 2007 Apr 19. PMID: 17443205.
4. He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: Meta-analysis of cohort studies. *Lancet.* 2006 Jan 28; 367 (9507): 320-326. Review. PMID: 16443039.

Primary Citations

1. Galeone C, Tavani A, Pelucchi C, Negri E, La Vecchia C. Allium vegetable intake and risk of acute myocardial infarction in Italy. *Eur J Nutr*. 2009 Mar; 48 (2): 120-123. Epub 2009 Jan 13. PMID: 19142565.
2. Genkinger JM, Platz EA, Hoffman SC, Comstock GW, Helzlsouer KJ. Fruit, vegetable and antioxidant intake and all-cause, cancer and cardiovascular disease mortality in a community-dwelling population in Washington County, Maryland. *Am J Epidemiol*. 2004 Dec 15; 160 (12): 1, 223-1, 233. PMID: 15583375.
3. Hung HC, Joshipura KJ, Jiang R, Hu FB, Hunter D, Smith-Warner SA, Colditz

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GA, Rosner B, Spiegelman D, Willett WC. Fruit and vegetable intake and risk of major chronic disease. *J Natl Cancer Inst*. 2004 Nov 3; 96 (21): 1, 577-1, 584. PMID: 15523086.
4. Joshipura KJ, Hung HC, Li TY, Hu FB, Rimm EB, Stampfer MJ, Colditz G, Willett WC. Intakes of fruits, vegetables and carbohydrate and the risk of CVD. *Public Health Nutr*. 2009 Jan; 12 (1): 115-121. Epub 2008 Apr 15. PMID: 18410704.
5. Nakamura K, Nagata C, Oba S, Takatsuka N, Shimizu H. Fruit and vegetable intake and mortality from cardiovascular disease are inversely associated in Japanese women but not in men. *J Nutr*. 2008 Jun; 138 (6): 1, 129-1, 134. PMID: 18492845.
6. Nikolic M, Nikic D, Petrovic B. Fruit and vegetable intake and the risk for developing coronary heart disease. *Cent Eur J Public Health*. 2008 Mar; 16 (1): 17-20. PMID: 18459474.
7. Takachi R, Inoue M, Ishihara J, Kurahashi N, Iwasaki M, Sasazuki S, Iso H, Tsubono Y, Tsugane S; JPHC Study Group. Fruit and vegetable intake and risk of total cancer and cardiovascular disease: Japan Public Health Center-Based Prospective Study. *Am J Epidemiol.* 2008 Jan 1; 167 (1): 59-70. Epub 2007 Oct 10. PMID: 17928402.
8. Tucker KL, Hallfrisch J, Qiao N, Muller D, Andres R, Fleg JL; Baltimore Longitudinal Study of Aging. The combination of high fruit and vegetable and low saturated fat intakes is more protective against mortality in aging men than is either alone: The Baltimore Longitudinal Study of Aging. *J Nutr*. 2005 Mar; 135 (3): 556-561. PMID: 15735093.

Blood Pressure/Hypertension

1. Mirmiran P, Noori N, Zavareh MB, Azizi F. Fruit and vegetable consumption and risk factors for cardiovascular disease. *Metabolism*. 2009 Apr; 58 (4): 460-468. PMID: 19303965.
2. Nuñez-Cordoba JM, Alonso A, Beunza JJ, Palma S, Gomez-Gracia E, Martinez-Gonzalez MA. Role of vegetables and fruits in Mediterranean diets to prevent hypertension. *Eur J Clin Nutr*. 2009 May; 63 (5): 605-612. Epub 2008 Feb 27. PMID: 18301434.
3. Radhika G, Sudha V, Mohan Sathya R, Ganesan A, Mohan V. Association of fruit and vegetable intake with cardiovascular risk factors in urban south Indians. *Br J Nutr.* 2008 Feb; 99 (2): 398-405. Epub 2007 Aug 3. PMID: 17678569.
4. Utsugi MT, Ohkubo T, Kikuya M, Kurimoto A, Sato RI, Suzuki K, Metoki H, Hara A, Tsubono Y, Imai Y. Fruit and vegetable consumption and the risk of hypertension determined by self measurement of blood pressure at home: The Ohasama study. *Hypertens Res.* 2008 Jul; 31 (7): 1, 435-1, 443. PMID: 18957815.
5. Wang YF, Yancy WS Jr, Yu D, Champagne C, Appel LJ, Lin PH. The relationship between dietary protein intake and blood pressure: Results from the PREMIER study. *J Hum Hypertens*. 2008 Nov; 22 (11): 745-754. Epub 2008 Jun 26. PMID: 18580887. (Hand search)

Blood Lipids

1. Kelley DS, Rasooly R, Jacob RA, Kader AA, Mackey BE. Consumption of Bing sweet cherries lowers circulating concentrations of inflammation

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markers in healthy men and women. *J Nutr*. 2006 Apr; 136 (4): 981-986. PMID: 16549461.
2. Mirmiran P, Noori N, Zavareh MB, Azizi F. Fruit and vegetable consumption and risk factors for cardiovascular disease. *Metabolism*. 2009 Apr; 58 (4): 460-468. PMID: 19303965.
3. Radhika G, Sudha V, Mohan Sathya R, Ganesan A, Mohan V. Association of fruit and vegetable intake with cardiovascular risk factors in urban south Indians. *Br J Nutr.* 2008 Feb; 99 (2): 398-405. Epub 2007 Aug 3. PMID: 17678569.

In adults, what is the relationship between the intake of vegetables and fruits, not including juice and body weight?

1. Bes-Rastrollo M, Martínez-González MA, Sánchez-Villegas A, de la Fuente Arrillaga C, Martínez JA. Association of fiber intake and fruit/vegetable consumption with weight gain in a Mediterranean population. *Nutrition*. 2006 May; 22 (5): 504-511. Epub 2006 Feb 24. PMID: 16500082.
2. Buijsse B, Feskens EJ, Schulze MB, Forouhi NG, Wareham NJ, Sharp S, Palli D, Tognon G, Halkjaer J, Tjønneland A, Jakobsen MU, Overvad K, van der A DL, Du H, Sørensen TI, Boeing H. Fruit and vegetable intakes and subsequent changes in body weight in European populations: Results from the project on Diet, Obesity and Genes (DiOGenes). *Am J Clin Nutr.* 2009 Jul; 90 (1): 202-209. Epub 2009 May 20. PMID: 19458016.
3. Davis JN, Hodges VA, Gillham MB. Normal-weight adults consume more fiber and fruit than their age- and height-matched overweight/obese counterparts. *J Am Diet Assoc.* 2006 Jun; 106 (6): 833-840. PMID: 16720124.
4. Fujioka K, Greenway F, Sheard J, Ying Y. The effects of grapefruit on weight and insulin resistance: Relationship to the metabolic syndrome. *J Med Food*. 2006 Spring; 9 (1): 49-54. PMID: 16579728.
5. Goss J, Grubbs L. Comparative analysis of body mass index, consumption of fruits and vegetables, smoking and physical activity among Florida residents. *J Community Health Nurs.* 2005 Spring; 22(1): 37-46. PMID: 15695195.
6. He K, Hu FB, Colditz GA, Manson JE, Willett WC, Liu S. Changes in intake of fruits and vegetables in relation to risk of obesity and weight gain among middle-aged women. *Int J Obes Relat Metab Disord*. 2004 Dec; 28 (12): 1, 569-1, 574. PMID: 15467774.
7. Ortega RM, Rodríguez-Rodríguez E, Aparicio A, Marín-Arias LI, López-Sobaler AM. Responses to two weight-loss programs based on approximating the diet to the ideal: Differences associated with increased cereal or vegetable consumption. *Int J Vitam Nutr Res*. 2006 Nov; 76 (6): 367-376. PMID: 17607956.
8. Radhika G, Sudha V, Mohan Sathya R, Ganesan A, Mohan V. Association of fruit and vegetable intake with cardiovascular risk factors in urban south Indians. *Br J Nutr*. 2008 Feb; 99 (2): 398-405. Epub 2007 Aug 3. PMID: 17678569.
9. Tanumihardjo SA, Valentine AR, Zhang Z, Whigham LD, Lai HJ, Atkinson RL. Strategies to increase vegetable or reduce energy and fat intake induce weight loss in adults. *Exp Biol Med* (Maywood). 2009 May; 234 (5): 542-552. Epub 2009 Feb 20. PMID: 19234056.

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10. Vioque J, Weinbrenner T, Castelló A, Asensio L, Garcia de la Hera M. Intake of fruits and vegetables in relation to 10-year weight gain among Spanish adults. *Obesity* (Silver Spring). 2008 Mar; 16 (3): 664-670. Epub 2008 Jan 17. PMID: 18239583.
11. Xu F, Yin XM, Tong SL. Association between excess bodyweight and intake of red meat and vegetables among urban and rural adult Chinese in Nanjing, China. *Asia Pac J Public Health*. 2007;19 (3): 3-9. PMID: 18330398.

In adults, what is the relationship between the intake of vegetables and fruits, not including juice and type 2 diabetes?

1. Bazzano LA, Li TY, Joshipura KJ, Hu FB. Intake of fruit, vegetables, and fruit juices and risk of diabetes in women. *Diabetes Care*. 2008 Jul; 31 (7): 1, 311-1, 317. Epub 2008 Apr 4. PMID: 18390796; PMCID: PMC2453647.
2. Halton TL, Willett WC, Liu S, Manson JE, Stampfer MJ, Hu FB. Potato and French fry consumption and risk of type 2 diabetes in women. *Am J Clin Nutr*. 2006 Feb; 83 (2): 284-290. PMID: 16469985.
3. Liu S, Serdula M, Janket SJ, Cook NR, Sesso HD, Willett WC, Manson JE, Buring JE. A prospective study of fruit and vegetable intake and the risk of type 2 diabetes in women. *Diabetes Care.* 2004 Dec; 27 (12): 2, 993-2, 996. PMID: 15562224.
4. Villegas R, Shu XO, Gao YT, Yang G, Elasy T, Li H, Zheng W. Vegetable but not fruit consumption reduces the risk of type 2 diabetes in Chinese women. *J Nutr*. 2008 Mar; 138 (3): 574-580. PMID: 18287369; PMCID: PMC2615491.
5. Wang L, Liu S, Manson JE, Gaziano JM, Buring JE, Sesso HD. The consumption of lycopene and tomato-based food products is not associated with the risk of type 2 diabetes in women. *J Nutr*. 2006 Mar; 136 (3): 620-625. PMID: 16484534.

Excluded articles

Article	Reason for Exclusion
Alonso A, de la Fuente C, Martín-Arnau AM, de Irala J, Martínez JA, Martínez-González MA. Fruit and vegetable consumption is inversely associated with blood pressure in a Mediterranean population with a high vegetable-fat intake: The Seguimiento Universidad de Navarra (SUN) Study.*Br J Nutr.* 2004 Aug; 92 (2): 311-319. PMID: 15333163.	Results reported based on the same dataset as Nunez-Cordoba, 2009.
Austin GL, Adair LS, Galanko JA, Martin CF, Satia JA, Sandler RS. A diet high in fruits and low in meats reduces the risk of colorectal adenomas. *J Nutr.* 2007 Apr; 137 (4): 999-1, 004. PMID: 17374667.	Cancer excluded as outcome of interest.

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Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Fruits and vegetables and endometrial cancer risk: A systematic literature review and meta-analysis. *Nutr Cancer.* 2007; 58 (1): 6-21. Review. PMID: 17571962.	Cancer excluded as outcome of interest.
Barros R, Moreira A, Fonseca J, de Oliveira JF, Delgado L, Castel-Branco MG, Haahtela T, Lopes C, Moreira P. Adherence to the Mediterranean diet and fresh fruit intake are associated with improved asthma control. *Allergy*. 2008 Jul; 63 (7): 917-923. PMID: 18588559.	Participants were diagnosed with asthma.
Benetou V, Orfanos P, Lagiou P, Trichopoulos D, Boffetta P, Trichopoulou A. Vegetables and fruits in relation to cancer risk: evidence from the Greek EPIC cohort study. *Cancer Epidemiol Biomarkers Prev.* 2008 Feb; 17 (2): 387-392. PMID: 18268122.	Cancer excluded as outcome of interest.
Boeing H, Dietrich T, Hoffmann K, Pischon T, Ferrari P, Lahmann PH, Boutron-Ruault MC, Clavel-Chapelon F, Allen N, Key T, Skeie G, Lund E, Olsen A, Tjonneland A, Overvad K, Jensen MK, Rohrmann S, Linseisen J, Trichopoulou A, Bamia C, Psaltopoulou T, Weinehall L, Johansson I, Sánchez MJ, Jakszyn P, Ardanaz E, Amiano P, Chirlaque MD, Quirós JR, Wirfalt E, Berglund G, Peeters PH, van Gils CH, Bueno-de-Mesquita HB, Büchner FL, Berrino F, Palli D, Sacerdote C, Tumino R, Panico S, Bingham S, Khaw KT, Slimani N, Norat T, Jenab M, Riboli E. Intake of fruits and vegetables and risk of cancer of the upper aero-digestive tract: The prospective EPIC-study. *Cancer Causes Control.* 2006 Sep; 17 (7): 957-969. PMID: 16841263.	Cancer excluded as outcome of interest.
Chan JM, Wang F, Holly EA. Vegetable and fruit intake and pancreatic cancer in a population-based case-control study in the San Francisco bay area. *Cancer Epidemiol Biomarkers Prev*. 2005 Sep; 14 (9): 2, 093-2, 097. PMID: 16172215.	Cancer excluded as outcome of interest.
Chen G, Heilbrun LK, Venkatramanamoorthy R, Maranci V, Redd JN, Klurfeld DM, Djuric Z. Effects of low-fat and/or high-fruit-and-vegetable diets on plasma levels of 8-isoprostane-F2alpha in the Nutrition and Breast Health study. *Nutr Cancer.* 2004; 50 (2): 155-160. PMID: 15623461.	Does not include breast cancer incidence in analyses: Measured intermediate outcome (8-isoprostane-F2alpha).

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Crujeiras AB, Parra MD, Rodríguez MC, Martínez de Morentin BE, Martínez JA. A role for fruit content in energy-restricted diets in improving antioxidant status in obese women during weight loss. *Nutrition.* 2006 Jun; 22 (6): 593-599. PMID: 16704952.	Sample size less than inclusion criteria.
Darmon N, Darmon M, Maillot M, Drewnowski A. A nutrient density standard for vegetables and fruits: Nutrients per calorie and nutrients per unit cost. *J Am Diet Assoc.* 2005 Dec; 105 (12): 1, 881-1, 887. PMID: 16321593.	Does not answer question: Does not examine the relationship between vegetables and fruits and health outcomes.
Dauchet L, Ferrières J, Arveiler D, Yarnell JW, Gey F, Ducimetière P, Ruidavets JB, Haas B, Evans A, Bingham A, Amouyel P, Dallongeville J. Frequency of fruit and vegetable consumption and coronary heart disease in France and Northern Ireland: The PRIME study.*Br J Nutr.* 2004 Dec; 92 (6): 963-972. PMID: 15613259.	Included in He, 2006.
de Oliveira MC, Sichieri R, Venturim Mozzer R. A low-energy-dense diet adding fruit reduces weight and energy intake in women. *Appetite.* 2008 Sep; 51 (2): 291-295. Epub 2008 Mar 7. PMID: 18439712.	Dropout rate higher than inclusion criteria.
De Stefani E, Boffetta P, Deneo-Pellegrini H, Ronco AL, Correa P, Mendilaharsu M. The role of vegetable and fruit consumption in the aetiology of squamous cell carcinoma of the oesophagus: A case-control study in Uruguay. *Int J Cancer*. 2005 Aug 10; 116 (1): 130-135. PMID: 15756680.	Cancer excluded as outcome of interest.
Do MH, Lee SS, Kim JY, Jung PJ, Lee MH. Fruits, vegetables, soy foods and breast cancer in pre- and postmenopausal Korean women: A case-control study. *Int J Vitam Nutr Res*. 2007 Mar; 77 (2): 130-141. PMID: 17896586.	Cancer excluded as outcome of interest.
Dosil-Díaz O, Ruano-Ravina A, Gestal-Otero JJ, Barros-Dios JM. Consumption of fruit and vegetables and risk of lung cancer: A case-control study in Galicia, Spain. *Nutrition*. 2008 May; 24 (5): 407-413. Epub 2008 Mar 7. PMID: 18314310.	Cancer excluded as outcome of interest.

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Dove ER, Hodgson JM, Puddey IB, Beilin LJ, Lee YP, Mori TA. Skim milk compared with a fruit drink acutely reduces appetite and energy intake in overweight men and women. *Am J Clin Nutr.* 2009 Jul; 90 (1): 70-75. Epub 2009 May 27. PMID: 19474132.	Does not include body weight in analyses.
Dubowitz T, Heron M, Bird CE, Lurie N, Finch BK, Basurto-Dávila R, Hale L, Escarce JJ. Neighborhood socioeconomic status and fruit and vegetable intake among whites, blacks and Mexican Americans in the United States. *Am J Clin Nutr*. 2008 Jun; 87 (6): 1, 883-1, 891. PMID: 18541581.	Does not answer question: Does not examine the relationship between vegetables and fruits and health outcomes.
Ellinger S, Ellinger J, Stehle P. Tomatoes, tomato products and lycopene in the prevention and treatment of prostate cancer: Do we have the evidence from intervention studies? *Curr Opin Clin Nutr Metab Care.* 2006 Nov; 9 (6): 722-727. Review. PMID: 17053426.	Study design is narrative review.
Ellingsen I, Hjerkinn EM, Seljeflot I, Arnesen H, Tonstad S. Consumption of fruit and berries is inversely associated with carotid atherosclerosis in elderly men.*Br J Nutr*. 2008 Mar; 99 (3): 674-681. Epub 2007 Sep 26. Erratum in: *Br J Nutr*. 2008 Mar; 99 (3): 697. PMID: 17894919.	Does not answer question: Does not include selected health outcome of interest.
Etminan M, Takkouche B, Caamaño-Isorna F. The role of tomato products and lycopene in the prevention of prostate cancer: A meta-analysis of observational studies. *Cancer Epidemiol Biomarkers Prev.* 2004 Mar; 13 (3): 340-345. PMID: 15006906.	Cancer excluded as outcome of interest.
Freedman ND, Park Y, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC. Fruit and vegetable intake and esophageal cancer in a large prospective cohort study. *Int J Cancer.* 2007 Dec 15; 121 (12): 2, 753-2, 760. PMID: 17691111.	Cancer excluded as outcome of interest.
Freedman ND, Park Y, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC. Fruit and vegetable intake and head and neck cancer risk in a large United States prospective cohort study. *Int J Cancer*. 2008 May 15; 122 (10): 2, 330-2, 336. PMID: 18092323.	Cancer excluded as outcome of interest.

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

Freedman ND, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC. Fruit and vegetable intake and gastric cancer risk in a large United States prospective cohort study. *Cancer Causes Control.* 2008 Jun; 19 (5): 459-467. Epub 2008 Jan 1. PMID: 18166992.	Cancer excluded as outcome of interest.
Galeone C, Negri E, Pelucchi C, La Vecchia C, Bosetti C, Hu J. Dietary intake of fruit and vegetable and lung cancer risk: A case-control study in Harbin, northeast China. *Ann Oncol.* 2007 Feb; 18 (2): 388-392. Epub 2006 Oct 23. PMID: 17060488.	Cancer excluded as outcome of interest.
Gallicchio L, Matanoski G, Tao XG, Chen L, Lam TK, Boyd K, Robinson KA, Balick L, Mickelson S, Caulfield LE, Herman JG, Guallar E, Alberg AJ. Adulthood consumption of preserved and non-preserved vegetables and the risk of nasopharyngeal carcinoma: A systematic review. *Int J Cancer*. 2006 Sep 1;119 (5): 1, 125-1, 135. Review. PubMed PMID: 16570274.	Cancer excluded as outcome of interest.
George SM, Park Y, Leitzmann MF, Freedman ND, Dowling EC, Reedy J, Schatzkin A, Hollenbeck A, Subar AF. Fruit and vegetable intake and risk of cancer: a prospective cohort study. *Am J Clin Nutr.* 2009 Jan; 89 (1): 347-353. Epub 2008 Dec 3. PMID: 19056579; Central PMCID: PMC2647712.	Cancer excluded as outcome of interest.
Giammarioli S, Filesi C, Vitale B, Cantagallo A, Dragoni F, Sanzini E. Effect of high intakes of fruit and vegetables on redox status in type 2 onset diabetes: A pilot study. *Int J Vitam Nutr Res.* 2004 Sep; 74 (5): 313-320. PMID: 15628668.	Participants diagnosed with type 2 diabetes.

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

González CA, Pera G, Agudo A, Bueno-de-Mesquita HB, Ceroti M, Boeing H, Schulz M, Del Giudice G, Plebani M, Carneiro F, Berrino F, Sacerdote C, Tumino R, Panico S, Berglund G, Simán H, Hallmans G, Stenling R, Martinez C, Dorronsoro M, Barricarte A, Navarro C, Quiros JR, Allen N, Key TJ, Bingham S, Day NE, Linseisen J, Nagel G, Overvad K, Jensen MK, Olsen A, Tjønneland A, Büchner FL, Peeters PH, Numans ME, Clavel-Chapelon F, Boutron-Ruault MC, Roukos D, Trichopoulou A, Psaltopoulou T, Lund E, Casagrande C, Slimani N, Jenab M, Riboli E. Fruit and vegetable intake and the risk of stomach and oesophagus adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST).*Int J Cancer*. 2006 May 15; 118 (10): 2, 559-2, 566. PMID: 16380980.	Cancer excluded as outcome of interest.
Gorinstein S, Caspi A, Libman I, Lerner HT, Huang D, Leontowicz H, Leontowicz M, Tashma Z, Katrich E, Feng S, Trakhtenberg S. Red grapefruit positively influences serum triglyceride level in patients suffering from coronary atherosclerosis: Studies in vitro and in humans. *J Agric Food Chem*. 2006 Mar 8; 54 (5): 1, 887-1, 892. PubMed PMID: 16506849.	Participants diagnosed with hyperlipidemia and had received coronary bypass surgery.
Holick CN, De Vivo I, Feskanich D, Giovannucci E, Stampfer M, Michaud DS. Intake of fruits and vegetables, carotenoids, folate and vitamins A, C, E and risk of bladder cancer among women (United States).Cancer Causes Control. 2005 Dec; 16 (10): 1, 135-1, 145. PMID: 16215863.	Cancer excluded as outcome of interest.
Holick CN, Giovannucci EL, Rosner B, Stampfer MJ, Michaud DS. Prospective study of intake of fruit, vegetables and carotenoids and the risk of adult glioma. *Am J Clin Nutr.* 2007 Mar; 85 (3): 877-886. PMID: 17344512.	Cancer excluded as outcome of interest.
Jansen MC, Bueno-de-Mesquita HB, Feskens EJ, Streppel MT, Kok FJ, Kromhout D. Quantity and variety of fruit and vegetable consumption and cancer risk. *Nutr Cancer.* 2004; 48 (2): 142-148. PMID: 15231448.	Cancer excluded as outcome of interest.
Johnsen SP. Intake of fruit and vegetables and risk of stroke: An overview. *Curr Opin Clin Nutr Metab Care*. 2004 Nov; 7 (6): 665-670. Review. PMID: 15534435.	Study design is narrative review.

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

Kavanaugh CJ, Trumbo PR, Ellwood KC. The U.S. Food and Drug Administration's evidence-based review for qualified health claims: Tomatoes, lycopene and cancer. *J Natl Cancer Inst.* 2007 Jul 18; 99 (14): 1, 074-1, 085. Epub 2007 Jul 10. Review. PMID: 17623802.	Cancer excluded as outcome of interest.
Kellen E, Zeegers M, Paulussen A, Van Dongen M, Buntinx F. Fruit consumption reduces the effect of smoking on bladder cancer risk. The Belgian case control study on bladder cancer. *Int J Cancer.* 2006 May 15; 118 (10): 2, 572-2, 578. PMID: 16380991.	Cancer excluded as outcome of interest.
Kim SY, Yoon S, Kwon SM, Park KS, Lee-Kim YC. Kale juice improves coronary artery disease risk factors in hypercholesterolemic men. *Biomed Environ Sci.* 2008 Apr; 21 (2): 91-97. PMID: 18548846.	Participants diagnosed with hypercholesterolemia.
Kirsh VA, Mayne ST, Peters U, Chatterjee N, Leitzmann MF, Dixon LB, Urban DA, Crawford ED, Hayes RB. A prospective study of lycopene and tomato product intake and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2006 Jan; 15 (1): 92-98. PMID: 16434593.	Cancer excluded as outcome of interest.
Kirsh VA, Peters U, Mayne ST, Subar AF, Chatterjee N, Johnson CC, Hayes RB; Prospective study of fruit and vegetable intake and risk of prostate cancer. Prospective study of fruit and vegetable intake and risk of prostate cancer. *J Natl Cancer Inst*. 2007 Aug 1; 99 (15): 1, 200-1, 209. Epub 2007 Jul 24. PMID: 17652276.	Cancer excluded as outcome of interest.
Klassen AC, Garrett-Mayer E, Houts PS, Shankar S, Torio CM. The relationship of body size to participation and success in a fruits and vegetables intervention among low-income women. *J Community Health*. 2008 Apr; 33 (2): 78-89. PMID: 18074208.	Does not answer question: Does not examine the relationship between vegetables and fruits and health outcomes.
Koushik A, Hunter DJ, Spiegelman D, Anderson KE, Arslan AA, Beeson WL, van den Brandt PA, Buring JE, Cerhan JR, Colditz GA, Fraser GE, Freudenheim JL, Genkinger JM, Goldbohm RA, Hankinson SE, Koenig KL, Larsson SC, Leitzmann M, McCullough ML, Miller AB, Patel A, Rohan TE, Schatzkin A, Smit E, Willett WC, Wolk A, Zhang SM, Smith-Warner SA. Fruits and vegetables and ovarian cancer risk in a pooled analysis of 12 cohort studies. *Cancer Epidemiol Biomarkers Prev.* 2005 Sep; 14 (9): 2, 160-2, 167. PMID: 16172226.	Cancer excluded as outcome of interest.

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

Koushik A, Hunter DJ, Spiegelman D, Beeson WL, van den Brandt PA, Buring JE, Calle EE, Cho E, Fraser GE, Freudenheim JL, Fuchs CS, Giovannucci EL, Goldbohm RA, Harnack L, Jacobs DR Jr, Kato I, Krogh V, Larsson SC, Leitzmann MF, Marshall JR, McCullough ML, Miller AB, Pietinen P, Rohan TE, Schatzkin A, Sieri S, Virtanen MJ, Wolk A, Zeleniuch-Jacquotte A, Zhang SM, Smith-Warner SA. Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies. *J Natl Cancer Inst*. 2007 Oct 3; 99 (19): 1, 471-1, 483. Epub 2007 Sep 25. PMID: 17895473.	Cancer excluded as outcome of interest.
Kurahashi N, Inoue M, Iwasaki M, Tanaka Y, Mizokami M, Tsugane S; JPHC Study Group. Vegetable, fruit and antioxidant nutrient consumption and subsequent risk of hepatocellular carcinoma: A prospective cohort study in Japan. *Br J Cancer*. 2009 Jan 13; 100 (1): 181-184. PMID: 19127270.	Cancer excluded as outcome of interest.
Lam TK, Gallicchio L, Lindsley K, Shiels M, Hammond E, Tao XG, Chen L, Robinson KA, Caulfield LE, Herman JG, Guallar E, Alberg AJ. Cruciferous vegetable consumption and lung cancer risk: a systematic review. *Cancer Epidemiol Biomarkers Prev.* 2009 Jan; 18 (1): 184-195. Review. PMID: 19124497.	Cancer excluded as outcome of interest.
Larsson SC, Andersson SO, Johansson JE, Wolk A. Fruit and vegetable consumption and risk of bladder cancer: A prospective cohort study. *Cancer Epidemiol Biomarkers Prev*. 2008 Sep; 17 (9): 2, 519-2, 522. PMID: 18768526.	Cancer excluded as outcome of interest.
Larsson SC, Bergkvist L, Wolk A. Fruit and vegetable consumption and incidence of gastric cancer: a prospective study. *Cancer Epidemiol Biomarkers Prev*. 2006 Oct; 15 (10): 1, 998-2, 001. PMID: 17035412.	Cancer excluded as outcome of interest.
Larsson SC, Håkansson N, Näslund I, Bergkvist L, Wolk A. Fruit and vegetable consumption in relation to pancreatic cancer risk: A prospective study. *Cancer Epidemiol Biomarkers Prev*. 2006 Feb; 15 (2): 301-305. PMID: 16492919.	Cancer excluded as outcome of interest.
Larsson SC, Holmberg L, Wolk A. Fruit and vegetable consumption in relation to ovarian cancer incidence: The Swedish Mammography Cohort.*Br J Cancer*. 2004 Jun 1; 90 (11): 2, 167-2, 170. PMID: 15150575.	Cancer excluded as outcome of interest.

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

Lee JE, Giovannucci E, Smith-Warner SA, Spiegelman D, Willett WC, Curhan GC. Intakes of fruits, vegetables, vitamins A, C, and E and carotenoids and risk of renal cell cancer. *Cancer Epidemiol Biomarkers Prev*. 2006 Dec; 15 (12): 2, 445-2, 452. PMID: 17164369.	Cancer excluded as outcome of interest.
Lin J, Zhang SM, Cook NR, Rexrode KM, Liu S, Manson JE, Lee IM, Buring JE. Dietary intakes of fruit, vegetables, and fiber and risk of colorectal cancer in a prospective cohort of women (United States).*Cancer Causes Control*. 2005 Apr; 16 (3): 225-233. PMID: 15947874.	Cancer excluded as outcome of interest.
Liu Y, Sobue T, Otani T, Tsugane S. Vegetables, fruit consumption and risk of lung cancer among middle-aged Japanese men and women: JPHC study. *Cancer Causes Control*. 2004 May; 15 (4): 349-357. PMID: 15141136.	Cancer excluded as outcome of interest.
Longo-Mbenza B, Tshimanga KB, Buassa-bu-Tsumbu B, Kabangu MJ. Diets rich in vegetables and physical activity are associated with a decreased risk of pregnancy induced hypertension among rural women from Kimpese, DR Congo. *Niger J Med*. 2008 Jul-Aug; 17 (3): 265-269. PMID: 18788250.	Study population not from a developed country as defined by the Human Development Index.
Lunet N, Lacerda-Vieira A, Barros H. Fruit and vegetables consumption and gastric cancer: a systematic review and meta-analysis of cohort studies. *Nutr Cancer*. 2005; 53 (1): 1-10. Review. PMID: 16351501.	Cancer excluded as outcome of interest.
Lunet N, Valbuena C, Vieira AL, Lopes C, Lopes C, David L, Carneiro F, Barros H. Fruit and vegetable consumption and gastric cancer by location and histological type: Case-control and meta-analysis. *Eur J Cancer Prev*. 2007 Aug; 16 (4): 312-327. PMID: 17554204.	Cancer excluded as outcome of interest.
Masala G, Ceroti M, Pala V, Krogh V, Vineis P, Sacerdote C, Saieva C, Salvini S, Sieri S, Berrino F, Panico S, Mattiello A, Tumino R, Giurdanella MC, Bamia C, Trichopoulou A, Riboli E, Palli D.A dietary pattern rich in olive oil and raw vegetables is associated with lower mortality in Italian elderly subjects.*Br J Nutr*. 2007 Aug; 98 (2): 406-415. Epub 2007 Apr 3. PMID: 17403268.	Does not answer question: Discusses vegetables and fruits as part of dietary pattern.

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Maserejian NN, Giovannucci E, Rosner B, Zavras A, Joshipura K. Prospective study of fruits and vegetables and risk of oral premalignant lesions in men. *Am J Epidemiol*. 2006 Sep 15; 164 (6): 556-566. Epub 2006 Jul 17. PMID: 16847039.	Cancer excluded as outcome of interest.
McCall DO, McGartland CP, McKinley MC, Patterson CC, Sharpe P, McCance DR, Young IS, Woodside JV. Dietary intake of fruits and vegetables improves microvascular function in hypertensive subjects in a dose-dependent manner. *Circulation*. 2009 Apr 28; 119 (16): 2, 153-2, 160. Epub 2009 Apr 13. PMID: 19364976.	Participants diagnosed with hypertension, and study did not measure identified outcome of interest.
McCullough ML, Bandera EV, Patel R, Patel AV, Gansler T, Kushi LH, Thun MJ, Calle EE. A prospective study of fruits, vegetables and risk of endometrial cancer. *Am J Epidemiol.* 2007 Oct 15; 166 (8): 902-911. Epub 2007 Aug 9. PMID: 17690222.	Cancer excluded as outcome of interest.
Michels KB, Giovannucci E, Chan AT, Singhania R, Fuchs CS, Willett WC. Fruit and vegetable consumption and colorectal adenomas in the Nurses' Health Study. *Cancer Res*. 2006 Apr 1; 66 (7): 3, 942-3, 953. PMID: 16585224.	Cancer excluded as outcome of interest.
Mikkelsen TB, Osler M, Orozova-Bekkevold I, Knudsen VK, Olsen SF. Association between fruit and vegetable consumption and birth weight: A prospective study among 43, 585 Danish women. *Scand J Public Health*. 2006; 34 (6): 616-622. PMID: 17132595.	Does not answer question: addresses vegetable and fruit intake during pregnancy and birth weight.
Millen AE, Subar AF, Graubard BI, Peters U, Hayes RB, Weissfeld JL, Yokochi LA, Ziegler RG; PLCO Cancer Screening Trial Project Team. Fruit and vegetable intake and prevalence of colorectal adenoma in a cancer screening trial. *Am J Clin Nutr*. 2007 Dec; 86 (6): 1, 754-1, 764. PMID: 18065596.	Cancer excluded as outcome of interest.
Mommers M, Schouten LJ, Goldbohm RA, van den Brandt PA. Consumption of vegetables and fruits and risk of ovarian carcinoma. *Cancer*. 2005 Oct 1; 104 (7): 1, 512-1, 519. PMID: 16104037.	Cancer excluded as outcome of interest.

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Nomura AM, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Pike MC, Kolonel LN. Association of vegetable, fruit, and grain intakes with colorectal cancer: The Multiethnic Cohort Study. *Am J Clin Nutr*. 2008 Sep; 88 (3): 730-737. PMID: 18779290.	Cancer excluded as outcome of interest.
Nöthlings U, Schulze MB, Weikert C, Boeing H, van der Schouw YT, Bamia C, Benetou V, Lagiou P, Krogh V, Beulens JW, Peeters PH, Halkjaer J, Tjønneland A, Tumino R, Panico S, Masala G, Clavel-Chapelon F, de Lauzon B, Boutron-Ruault MC, Vercambre MN, Kaaks R, Linseisen J, Overvad K, Arriola L, Ardanaz E, Gonzalez CA, Tormo MJ, Bingham S, Khaw KT, Key TJ, Vineis P, Riboli E, Ferrari P, Boffetta P, Bueno-de-Mesquita HB, van der A DL, Berglund G, Wirfält E, Hallmans G, Johansson I, Lund E, Trichopoulo A. Intake of vegetables, legumes, and fruit, and risk for all-cause, cardiovascular and cancer mortality in a European diabetic population. *J Nutr*. 2008 Apr; 138 (4): 775-781. PMID: 18356334.	Participants were diagnosed with diabetes.
Nöthlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN. Vegetable intake and pancreatic cancer risk: The multiethnic cohort study. *Am J Epidemiol*. 2007 Jan 15; 165 (2): 138-147. Epub 2006 Oct 26. PMID: 17068094.	Cancer excluded as outcome of interest.
Nouraie M, Pietinen P, Kamangar F, Dawsey SM, Abnet CC, Albanes D, Virtamo J, Taylor PR. Fruits, vegetables, and antioxidants and risk of gastric cancer among male smokers. *Cancer Epidemiol Biomarkers Prev*. 2005 Sep; 14 (9): 2, 087-2, 092. PMID: 16172214.	Cancer excluded as outcome of interest.
Orjuela MA, Titievsky L, Liu X, Ramirez-Ortiz M, Ponce-Castaneda V, Lecona E, Molina E, Beaverson K, Abramson DH, Mueller NE. Fruit and vegetable intake during pregnancy and risk for development of sporadic retinoblastoma. *Cancer Epidemiol Biomarkers Prev*. 2005 Jun; 14 (6): 1, 433-1, 440. PMID: 15941952.	Does not answer question: does not address outcomes of interest (examines retinoblastoma).
Papanikolaou Y, Fulgoni VL 3rd. Bean consumption is associated with greater nutrient intake, reduced systolic blood pressure, lower body weight and a smaller waist circumference in adults: Results from the National Health and Nutrition Examination Survey 1999-2002.*J Am Coll Nutr*. 2008 Oct; 27 (5): 569-576. PMID: 18845707.	Beans considered in separate question on cooked dry beans and peas and selected health outcomes.

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Pavia M, Pileggi C, Nobile CG, Angelillo IF. Association between fruit and vegetable consumption and oral cancer: A meta-analysis of observational studies. *Am J Clin Nutr*. 2006 May; 83 (5): 1, 126-1, 134. PMID: 16685056.	Cancer excluded as outcome of interest.
Pham TM, Fujino Y, Ide R, Kubo T, Shirane K, Tokui N, Mizoue T, Ogimoto I, Matsuda S, Yoshimura T. Prospective study of vegetable consumption and liver cancer in Japan. *Int J Cancer.* 2006 Nov 15; 119 (10): 2, 408-2, 411. PMID: 16894561.	Cancer excluded as outcome of interest.
Pomerleau J, Lock K, Knai C, McKee M. Interventions designed to increase adult fruit and vegetable intake can be effective: A systematic review of the literature. *J Nutr*. 2005 Oct; 135 (10): 2, 486-2, 495. Review. PMID: 16177217.	Does not answer question: Evaluates interventions to increase fruit and vegetable intake.
Prynne CJ, Mishra GD, O'Connell MA, Muniz G, Laskey MA, Yan L, Prentice A, Ginty F. Fruit and vegetable intakes and bone mineral status: A cross sectional study in five age and sex cohorts. *Am J Clin Nutr*. 2006 Jun; 83 (6): 1, 420-1, 428. PMID: 16789345.	Does not answer question: Does not address outcomes of interest.
Rai A, Mohapatra SC, Shukla HS. Correlates between vegetable consumption and gallbladder cancer. Eu*r J Cancer Prev*. 2006 Apr; 15 (2): 134-137. PMID: 16523010.	Participants diagnosed with gallbladder cancer or gallstone disease.
Ramón R, Ballester F, Iñiguez C, Rebagliato M, Murcia M, Esplugues A, Marco A, García de la Hera M, Vioque J. Vegetable but not fruit intake during pregnancy is associated with newborn anthropometric measures. *J Nutr*. 2009 Mar; 139 (3): 561-567. Epub 2009 Jan 21. PMID: 19158218.	Does not answer question: Addresses fruit and vegetable intake during pregnancy and birth outcomes.
Rashidkhani B, Lindblad P, Wolk A. Fruits, vegetables and risk of renal cell carcinoma: a prospective study of Swedish women.*Int J Cancer*. 2005 Jan 20; 113 (3): 451-455. PMID: 15455348.	Cancer excluded as outcome of interest.
Rodríguez MC, Parra MD, Marques-Lopes I, De Morentin BE, González A, Martínez JA. Effects of two energy-restricted diets containing different fruit amounts on body weight loss and macronutrient oxidation. *Plant Foods Hum Nutr*. 2005 Dec; 60 (4): 219-224. PMID: 16395633.	Does not meet inclusion criteria for sample size.

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Romieu I, Varraso R, Avenel V, Leynaert B, Kauffmann F, Clavel-Chapelon F. Fruit and vegetable intakes and asthma in the E3N study. *Thorax.* 2006 Mar; 61 (3): 209-215. Epub 2006 Jan 5. PMID: 16396945; PMCID: PMC1974844.	Does not answer question: Does not measure an identified outcome of interest.
Sandoval M, Font R, Mañós M, Dicenta M, Quintana MJ, Bosch FX, Castellsagué X. The role of vegetable and fruit consumption and other habits on survival following the diagnosis of oral cancer: A prospective study in Spain. *Int J Oral Maxillofac Surg*. 2009 Jan; 38 (1): 31-39. Epub 2008 Oct 31. PubMed PMID: 18951763.	Participants diagnosed with oral cancer.
Sartorelli DS, Franco LJ, Cardoso MA. High intake of fruits and vegetables predicts weight loss in Brazilian overweight adults. *Nutr Res*. 2008 Apr; 28 (4): 233-238. PMID: 19083413.	Dropout rate higher than inclusion criteria.
Sato K, Kawakami N, Ohtsu T, Tsutsumi A, Miyazaki S, Masumoto T, Horie S, Haratani T, Kobayashi F, Araki S. Broccoli consumption and chronic atrophic gastritis among Japanese males: An epidemiological investigation. *Acta Med Okayama*. 2004 Jun; 58 (3): 127-133. PMID: 15471434.	Does not answer question: Does not include outcome of interest (measured chronic atrophic gastritis).
Sato Y, Tsubono Y, Nakaya N, Ogawa K, Kurashima K, Kuriyama S, Hozawa A, Nishino Y, Shibuya D, Tsuji I. Fruit and vegetable consumption and risk of colorectal cancer in Japan: The Miyagi Cohort Study. *Public Health Nutr.* 2005 May; 8 (3): 309-314. PMID: 15918928.	Cancer excluded as outcome of interest.
Schnäbele K, Briviba K, Bub A, Roser S, Pool-Zobel BL, Rechkemmer G. Effects of carrot and tomato juice consumption on faecal markers relevant to colon carcinogenesis in humans.*Br J Nutr*. 2008 Mar; 99 (3): 606-613. PMID: 18254985.	Does not answer question: Does not include outcome of interest.

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

Schulz M, Lahmann PH, Boeing H, Hoffmann K, Allen N, Key TJ, Bingham S, Wirfält E, Berglund G, Lundin E, Hallmans G, Lukanova A, Martínez Garcia C, González CA, Tormo MJ, Quirós JR, Ardanaz E, Larrañaga N, Lund E, Gram IT, Skeie G, Peeters PH, van Gils CH, Bueno-de-Mesquita HB, Büchner FL, Pasanisi P, Galasso R, Palli D, Tumino R, Vineis P, Trichopoulou A, Kalapothaki V, Trichopoulos D, Chang-Claude J, Linseisen J, Boutron-Ruault MC, Touillaud M, Clavel-Chapelon F, Olsen A, Tjønneland A, Overvad K, Tetsche M, Jenab M, Norat T, Kaaks R, Riboli E. Fruit and vegetable consumption and risk of epithelial ovarian cancer: The European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiol Biomarkers Prev*. 2005 Nov; 14 (11 Pt 1): 2, 531-2, 535. PMID: 16284374.	Cancer excluded as outcome of interest.
Setiawan VW, Yu GP, Lu QY, Lu ML, Yu SZ, Mu L, Zhang JG, Kurtz RC, Cai L, Hsieh CC, Zhang ZF. Allium vegetables and stomach cancer risk in China. *Asian Pac J Cancer Prev.* 2005 Jul-Sep; 6 (3): 387-395. PMID: 16236005.	Cancer excluded as outcome of interest.
Shi Z, Hu X, Yuan B, Hu G, Pan X, Dai Y, Byles JE, Holmboe-Ottesen G. Vegetable-rich food pattern is related to obesity in China. *Int J Obes* (Lond). 2008 Jun; 32 (6): 975-984. Epub 2008 Mar 4. PMID: 18317472.	Includes fruits, vegetables, and whole grains as part of vegetable-rich food pattern. Does not evaluate vegetable and fruit and health outcomes specifically.
Skuladottir H, Tjoenneland A, Overvad K, Stripp C, Olsen JH. Does high intake of fruit and vegetables improve lung cancer survival? *Lung Cancer*. 2006 Mar; 51 (3): 267-273. Epub 2006 Feb 15. PMID: 16469411.	Participants diagnosed with lung cancer.
Stoner GD, Wang LS, Casto BC. Laboratory and clinical studies of cancer chemoprevention by antioxidants in berries. *Carcinogenesis*. 2008 Sep; 29 (9): 1, 665-1, 674. Epub 2008 Jun 9. Review. PMID: 18544560.	Study design is narrative review.
Sunny L. A low fat diet rich in fruits and vegetables may reduce the risk of developing prostate cancer. *Asian Pac J Cancer Prev*. 2005 Oct-Dec; 6 (4): 490-496. PMID: 16435998.	Cancer excluded as outcome of interest.

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Tang L, Zirpoli GR, Guru K, Moysich KB, Zhang Y, Ambrosone CB, McCann SE. Consumption of raw cruciferous vegetables is inversely associated with bladder cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2008 Apr; 17 (4): 938-944. PMID: 18398034.	Cancer excluded as outcome of interest.
Tao MH, Xu WH, Zheng W, Gao YT, Ruan ZX, Cheng JR, Xiang YB, Shu XO. A case-control study in Shanghai of fruit and vegetable intake and endometrial cancer. *Br J Cancer*. 2005 Jun 6; 92 (11): 2, 059-2, 064. PMID: 15886701.	Cancer excluded as outcome of interest.
te Velde SJ, Twisk JW, Brug J. Tracking of fruit and vegetable consumption from adolescence into adulthood and its longitudinal association with overweight. *Br J Nutr*. 2007 Aug; 98 (2): 431-438. Epub 2007 Apr 16. Erratum in: *Br J Nutr.* 2007 Oct; 98 (4): 871. PMID: 17433126.	Adolescents considered in the Energy Balance section.
Thomson CA, Rock CL, Giuliano AR, Newton TR, Cui H, Reid PM, Green TL, Alberts DS; Women's Healthy Eating & Living Study Group. Longitudinal changes in body weight and body composition among women previously treated for breast cancer consuming a high-vegetable, fruit and fiber, low-fat diet. *Eur J Nutr*. 2005 Feb; 44 (1): 18-25. Epub 2004 Mar 5. PMID: 15309460.	Participants were women who had been treated for breast cancer.
Tobias M, Turley M, Stefanogiannis N, Vander Hoorn S, Lawes C, Mhurchu CN, Rodgers A. Vegetable and fruit intake and mortality from chronic disease in New Zealand. *Aust N Z J Public Health.* 2006 Feb; 30 (1): 26-31. PMID: 16502948.	Does not answer question: Does not examine relationship between vegetable and fruit intake and disease.
Tohill BC, Seymour J, Serdula M, Kettel-Khan L, Rolls BJ. What epidemiologic studies tell us about the relationship between fruit and vegetable consumption and body weight. *Nutr Rev*. 2004 Oct; 62 (10): 365-374. Review. PMID: 15508906.	Study design is narrative review.
Traka M, Gasper AV, Melchini A, Bacon JR, Needs PW, Frost V, Chantry A, Jones AM, Ortori CA, Barrett DA, Ball RY, Mills RD, Mithen RF. Broccoli consumption interacts with GSTM1 to perturb oncogenic signaling pathways in the prostate. *PLoS One*. 2008 Jul 2; 3 (7): e2568. PMID: 18596959; PMCID: PMC2430620.	Does not answer question: Does not include outcome of interest.

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Tsubono Y, Otani T, Kobayashi M, Yamamoto S, Sobue T, Tsugane S; JPHC Study Group. No association between fruit or vegetable consumption and the risk of colorectal cancer in Japan.*Br J Cancer*. 2005 May 9; 92 (9): 1, 782-1, 784. PMID: 15856039.	Cancer excluded as outcome of interest.
Turner F, Smith G, Sachse C, Lightfoot T, Garner RC, Wolf CR, Forman D, Bishop DT, Barrett JH. Vegetable, fruit and meat consumption and potential risk modifying genes in relation to colorectal cancer. *Int J Cancer*. 2004 Nov 1; 112 (2): 259-264. PMID: 15352038.	Cancer excluded as outcome of interest.
van Dijk BA, Schouten LJ, Kiemeney LA, Goldbohm RA, van den Brandt PA. Vegetable and fruit consumption and risk of renal cell carcinoma: Results from the Netherlands cohort study. *Int J Cancer*. 2005 Nov 20; 117 (4): 648-654. PMID: 15929109.	Cancer excluded as outcome of interest.
van Duijnhoven FJ, Bueno-De-Mesquita HB, Ferrari P, Jenab M, Boshuizen HC, Ros MM, Casagrande C, Tjønneland A, Olsen A, Overvad K, Thorlacius-Ussing O, Clavel-Chapelon F, Boutron-Ruault MC, Morois S, Kaaks R, Linseisen J, Boeing H, Nöthlings U, Trichopoulou A, Trichopoulos D, Misirli G, Palli D, Sieri S, Panico S, Tumino R, Vineis P, Peeters PH, van Gils CH, Ocké MC, Lund E, Engeset D, Skeie G, Suárez LR, González CA, Sánchez MJ, Dorronsoro M, Navarro C, Barricarte A, Berglund G, Manjer J, Hallmans G, Palmqvist R, Bingham SA, Khaw KT, Key TJ, Allen NE, Boffetta P, Slimani N, Rinaldi S, Gallo V, Norat T, Riboli E. Fruit, vegetables and colorectal cancer risk: The European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr*. 2009 May; 89 (5): 1, 441-1, 452. Epub 2009 Apr 1. PMID: 19339391.	Cancer excluded as outcome of interest.
van Gils CH, Peeters PH, Bueno-de-Mesquita HB, Boshuizen HC, Lahmann PH, Clavel-Chapelon F, Thiébaut A, Kesse E, Sieri S, Palli D, Tumino R, Panico S, Vineis P, Gonzalez CA, Ardanaz E, Sánchez MJ, Amiano P, Navarro C, Quirós JR, Key TJ, Allen N, Khaw KT, Bingham SA, Psaltopoulou T, Koliva M, Trichopoulou A, Nagel G, Linseisen J, Boeing H, Berglund G, Wirfält E, Hallmans G, Lenner P, Overvad K, Tjønneland A, Olsen A, Lund E, Engeset D, Alsaker E, Norat T, Kaaks R, Slimani N, Riboli E. Consumption of vegetables and fruits and risk of breast cancer. *JAMA*. 2005 Jan 12; 293 (2): 183-193. PMID: 15644545.	Cancer excluded as outcome of interest.

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Wakita Asano A, Miyoshi M, Arai Y, Yoshita K, Yamamoto S, Yoshiike N. Association between vegetable intake and dietary quality in Japanese adults: A secondary analysis from the National Health and Nutrition Survey, 2003.*J Nutr Sci Vitaminol* (Tokyo). 2008 Oct; 54 (5): 384-391. PMID: 19001770.	Does not answer question: Does not examine the relationship between vegetables and fruits and health outcomes.
Wang LI, Giovannucci EL, Hunter D, Neuberg D, Su L, Christiani DC. Dietary intake of Cruciferous vegetables, Glutathione S-transferase (GST) polymorphisms and lung cancer risk in a Caucasian population. *Cancer Causes Control*. 2004 Dec; 15 (10): 977-985. PMID: 15801482.	Cancer excluded as outcome of interest.
Wark PA, Grubben MJ, Peters WH, Nagengast FM, Kampman E, Kok FJ, van 't Veer P. Habitual consumption of fruits and vegetables: associations with human rectal glutathione S-transferase. *Carcinogenesis*. 2004 Nov; 25 (11): 2, 135-2, 142. Epub 2004 Jul 29. PMID: 15284178.	Does not answer question: Does not include outcome of interest.
Wark PA, Weijenberg MP, van 't Veer P, van Wijhe G, Lüchtenborg M, van Muijen GN, de Goeij AF, Goldbohm RA, van den Brandt PA. Fruits, vegetables, and hMLH1 protein-deficient and -proficient colon cancer: The Netherlands cohort study. *Cancer Epidemiol Biomarkers Prev*. 2005 Jul; 14 (7): 1, 619-1, 625. PMID: 16030092.	Cancer excluded as outcome of interest.
Weikert S, Boeing H, Pischon T, Olsen A, Tjonneland A, Overvad K, Becker N, Linseisen J, Lahmann PH, Arvaniti A, Kassapa C, Trichoupoulou A, Sieri S, Palli D, Tumino R, Vineis P, Panico S, van Gils CH, Peeters PH, Bueno-de-Mesquita HB, Büchner FL, Ljungberg B, Hallmans G, Berglund G, Wirfält E, Pera G, Dorronsoro M, Gurrea AB, Navarro C, Martinez C, Quirós JR, Allen N, Roddam A, Bingham S, Jenab M, Slimani N, Norat T, Riboli E. Fruits and vegetables and renal cell carcinoma: findings from the European prospective investigation into cancer and nutrition (EPIC).*Int J Cancer.* 2006 Jun 15; 118 (12): 3, 133-3, 139. PMID: 16425278.	Cancer excluded as outcome of interest.
Whybrow S, Harrison CL, Mayer C, James Stubbs R. Effects of added fruits and vegetables on dietary intakes and body weight in Scottish adults.*Br J Nutr*. 2006 Mar; 95 (3): 496-503. PMID: 16512935.	Does not answer question: Includes supplements, not food, in analyses.

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Williams MT, Hord NG. The role of dietary factors in cancer prevention: Beyond fruits and vegetables. *Nutr Clin Pract.* 2005 Aug; 20 (4): 451-459. Review. PMID: 16207684.	Study design is narrative review.
Wright ME, Park Y, Subar AF, Freedman ND, Albanes D, Hollenbeck A, Leitzmann MF, Schatzkin A. Intakes of fruit, vegetables and specific botanical groups in relation to lung cancer risk in the NIH-AARP Diet and Health Study. *Am J Epidemiol*. 2008 Nov 1; 168 (9): 1, 024-1, 034. Epub 2008 Sep 12. PMID: 18791192; PMCID: PMC2631557.	Cancer excluded as outcome of interest.
Wu H, Dai Q, Shrubsole MJ, Ness RM, Schlundt D, Smalley WE, Chen H, Li M, Shyr Y, Zheng W. Fruit and vegetable intakes are associated with lower risk of colorectal adenomas. *J Nutr.* 2009 Feb; 139 (2): 340-344. Epub 2008 Dec 17. PMID: 19091801; PMCID: PMC2646202.	Cancer excluded as outcome of interest.
Yamaji T, Inoue M, Sasazuki S, Iwasaki M, Kurahashi N, Shimazu T, Tsugane S; Japan Public Health Center-based Prospective Study Group. Fruit and vegetable consumption and squamous cell carcinoma of the esophagus in Japan: The JPHC study. *Int J Cancer*. 2008 Oct 15; 123 (8): 1, 935-1, 940. PMID: 18688852.	Cancer excluded as outcome of interest.
Yeh M, Moysich KB, Jayaprakash V, Rodabaugh KJ, Graham S, Brasure JR, McCann SE. Higher intakes of vegetables and vegetable-related nutrients are associated with lower endometrial cancer risks. *J Nutr*. 2009 Feb; 139 (2): 317-322. Epub 2008 Dec 11. PMID: 19074206.	Cancer excluded as outcome of interest.
Zhang CX, Ho SC, Chen YM, Fu JH, Cheng SZ, Lin FY. Greater vegetable and fruit intake is associated with a lower risk of breast cancer among Chinese women. *Int J Cancer*. 2009 Jul 1; 125 (1): 181-188. PMID: 19358284.	Cancer excluded as outcome of interest.

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CHAPTER 11. VEGETABLES AND FRUITS – BODY WEIGHT

IN ADULTS, WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF VEGETABLES AND FRUITS, NOT INCLUDING JUICE, AND BODY WEIGHT?

Conclusion statement

The evidence for an association between increased fruit and vegetable intake and lower body weight is modest with a trend towards decreased weight gain over five or more years in middle adulthood. No conclusions can be drawn from the evidence on the efficacy of increased fruit and vegetable consumption in weight loss diets.

Grade

Moderate

Evidence summary overview

A modest association with decreased weight gain over five or more years in middle adulthood has been reported with increased vegetable and fruit. However, based on current studies, no conclusions can be drawn about the efficacy of increasing vegetable and fruit consumption in achieving weight loss, nor can any distinction be made about the relative influence of fruits vs. vegetables on weight status.

The review of evidence regarding weight gain and vegetable and fruit consumption was based on 11 studies (Bes-Rastrollo, 2006; Buijee, 2009; Davis, 2006; Fujioka, 2006; Goss, 2005; He, 2004; Ortega, 2006; Radhika, 2008; Tanumibardjo, 2009; Vioque, 2008; Xu, 2007). These studies were conducted around the globe and varied considerably in length of observation. Two of the randomized controlled trials (RCTs) (Fujioka, 2006; Ortega, 2006) collected data at an endpoint of only six weeks; a third RCT evaluated participants at three, 12 and 18 months. All indicated small, but significant, and non-sustainable weight loss over time with an intensive addition of vegetables and fruits to the diet. Similar results showing weak inverse relationships between vegetable and fruit consumption and weight gain were noted in the prospective (Buijsee, 2009; He, 2004; Vioque, 2008), case control (David, 2006) and cross-sectional studies (Bes-Rastrollo, 2006; Goss, 2005; Radhika, 2008) that followed participants over a longer time. The evidence is insufficient to ascertain the value of vegetable and fruit consumption in weight loss diets.

Evidence summary paragraphs

Randomized Controlled Trials

Fujioka et al, 2006 (positive quality), a randomized, double-blind, placebo-controlled study compared the effects of fresh grapefruit, grapefruit juice, grapefruit capsules and placebo capsules on body weight and metabolic syndrome. Participants were 91 obese adults who were randomly assigned to four groups: 1) Placebo capsules and seven ounces of apple juice; 2) Grapefruit capsules with seven ounces of apple juice; 3) Eight ounces of grapefruit juice with placebo capsules; 4) Half of a fresh grapefruit (eaten before meals) with placebo capsules three times a day. Participants were asked to maintain their usual diet and were encouraged to walk 20 to 30 minutes, three to four times a week. Assessments were completed at baseline and 12 weeks; 77 participants completed

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the study. After 12 weeks, the fresh grapefruit group lost 1.6kg, the grapefruit juice group lost 1.5kg, the grapefruit capsule group lost 1.1kg, and the placebo group lost 0.3kg. Weight loss in the fresh grapefruit group (1.6kg) was significantly greater compared to placebo (0.3kg) after 12 weeks of treatment (P=0.048). In a secondary analysis of those with metabolic syndrome (34%), those in the grapefruit, grapefruit capsule and grapefruit juice groups demonstrated a significantly greater weight loss than those in the placebo group (P<0.02). The authors concluded that eating half a fresh grapefruit before each meal three times a day is associated with weight loss over three months in obese subjects.

Ortega et al, 2006 (positive quality), a randomized trial conducted in Spain, examined the effect of two hypocaloric diets promoting cereal or vegetable intake on weight loss in women. A total of 67 women began the study and 57 completed the six-week dietary intervention. Participants in the C group were encouraged to increase their consumption of cereal, especially breakfast cereal. Participants in the V group were encouraged to increase their consumption of greens and vegetables. At both two and six weeks, diet V was associated with an increase in the consumption of vegetables and diet C was associated with an increase in intake of cereals. Both diets led to a significant reduction in body weight and body mass index (BMI), both at week two and six. At six weeks, mean weight loss on diet C was significantly greater than diet V [mean (SD) = 2.8 (1.4) vs. 2.0 (1.3) kg, respectively; P<0.05]. The authors concluded that both diets were successful in reducing body weight and BMI, but diet C was significantly more effective than diet V.

Tanumihardjo et al, 2009 (positive quality), an RCT conducted in the US, investigated if encouraging high vegetable (eight servings) and moderate fruit (two to three servings) intake would result in weight reduction in obese individuals. Participants were 60 obese adults (73% female; 78% Caucasian; 21 to 50 years old) who were randomly assigned to High Vegetable Group or Reduction Group. Both groups received food (two meals and one snack a day, five days a week) and education (two group lessons a week plus individual consultation, as requested) for the first three months followed by a one-month transition that included food two days a week and limited education (no group sessions, but individual consultations, as requested). During month five to 18, participants were asked to maintain their dietary strategy, and support calls were provided with gradually decreasing frequency (from weekly to monthly). Both groups were taught to follow a healthy eating plan as described by the Food Guide Pyramid. The High Vegetable Group was provided seven to eight servings of vegetables and two servings of fruit a day, and they were asked not to eat potato chips, fried vegetables or fruit or vegetable juices to meet goals. The Reduction Group was provided 3.5 to four servings of vegetables and two servings of fruit a day and they were encouraged to reduce caloric intake by 500kcal a day from estimated kcal needed for weight maintenance and to consume less than 25% of kcal from fat. Assessments were completed at baseline, three, 12, and 18 months [dietary intake: three-day diet records; height, weight, and body composition (air displacement plethysmography) measured by study personnel]. Three-, 12-, and 18-month follow-up was completed by 93%, 75% and 53%, respectively. Both groups lost weight after three months, but only the Reduction Group maintained weight loss at 12 and 18 months. However, the High Vegetable Group did not regain weight above baseline. In the High Vegetable Group, weight and fat-mass were lower than baseline at three months (P=0.0087

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and P=0.0002, respectively), while fat-free mass increased from baseline at three months (P=0.0075). Body mass index (BMI) was lower than baseline at only three months (P=0.014). The Reduction Group decreased weight at three (P<0.0001), 12 (P=0.0001), and 18 (P=0.019) months. Fat mass was lower than baseline at three (P<0.0001) and 12 (P=0.0032) months, and fat-free mass did not differ from baseline at any follow-up (P>0.058). Mean BMI was lower than baseline at all three follow-ups (P<0.045). Daily energy consumed did not differ between the groups long-term, but the Reduction Group consumed fewer kcals per day than the High Vegetable Group at three months (P=0.033). The Reduction Group also increased their physical activity relative to baseline, and the High Vegetable Group did not. At three months, only 39.1% of the High Vegetable Group consumed more than seven servings of vegetables a day. The increased vegetable and moderate amounts of fruit diet was not as effective for weight loss as the more traditional energy and fat restriction diet after three months of an intensive food and education intervention or for weight loss maintenance long-term.

Prospective Cohort Studies

Buijsse et al, 2009 (positive quality), the prospective European Prospective Investigation into Cancer and Nutrition (EPIC) study, assessed whether baseline fruit and vegetable intake was associated with subsequent changes in body weight. A total of 89,432 men and women from Denmark, Germany, United Kingdom, Italy and the Netherlands were included in the analysis. Over a mean follow-up of 6.5 years, men and women gained weight over time in all cohorts, with an overall mean weight change of 330g per year. Fruit and vegetable intake was weakly inversely associated with weight change; per 100g intake of fruit and vegetables, weight change was -14g per year (95% CI: -19, -9g per year).

He et al, 2004 (positive quality), a prospective cohort study (Nurses' Health Study) examined the changes in intake of fruits and vegetables with respect to the risk of obesity and weight gain among middle-aged women. The authors analyzed data from 74,063 female nurses aged 38 to 63 years [free of cardiovascular disease (CVD), cancer and diabetes at baseline] from 11 US states. Median daily intake of fruits was 1.9 servings and of vegetables was 3.2 servings. Participants with high fruit and vegetable intakes exercised more, smoked less and were more likely to use postmenopausal hormones. During the 12-year follow-up, participants tended to gain weight with aging, but those with the largest increase in fruit and vegetable intake had a 24% lower risk of becoming obese compared with those who had the largest decrease in intake after adjustment for age, physical activity, smoking, total energy intake and other lifestyle variables (RR=0.76; 95% CI: 0.69, 0.86; P<0.0001). For major weight gain (25kg or more), women with the largest increase in intake of fruits and vegetables had a 28% lower risk compared to those in the other extreme group (RR=0.72; 95% CI: 0.55, 0.93; P=0.01). Similar results were observed for changes in intake of fruits and vegetables when analyzed separately.

Vioque et al, 2008 (neutral quality), a cohort study conducted in Spain, investigated the association between the intake of fruits and vegetables and weight gain over a 10-year period in an adult Mediterranean population. A total of 89 men and 117 women were included in the analysis. The 10-year weight gain was significantly lower with increasing quartile of fruit and vegetable intake (P=0.0001). Compared to participants in the lowest quartile of fruit consumption (less than 149gper day),

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participants in the third quartile (249 to 386g per day) reduced their risk of gaining more than 3.41kg by 69% (OR=0.31, 95% CI: 0.11, 0.85; P=0.044). Concerning vegetable intake, the risk of weight gain was lowest in participants of the fourth quartile (more than 333g per day), which had an 82% reduced risk of gaining 3.41kg or more over the 10-year period (OR=0.18; 95% CI: 0.05, 0.66; P=0.017). When fruits and vegetables were combined, the risk of weight gain decreased across quartiles, with the lowest risk among those in the fourth quartile (OR=0.22; 95% CI: 0.06, 0.81; P=0.022).

Case-Control Study

Davis et al, 2006 (positive quality), a case-control study conducted in the US, assessed differences in dietary intake between overweight and obese subjects and normal weight controls matched for age, sex and height. A total of 138 subjects were initially included; the final sample consisted of 104 adults, 52 overweight or obese subjects and 52 normal weight controls. The overweight and obese group was 31kg heavier and had 71% more body fat than their controls; they also consumed significantly more total fat, saturated fat and cholesterol and significantly less carbohydrate (CHO), complex CHO and dietary fiber per 1,000kcal (all P<0.01). On average, overweight or obese subjects consumed one less fruit serving per day than their normal weight counterpart (P<0.01) and servings of fruit per day were negatively related to percent body fat (R=-0.40, P<0.01).

Cross-Sectional Studies

Bes-Rastrollo et al, 2006 (neutral quality), a cross-sectional analysis of the Seguimiento Universidad de Navarra (SUN) prospective cohort study conducted in Spain, determined the association between fiber intake and fruit and vegetable consumption with the likelihood of weight gain in the previous five years in a Mediterranean population. A total of 5,094 men and 6,613 women were included in the analysis. Multivariate-adjusted OR for self-reported weight gain across quintiles of fiber intake were 1.00 (reference), 0.86, 0.86, 0.70 and 0.52 (P<0.001) among men and 1.00 (reference), 0.99, 1.08, 1.05 and 0.72 (P=0.005) among women. There was a significant inverse association between total fruit and vegetable consumption and weight gain, but only among men (adjusted OR across quintiles: 1.00, 0.78, 0.89, 0.70, and 0.54, P<0.001).

Goss et al, 2005 (neutral quality), a cross-sectional study compared BMI, consumption of fruits and vegetables, smoking and physical activity in residents of the seven Florida counties with the highest reported BMI (N=3,559) and the seven Florida counties with the lowest reported BMI (N=3,501). The authors utilized the 2002 data from the Florida Department of Health Behavioral Risk Factor Surveillance System. In counties with the highest mean BMI, 40.5% ate three or less fruits and vegetables per day, compared to 30.3% in counties with the lowest mean BMI. Similarly, 59.6% in the counties with the highest mean BMI ate three or more fruits and vegetables per day, compared with 69.6% of respondents from counties with the lowest mean BMI. Pearson chi-square analyses showed a significant difference for fruit and vegetable consumption between the seven highest and lowest mean BMI counties $\chi 2$ (3, N=7,054) = 89.0, P<0.001. A positive relationship between mean BMI and consumption of fruits and vegetables remained when controlled for physical activity, but not for smoking.

Radhika et al, 2008 (positive quality), a population-based cross-sectional study,

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evaluated the association of fruit and vegetable intake with cardiovascular risk factors such as obesity, hypertension (HTN), fasting plasma glucose and dyslipidemia in urban Asian Indians living in southern India. A total of 983 adults were included in the analysis. After adjusting for potential confounders, the highest quartile of fruit and vegetable intake (g per day) showed a significant inverse association with BMI (β=-2.3kg/m^2; 95% CI: -2.96, -1.57, P<0.0001) and waist circumference (WC) (β=-2.6cm; 95% CI: -3.69, -1.46, P<0.0001) when compared with the lowest quartile.

Xu et al, 2007 (neutral quality), a cross-sectional study examined the association of red meat and vegetable consumption with excess body weight. Data (N=23,316) from a large-scale population-based cross sectional study from Nanjing municipality (three urban districts and two rural counties) was used to evaluate meat and vegetable consumption as well as anthropometrics. Results showed that 95.3% of participants consumed more than 100g of vegetable per day. Urban residents consumed more red meat (OR=3.96; 95% CI: 3.79, 4.13) and fewer vegetables (OR=0.84; 95% CI: 0.80, 0.88). Excess body weight was not statistically associated with consumption of vegetables (OR=1.05; 95% CI: 0.91, 1.21).

Overview table

Study	Study Type	Association: Pos, Neg, None
Fujioka et al, 2006 Positive Quality	RCT, consumption of various forms of grapefruit vs. placebo, US.	Fresh grapefruit associated with weight loss.
Ortega et al, 2006 Positive Quality	RCT, compared two weight loss programs promoting cereal or vegetable intake, Spain.	Both groups lost weight, but weight loss was greater in cereal group.
Tanumihardjo et al, 2009 Positive Quality	RCT, compared two weight loss programs - one with seven to eight servings of vegetables a day and the other with 3.5 to five servings of vegetables a day, US.	Both groups lost weight, but the moderate vegetable diet was more effective than high vegetable diet over the long term (18 months).
Buijsse et al, 2009 Positive Quality	Prospective cohort study, EPIC, UK and Europe.	Weight gain: (-) Vegetable and fruit.

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He et al, 2004 Positive Quality	Prospective cohort study, Nurses' Health Study, US.	Weight gain: (-) Vegetable and/or fruit.
Vioque et al, 2008 Neutral Quality	Prospective cohort study, Spain.	Weight gain: (-) Vegetable and/or fruit.
Davis et al, 2006 Positive Quality	Case-control, US.	Overweight or obese subjects consumed less fruit than normal-weight controls.
Bes-Rastrollo et al, 2006 Neutral Quality	Cross-sectional analysis of prospective cohort, SUN Prospective Cohort, Spain.	Weight gain: (-) vegetable and fruit (men), Ø vegetable and fruit (women).
Goss & Grubbs, 2005 Neutral Quality	Cross-sectional, US.	BMI: (-) Vegetable and fruit.
Radhika et al, 2008 Positive Quality	Cross-sectional, India.	BMI: (-) Vegetable and fruit.
Xu et al, 2007 Neutral Quality	Cross-sectional, China.	Excess body weight: Ø Vegetables (fruit not examined).

Search plan and results

Inclusion criteria

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

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Exclusion criteria

- Studies that only consider cancer outcomes
- Studies that considered vegetables and fruits as part of a larger dietary pattern
- Medical treatment/therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human Development Index (http://hdr.undp.org/en/statistics/)
- Animal studies
- In vitro studies
- Articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed

  ("Fruit"[majr:NoExp] OR fruit OR "Vegetables"[majr]) AND ("Adiposity"[majr] OR "Overweight"[majr] OR "Obesity"[majr] OR "Weight Gain"[majr] OR "Body Weights and Measures"[Majr] OR "body mass index"[majr] OR "body composition"[majr] OR "energy intake"[majr] OR caloric intake*)

  ("Fruit"[majr:NoExp] OR "Vegetables"[majr]) AND ("Diabetes Mellitus, Type 2"[majr] OR "metabolic syndrome X"[majr] OR "hypertension"[majr] OR "dyslipidemias"[MeSH Terms] OR "cardiovascular diseases"[majr] OR "heart diseases"[majr] OR "chronic disease"[mh] OR "Neoplasms"[majr])

Date searched: 07/23/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 626
- Total articles identified to review from electronic databases: 143
- Articles identified via handsearch or other means: 1
- Number of Primary Articles Identified: 29
- Number of Review Articles Identified: 4
- Total Number of Articles Identified: 33
- Number of Articles Reviewed but Excluded: 111

Included articles (References)

In adults, what is the relationship between the intake of vegetables and fruits, not including juice and cardiovascular disease?

Systematic Reviews/Meta-analyses

1. Dauchet L, Amouyel P, Hercberg S, Dallongeville J. Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. *J Nutr.* 2006 Oct; 136 (10): 2, 588-2, 593. PMID: 16988131.
2. Dauchet L, Amouyel P, Dallongeville J. Fruit and vegetable consumption and risk of stroke: A meta-analysis of cohort studies. *Neurology*. 2005 Oct 25; 65 (8): 1, 193-1, 197. PMID: 16247045.
3. He FJ, Nowson CA, Lucas M, MacGregor GA. Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: Meta-

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analysis of cohort studies. *J Hum Hypertens.* 2007 Sep; 21 (9): 717-728. Epub 2007 Apr 19. PMID: 17443205.
4. He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: Meta-analysis of cohort studies. *Lancet.* 2006 Jan 28; 367 (9507): 320-326. Review. PMID: 16443039.

Primary Citations

1. Galeone C, Tavani A, Pelucchi C, Negri E, La Vecchia C. Allium vegetable intake and risk of acute myocardial infarction in Italy. *Eur J Nutr*. 2009 Mar; 48 (2): 120-123. Epub 2009 Jan 13. PMID: 19142565.
2. Genkinger JM, Platz EA, Hoffman SC, Comstock GW, Helzlsouer KJ. Fruit, vegetable and antioxidant intake and all-cause, cancer and cardiovascular disease mortality in a community-dwelling population in Washington County, Maryland. *Am J Epidemiol*. 2004 Dec 15; 160 (12): 1, 223-1, 233. PMID: 15583375.
3. Hung HC, Joshipura KJ, Jiang R, Hu FB, Hunter D, Smith-Warner SA, Colditz GA, Rosner B, Spiegelman D, Willett WC. Fruit and vegetable intake and risk of major chronic disease. *J Natl Cancer Inst*. 2004 Nov 3; 96 (21): 1, 577-1, 584. PMID: 15523086.
4. Joshipura KJ, Hung HC, Li TY, Hu FB, Rimm EB, Stampfer MJ, Colditz G, Willett WC. Intakes of fruits, vegetables and carbohydrate and the risk of CVD. *Public Health Nutr*. 2009 Jan; 12 (1): 115-121. Epub 2008 Apr 15. PMID: 18410704.
5. Nakamura K, Nagata C, Oba S, Takatsuka N, Shimizu H. Fruit and vegetable intake and mortality from cardiovascular disease are inversely associated in Japanese women but not in men. *J Nutr*. 2008 Jun; 138 (6): 1, 129-1, 134. PMID: 18492845.
6. Nikolic M, Nikic D, Petrovic B. Fruit and vegetable intake and the risk for developing coronary heart disease. *Cent Eur J Public Health*. 2008 Mar; 16 (1): 17-20. PMID: 18459474.
7. Takachi R, Inoue M, Ishihara J, Kurahashi N, Iwasaki M, Sasazuki S, Iso H, Tsubono Y, Tsugane S; JPHC Study Group. Fruit and vegetable intake and risk of total cancer and cardiovascular disease: Japan Public Health Center-Based Prospective Study. *Am J Epidemiol.* 2008 Jan 1; 167 (1): 59-70. Epub 2007 Oct 10. PMID: 17928402.
8. Tucker KL, Hallfrisch J, Qiao N, Muller D, Andres R, Fleg JL; Baltimore Longitudinal Study of Aging. The combination of high fruit and vegetable and low saturated fat intakes is more protective against mortality in aging men than is either alone: The Baltimore Longitudinal Study of Aging. *J Nutr*. 2005 Mar; 135 (3): 556-561. PMID: 15735093.

Blood Pressure/Hypertension

1. Mirmiran P, Noori N, Zavareh MB, Azizi F. Fruit and vegetable consumption and risk factors for cardiovascular disease. *Metabolism*. 2009 Apr; 58 (4): 460-468. PMID: 19303965.
2. Nuñez-Cordoba JM, Alonso A, Beunza JJ, Palma S, Gomez-Gracia E, Martinez-Gonzalez MA. Role of vegetables and fruits in Mediterranean diets to prevent hypertension. *Eur J Clin Nutr*. 2009 May; 63 (5): 605-612. Epub 2008 Feb 27. PMID: 18301434.
3. Radhika G, Sudha V, Mohan Sathya R, Ganesan A, Mohan V. Association of

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fruit and vegetable intake with cardiovascular risk factors in urban south Indians. *Br J Nutr.* 2008 Feb; 99 (2): 398-405. Epub 2007 Aug 3. PMID: 17678569.
4. Utsugi MT, Ohkubo T, Kikuya M, Kurimoto A, Sato RI, Suzuki K, Metoki H, Hara A, Tsubono Y, Imai Y. Fruit and vegetable consumption and the risk of hypertension determined by self measurement of blood pressure at home: The Ohasama study. *Hypertens Res.* 2008 Jul; 31 (7): 1, 435-1, 443. PMID: 18957815.
5. Wang YF, Yancy WS Jr, Yu D, Champagne C, Appel LJ, Lin PH. The relationship between dietary protein intake and blood pressure: Results from the PREMIER study. *J Hum Hypertens*. 2008 Nov; 22 (11): 745-754. Epub 2008 Jun 26. PMID: 18580887. (Hand search)

Blood Lipids

1. Kelley DS, Rasooly R, Jacob RA, Kader AA, Mackey BE. Consumption of Bing sweet cherries lowers circulating concentrations of inflammation markers in healthy men and women. *J Nutr*. 2006 Apr; 136 (4): 981-986. PMID: 16549461.
2. Mirmiran P, Noori N, Zavareh MB, Azizi F. Fruit and vegetable consumption and risk factors for cardiovascular disease. *Metabolism*. 2009 Apr; 58 (4): 460-468. PMID: 19303965.
3. Radhika G, Sudha V, Mohan Sathya R, Ganesan A, Mohan V. Association of fruit and vegetable intake with cardiovascular risk factors in urban south Indians. *Br J Nutr.* 2008 Feb; 99 (2): 398-405. Epub 2007 Aug 3. PMID: 17678569.

In adults, what is the relationship between the intake of vegetables and fruits, not including juice and body weight?

1. Bes-Rastrollo M, Martínez-González MA, Sánchez-Villegas A, de la Fuente Arrillaga C, Martínez JA. Association of fiber intake and fruit/vegetable consumption with weight gain in a Mediterranean population. *Nutrition*. 2006 May; 22 (5): 504-511. Epub 2006 Feb 24. PMID: 16500082.
2. Buijsse B, Feskens EJ, Schulze MB, Forouhi NG, Wareham NJ, Sharp S, Palli D, Tognon G, Halkjaer J, Tjønneland A, Jakobsen MU, Overvad K, van der A DL, Du H, Sørensen TI, Boeing H. Fruit and vegetable intakes and subsequent changes in body weight in European populations: Results from the project on Diet, Obesity and Genes (DiOGenes). *Am J Clin Nutr.* 2009 Jul; 90 (1): 202-209. Epub 2009 May 20. PMID: 19458016.
3. Davis JN, Hodges VA, Gillham MB. Normal-weight adults consume more fiber and fruit than their age- and height-matched overweight/obese counterparts. *J Am Diet Assoc.* 2006 Jun; 106 (6): 833-840. PMID: 16720124.
4. Fujioka K, Greenway F, Sheard J, Ying Y. The effects of grapefruit on weight and insulin resistance: Relationship to the metabolic syndrome. *J Med Food*. 2006 Spring; 9 (1): 49-54. PMID: 16579728.
5. Goss J, Grubbs L. Comparative analysis of body mass index, consumption of fruits and vegetables, smoking and physical activity among Florida residents. *J Community Health Nurs.* 2005 Spring; 22(1): 37-46. PMID: 15695195.
6. He K, Hu FB, Colditz GA, Manson JE, Willett WC, Liu S. Changes in intake of

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fruits and vegetables in relation to risk of obesity and weight gain among middle-aged women. *Int J Obes Relat Metab Disord*. 2004 Dec; 28 (12): 1, 569-1, 574. PMID: 15467774.

7. Ortega RM, Rodríguez-Rodríguez E, Aparicio A, Marín-Arias LI, López-Sobaler AM. Responses to two weight-loss programs based on approximating the diet to the ideal: Differences associated with increased cereal or vegetable consumption. *Int J Vitam Nutr Res*. 2006 Nov; 76 (6): 367-376. PMID: 17607956.
8. Radhika G, Sudha V, Mohan Sathya R, Ganesan A, Mohan V. Association of fruit and vegetable intake with cardiovascular risk factors in urban south Indians. *Br J Nutr*. 2008 Feb; 99 (2): 398-405. Epub 2007 Aug 3. PMID: 17678569.
9. Tanumihardjo SA, Valentine AR, Zhang Z, Whigham LD, Lai HJ, Atkinson RL. Strategies to increase vegetable or reduce energy and fat intake induce weight loss in adults. *Exp Biol Med* (Maywood). 2009 May; 234 (5): 542-552. Epub 2009 Feb 20. PMID: 19234056.
10. Vioque J, Weinbrenner T, Castelló A, Asensio L, Garcia de la Hera M. Intake of fruits and vegetables in relation to 10-year weight gain among Spanish adults. *Obesity* (Silver Spring). 2008 Mar; 16 (3): 664-670. Epub 2008 Jan 17. PMID: 18239583.
11. Xu F, Yin XM, Tong SL. Association between excess bodyweight and intake of red meat and vegetables among urban and rural adult Chinese in Nanjing, China. *Asia Pac J Public Health*. 2007;19 (3): 3-9. PMID: 18330398.

In adults, what is the relationship between the intake of vegetables and fruits, not including juice and type 2 diabetes?

1. Bazzano LA, Li TY, Joshipura KJ, Hu FB. Intake of fruit, vegetables, and fruit juices and risk of diabetes in women. *Diabetes Care*. 2008 Jul; 31 (7): 1, 311-1, 317. Epub 2008 Apr 4. PMID: 18390796; PMCID: PMC2453647.
2. Halton TL, Willett WC, Liu S, Manson JE, Stampfer MJ, Hu FB. Potato and French fry consumption and risk of type 2 diabetes in women. *Am J Clin Nutr*. 2006 Feb; 83 (2): 284-290. PMID: 16469985.
3. Liu S, Serdula M, Janket SJ, Cook NR, Sesso HD, Willett WC, Manson JE, Buring JE. A prospective study of fruit and vegetable intake and the risk of type 2 diabetes in women. *Diabetes Care.* 2004 Dec; 27 (12): 2, 993-2, 996. PMID: 15562224.
4. Villegas R, Shu XO, Gao YT, Yang G, Elasy T, Li H, Zheng W. Vegetable but not fruit consumption reduces the risk of type 2 diabetes in Chinese women. *J Nutr*. 2008 Mar; 138 (3): 574-580. PMID: 18287369; PMCID: PMC2615491.
5. Wang L, Liu S, Manson JE, Gaziano JM, Buring JE, Sesso HD. The consumption of lycopene and tomato-based food products is not associated with the risk of type 2 diabetes in women. *J Nutr*. 2006 Mar; 136 (3): 620-625. PMID: 16484534.

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Excluded articles

Article	Reason for Exclusion
Alonso A, de la Fuente C, Martín-Arnau AM, de Irala J, Martínez JA, Martínez-González MA. Fruit and vegetable consumption is inversely associated with blood pressure in a Mediterranean population with a high vegetable-fat intake: The Seguimiento Universidad de Navarra (SUN) Study.*Br J Nutr.* 2004 Aug; 92 (2): 311-319. PMID: 15333163.	Results reported based on the same dataset as Nunez-Cordoba, 2009.
Austin GL, Adair LS, Galanko JA, Martin CF, Satia JA, Sandler RS. A diet high in fruits and low in meats reduces the risk of colorectal adenomas. *J Nutr.* 2007 Apr; 137 (4): 999-1, 004. PMID: 17374667.	Cancer excluded as outcome of interest.
Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Fruits and vegetables and endometrial cancer risk: A systematic literature review and meta-analysis. *Nutr Cancer.* 2007; 58 (1): 6-21. Review. PMID: 17571962.	Cancer excluded as outcome of interest.
Barros R, Moreira A, Fonseca J, de Oliveira JF, Delgado L, Castel-Branco MG, Haahtela T, Lopes C, Moreira P. Adherence to the Mediterranean diet and fresh fruit intake are associated with improved asthma control. *Allergy*. 2008 Jul; 63 (7): 917-923. PMID: 18588559.	Participants were diagnosed with asthma.
Benetou V, Orfanos P, Lagiou P, Trichopoulos D, Boffetta P, Trichopoulou A. Vegetables and fruits in relation to cancer risk: evidence from the Greek EPIC cohort study. *Cancer Epidemiol Biomarkers Prev.* 2008 Feb; 17 (2): 387-392. PMID: 18268122.	Cancer excluded as outcome of interest.

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Boeing H, Dietrich T, Hoffmann K, Pischon T, Ferrari P, Lahmann PH, Boutron-Ruault MC, Clavel-Chapelon F, Allen N, Key T, Skeie G, Lund E, Olsen A, Tjonneland A, Overvad K, Jensen MK, Rohrmann S, Linseisen J, Trichopoulou A, Bamia C, Psaltopoulou T, Weinehall L, Johansson I, Sánchez MJ, Jakszyn P, Ardanaz E, Amiano P, Chirlaque MD, Quirós JR, Wirfalt E, Berglund G, Peeters PH, van Gils CH, Bueno-de-Mesquita HB, Büchner FL, Berrino F, Palli D, Sacerdote C, Tumino R, Panico S, Bingham S, Khaw KT, Slimani N, Norat T, Jenab M, Riboli E. Intake of fruits and vegetables and risk of cancer of the upper aero-digestive tract: The prospective EPIC-study. *Cancer Causes Control.* 2006 Sep; 17 (7): 957-969. PMID: 16841263.	Cancer excluded as outcome of interest.
Chan JM, Wang F, Holly EA. Vegetable and fruit intake and pancreatic cancer in a population-based case-control study in the San Francisco bay area. *Cancer Epidemiol Biomarkers Prev*. 2005 Sep; 14 (9): 2, 093-2, 097. PMID: 16172215.	Cancer excluded as outcome of interest.
Chen G, Heilbrun LK, Venkatramanamoorthy R, Maranci V, Redd JN, Klurfeld DM, Djuric Z. Effects of low-fat and/or high-fruit-and-vegetable diets on plasma levels of 8-isoprostane-F2alpha in the Nutrition and Breast Health study. *Nutr Cancer.* 2004; 50 (2): 155-160. PMID: 15623461.	Does not include breast cancer incidence in analyses: Measured intermediate outcome (8-isoprostane-F2alpha).
Crujeiras AB, Parra MD, Rodríguez MC, Martínez de Morentin BE, Martínez JA. A role for fruit content in energy-restricted diets in improving antioxidant status in obese women during weight loss. *Nutrition.* 2006 Jun; 22 (6): 593-599. PMID: 16704952.	Sample size less than inclusion criteria.
Darmon N, Darmon M, Maillot M, Drewnowski A. A nutrient density standard for vegetables and fruits: Nutrients per calorie and nutrients per unit cost. *J Am Diet Assoc.* 2005 Dec; 105 (12): 1, 881-1, 887. PMID: 16321593.	Does not answer question: Does not examine the relationship between vegetables and fruits and health outcomes.
Dauchet L, Ferrières J, Arveiler D, Yarnell JW, Gey F, Ducimetière P, Ruidavets JB, Haas B, Evans A, Bingham A, Amouyel P, Dallongeville J. Frequency of fruit and vegetable consumption and coronary heart disease in France and Northern Ireland: The PRIME study.*Br J Nutr.* 2004 Dec; 92 (6): 963-972. PMID: 15613259.	Included in He, 2006.

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de Oliveira MC, Sichieri R, Venturim Mozzer R. A low-energy-dense diet adding fruit reduces weight and energy intake in women. *Appetite.* 2008 Sep; 51 (2): 291-295. Epub 2008 Mar 7. PMID: 18439712.	Dropout rate higher than inclusion criteria.
De Stefani E, Boffetta P, Deneo-Pellegrini H, Ronco AL, Correa P, Mendilaharsu M. The role of vegetable and fruit consumption in the aetiology of squamous cell carcinoma of the oesophagus: A case-control study in Uruguay. *Int J Cancer*. 2005 Aug 10; 116 (1): 130-135. PMID: 15756680.	Cancer excluded as outcome of interest.
Do MH, Lee SS, Kim JY, Jung PJ, Lee MH. Fruits, vegetables, soy foods and breast cancer in pre- and postmenopausal Korean women: A case-control study. *Int J Vitam Nutr Res*. 2007 Mar; 77 (2): 130-141. PMID: 17896586.	Cancer excluded as outcome of interest.
Dosil-Díaz O, Ruano-Ravina A, Gestal-Otero JJ, Barros-Dios JM. Consumption of fruit and vegetables and risk of lung cancer: A case-control study in Galicia, Spain. *Nutrition*. 2008 May; 24 (5): 407-413. Epub 2008 Mar 7. PMID: 18314310.	Cancer excluded as outcome of interest.
Dove ER, Hodgson JM, Puddey IB, Beilin LJ, Lee YP, Mori TA. Skim milk compared with a fruit drink acutely reduces appetite and energy intake in overweight men and women. *Am J Clin Nutr.* 2009 Jul; 90 (1): 70-75. Epub 2009 May 27. PMID: 19474132.	Does not include body weight in analyses.
Dubowitz T, Heron M, Bird CE, Lurie N, Finch BK, Basurto-Dávila R, Hale L, Escarce JJ. Neighborhood socioeconomic status and fruit and vegetable intake among whites, blacks and Mexican Americans in the United States. *Am J Clin Nutr*. 2008 Jun; 87 (6): 1, 883-1, 891. PMID: 18541581.	Does not answer question: Does not examine the relationship between vegetables and fruits and health outcomes.
Ellinger S, Ellinger J, Stehle P. Tomatoes, tomato products and lycopene in the prevention and treatment of prostate cancer: Do we have the evidence from intervention studies? *Curr Opin Clin Nutr Metab Care.* 2006 Nov; 9 (6): 722-727. Review. PMID: 17053426.	Study design is narrative review.

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Ellingsen I, Hjerkinn EM, Seljeflot I, Arnesen H, Tonstad S. Consumption of fruit and berries is inversely associated with carotid atherosclerosis in elderly men.*Br J Nutr*. 2008 Mar; 99 (3): 674-681. Epub 2007 Sep 26. Erratum in: *Br J Nutr*. 2008 Mar; 99 (3): 697. PMID: 17894919.	Does not answer question: Does not include selected health outcome of interest.
Etminan M, Takkouche B, Caamaño-Isorna F. The role of tomato products and lycopene in the prevention of prostate cancer: A meta-analysis of observational studies. *Cancer Epidemiol Biomarkers Prev.* 2004 Mar; 13 (3): 340-345. PMID: 15006906.	Cancer excluded as outcome of interest.
Freedman ND, Park Y, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC. Fruit and vegetable intake and esophageal cancer in a large prospective cohort study. *Int J Cancer.* 2007 Dec 15; 121 (12): 2, 753-2, 760. PMID: 17691111.	Cancer excluded as outcome of interest.
Freedman ND, Park Y, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC. Fruit and vegetable intake and head and neck cancer risk in a large United States prospective cohort study. *Int J Cancer*. 2008 May 15; 122 (10): 2, 330-2, 336. PMID: 18092323.	Cancer excluded as outcome of interest.
Freedman ND, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC. Fruit and vegetable intake and gastric cancer risk in a large United States prospective cohort study. *Cancer Causes Control.* 2008 Jun; 19 (5): 459-467. Epub 2008 Jan 1. PMID: 18166992.	Cancer excluded as outcome of interest.
Galeone C, Negri E, Pelucchi C, La Vecchia C, Bosetti C, Hu J. Dietary intake of fruit and vegetable and lung cancer risk: A case-control study in Harbin, northeast China. *Ann Oncol.* 2007 Feb; 18 (2): 388-392. Epub 2006 Oct 23. PMID: 17060488.	Cancer excluded as outcome of interest.
Gallicchio L, Matanoski G, Tao XG, Chen L, Lam TK, Boyd K, Robinson KA, Balick L, Mickelson S, Caulfield LE, Herman JG, Guallar E, Alberg AJ. Adulthood consumption of preserved and non-preserved vegetables and the risk of nasopharyngeal carcinoma: A systematic review. *Int J Cancer*. 2006 Sep 1;119 (5): 1, 125-1, 135. Review. PubMed PMID: 16570274.	Cancer excluded as outcome of interest.

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George SM, Park Y, Leitzmann MF, Freedman ND, Dowling EC, Reedy J, Schatzkin A, Hollenbeck A, Subar AF. Fruit and vegetable intake and risk of cancer: a prospective cohort study. *Am J Clin Nutr.* 2009 Jan; 89 (1): 347-353. Epub 2008 Dec 3. PMID: 19056579; Central PMCID: PMC2647712.	Cancer excluded as outcome of interest.
Giammarioli S, Filesi C, Vitale B, Cantagallo A, Dragoni F, Sanzini E. Effect of high intakes of fruit and vegetables on redox status in type 2 onset diabetes: A pilot study. *Int J Vitam Nutr Res.* 2004 Sep; 74 (5): 313-320. PMID: 15628668.	Participants diagnosed with type 2 diabetes.
González CA, Pera G, Agudo A, Bueno-de-Mesquita HB, Ceroti M, Boeing H, Schulz M, Del Giudice G, Plebani M, Carneiro F, Berrino F, Sacerdote C, Tumino R, Panico S, Berglund G, Simán H, Hallmans G, Stenling R, Martinez C, Dorronsoro M, Barricarte A, Navarro C, Quiros JR, Allen N, Key TJ, Bingham S, Day NE, Linseisen J, Nagel G, Overvad K, Jensen MK, Olsen A, Tjønneland A, Büchner FL, Peeters PH, Numans ME, Clavel-Chapelon F, Boutron-Ruault MC, Roukos D, Trichopoulou A, Psaltopoulou T, Lund E, Casagrande C, Slimani N, Jenab M, Riboli E. Fruit and vegetable intake and the risk of stomach and oesophagus adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST).*Int J Cancer*. 2006 May 15; 118 (10): 2, 559-2, 566. PMID: 16380980.	Cancer excluded as outcome of interest.
Gorinstein S, Caspi A, Libman I, Lerner HT, Huang D, Leontowicz H, Leontowicz M, Tashma Z, Katrich E, Feng S, Trakhtenberg S. Red grapefruit positively influences serum triglyceride level in patients suffering from coronary atherosclerosis: Studies in vitro and in humans. *J Agric Food Chem*. 2006 Mar 8; 54 (5): 1, 887-1, 892. PubMed PMID: 16506849.	Participants diagnosed with hyperlipidemia and had received coronary bypass surgery.
Holick CN, De Vivo I, Feskanich D, Giovannucci E, Stampfer M, Michaud DS. Intake of fruits and vegetables, carotenoids, folate and vitamins A, C, E and risk of bladder cancer among women (United States).Cancer Causes Control. 2005 Dec; 16 (10): 1, 135-1, 145. PMID: 16215863.	Cancer excluded as outcome of interest.

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Holick CN, Giovannucci EL, Rosner B, Stampfer MJ, Michaud DS. Prospective study of intake of fruit, vegetables and carotenoids and the risk of adult glioma. *Am J Clin Nutr.* 2007 Mar; 85 (3): 877-886. PMID: 17344512.	Cancer excluded as outcome of interest.
Jansen MC, Bueno-de-Mesquita HB, Feskens EJ, Streppel MT, Kok FJ, Kromhout D. Quantity and variety of fruit and vegetable consumption and cancer risk. *Nutr Cancer.* 2004; 48 (2): 142-148. PMID: 15231448.	Cancer excluded as outcome of interest.
Johnsen SP. Intake of fruit and vegetables and risk of stroke: An overview. *Curr Opin Clin Nutr Metab Care*. 2004 Nov; 7 (6): 665-670. Review. PMID: 15534435.	Study design is narrative review.
Kavanaugh CJ, Trumbo PR, Ellwood KC. The U.S. Food and Drug Administration's evidence-based review for qualified health claims: Tomatoes, lycopene and cancer. *J Natl Cancer Inst.* 2007 Jul 18; 99 (14): 1, 074-1, 085. Epub 2007 Jul 10. Review. PMID: 17623802.	Cancer excluded as outcome of interest.
Kellen E, Zeegers M, Paulussen A, Van Dongen M, Buntinx F. Fruit consumption reduces the effect of smoking on bladder cancer risk. The Belgian case control study on bladder cancer. *Int J Cancer.* 2006 May 15; 118 (10): 2, 572-2, 578. PMID: 16380991.	Cancer excluded as outcome of interest.
Kim SY, Yoon S, Kwon SM, Park KS, Lee-Kim YC. Kale juice improves coronary artery disease risk factors in hypercholesterolemic men. *Biomed Environ Sci.* 2008 Apr; 21 (2): 91-97. PMID: 18548846.	Participants diagnosed with hypercholesterolemia.
Kirsh VA, Mayne ST, Peters U, Chatterjee N, Leitzmann MF, Dixon LB, Urban DA, Crawford ED, Hayes RB. A prospective study of lycopene and tomato product intake and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2006 Jan; 15 (1): 92-98. PMID: 16434593.	Cancer excluded as outcome of interest.
Kirsh VA, Peters U, Mayne ST, Subar AF, Chatterjee N, Johnson CC, Hayes RB; Prospective study of fruit and vegetable intake and risk of prostate cancer. Prospective study of fruit and vegetable intake and risk of prostate cancer. *J Natl Cancer Inst*. 2007 Aug 1; 99 (15): 1, 200-1, 209. Epub 2007 Jul 24. PMID: 17652276.	Cancer excluded as outcome of interest.

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Klassen AC, Garrett-Mayer E, Houts PS, Shankar S, Torio CM. The relationship of body size to participation and success in a fruits and vegetables intervention among low-income women. *J Community Health*. 2008 Apr; 33 (2): 78-89. PMID: 18074208.	Does not answer question: Does not examine the relationship between vegetables and fruits and health outcomes.
Koushik A, Hunter DJ, Spiegelman D, Anderson KE, Arslan AA, Beeson WL, van den Brandt PA, Buring JE, Cerhan JR, Colditz GA, Fraser GE, Freudenheim JL, Genkinger JM, Goldbohm RA, Hankinson SE, Koenig KL, Larsson SC, Leitzmann M, McCullough ML, Miller AB, Patel A, Rohan TE, Schatzkin A, Smit E, Willett WC, Wolk A, Zhang SM, Smith-Warner SA. Fruits and vegetables and ovarian cancer risk in a pooled analysis of 12 cohort studies. *Cancer Epidemiol Biomarkers Prev.* 2005 Sep; 14 (9): 2, 160-2, 167. PMID: 16172226.	Cancer excluded as outcome of interest.
Koushik A, Hunter DJ, Spiegelman D, Beeson WL, van den Brandt PA, Buring JE, Calle EE, Cho E, Fraser GE, Freudenheim JL, Fuchs CS, Giovannucci EL, Goldbohm RA, Harnack L, Jacobs DR Jr, Kato I, Krogh V, Larsson SC, Leitzmann MF, Marshall JR, McCullough ML, Miller AB, Pietinen P, Rohan TE, Schatzkin A, Sieri S, Virtanen MJ, Wolk A, Zeleniuch-Jacquotte A, Zhang SM, Smith-Warner SA. Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies. *J Natl Cancer Inst*. 2007 Oct 3; 99 (19): 1, 471-1, 483. Epub 2007 Sep 25. PMID: 17895473.	Cancer excluded as outcome of interest.
Kurahashi N, Inoue M, Iwasaki M, Tanaka Y, Mizokami M, Tsugane S; JPHC Study Group. Vegetable, fruit and antioxidant nutrient consumption and subsequent risk of hepatocellular carcinoma: A prospective cohort study in Japan. *Br J Cancer*. 2009 Jan 13; 100 (1): 181-184. PMID: 19127270.	Cancer excluded as outcome of interest.
Lam TK, Gallicchio L, Lindsley K, Shiels M, Hammond E, Tao XG, Chen L, Robinson KA, Caulfield LE, Herman JG, Guallar E, Alberg AJ. Cruciferous vegetable consumption and lung cancer risk: a systematic review. *Cancer Epidemiol Biomarkers Prev.* 2009 Jan; 18 (1): 184-195. Review. PMID: 19124497.	Cancer excluded as outcome of interest.

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Larsson SC, Andersson SO, Johansson JE, Wolk A. Fruit and vegetable consumption and risk of bladder cancer: A prospective cohort study. *Cancer Epidemiol Biomarkers Prev*. 2008 Sep; 17 (9): 2, 519-2, 522. PMID: 18768526.	Cancer excluded as outcome of interest.
Larsson SC, Bergkvist L, Wolk A. Fruit and vegetable consumption and incidence of gastric cancer: a prospective study. *Cancer Epidemiol Biomarkers Prev*. 2006 Oct; 15 (10): 1, 998-2, 001. PMID: 17035412.	Cancer excluded as outcome of interest.
Larsson SC, Håkansson N, Näslund I, Bergkvist L, Wolk A. Fruit and vegetable consumption in relation to pancreatic cancer risk: A prospective study. *Cancer Epidemiol Biomarkers Prev*. 2006 Feb; 15 (2): 301-305. PMID: 16492919.	Cancer excluded as outcome of interest.
Larsson SC, Holmberg L, Wolk A. Fruit and vegetable consumption in relation to ovarian cancer incidence: The Swedish Mammography Cohort. *Br J Cancer*. 2004 Jun 1; 90 (11): 2, 167-2, 170. PMID: 15150575.	Cancer excluded as outcome of interest.
Lee JE, Giovannucci E, Smith-Warner SA, Spiegelman D, Willett WC, Curhan GC. Intakes of fruits, vegetables, vitamins A, C, and E and carotenoids and risk of renal cell cancer. *Cancer Epidemiol Biomarkers Prev*. 2006 Dec; 15 (12): 2, 445-2, 452. PMID: 17164369.	Cancer excluded as outcome of interest.
Lin J, Zhang SM, Cook NR, Rexrode KM, Liu S, Manson JE, Lee IM, Buring JE. Dietary intakes of fruit, vegetables, and fiber and risk of colorectal cancer in a prospective cohort of women (United States).*Cancer Causes Control*. 2005 Apr; 16 (3): 225-233. PMID: 15947874.	Cancer excluded as outcome of interest.
Liu Y, Sobue T, Otani T, Tsugane S. Vegetables, fruit consumption and risk of lung cancer among middle-aged Japanese men and women: JPHC study. *Cancer Causes Control*. 2004 May; 15 (4): 349-357. PMID: 15141136.	Cancer excluded as outcome of interest.
Longo-Mbenza B, Tshimanga KB, Buassa-bu-Tsumbu B, Kabangu MJ. Diets rich in vegetables and physical activity are associated with a decreased risk of pregnancy induced hypertension among rural women from Kimpese, DR Congo. *Niger J Med*. 2008 Jul-Aug; 17 (3): 265-269. PMID: 18788250.	Study population not from a developed country as defined by the Human Development Index.

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Lunet N, Lacerda-Vieira A, Barros H. Fruit and vegetables consumption and gastric cancer: a systematic review and meta-analysis of cohort studies. *Nutr Cancer*. 2005; 53 (1): 1-10. Review. PMID: 16351501.	Cancer excluded as outcome of interest.
Lunet N, Valbuena C, Vieira AL, Lopes C, Lopes C, David L, Carneiro F, Barros H. Fruit and vegetable consumption and gastric cancer by location and histological type: Case-control and meta-analysis. *Eur J Cancer Prev*. 2007 Aug; 16 (4): 312-327. PMID: 17554204.	Cancer excluded as outcome of interest.
Masala G, Ceroti M, Pala V, Krogh V, Vineis P, Sacerdote C, Saieva C, Salvini S, Sieri S, Berrino F, Panico S, Mattiello A, Tumino R, Giurdanella MC, Bamia C, Trichopoulou A, Riboli E, Palli D.A dietary pattern rich in olive oil and raw vegetables is associated with lower mortality in Italian elderly subjects.*Br J Nutr*. 2007 Aug; 98 (2): 406-415. Epub 2007 Apr 3. PMID: 17403268.	Does not answer question: Discusses vegetables and fruits as part of dietary pattern.
Maserejian NN, Giovannucci E, Rosner B, Zavras A, Joshipura K. Prospective study of fruits and vegetables and risk of oral premalignant lesions in men. *Am J Epidemiol*. 2006 Sep 15; 164 (6): 556-566. Epub 2006 Jul 17. PMID: 16847039.	Cancer excluded as outcome of interest.
McCall DO, McGartland CP, McKinley MC, Patterson CC, Sharpe P, McCance DR, Young IS, Woodside JV. Dietary intake of fruits and vegetables improves microvascular function in hypertensive subjects in a dose-dependent manner. *Circulation*. 2009 Apr 28; 119 (16): 2, 153-2, 160. Epub 2009 Apr 13. PMID: 19364976.	Participants diagnosed with hypertension, and study did not measure identified outcome of interest.
McCullough ML, Bandera EV, Patel R, Patel AV, Gansler T, Kushi LH, Thun MJ, Calle EE. A prospective study of fruits, vegetables and risk of endometrial cancer. *Am J Epidemiol.* 2007 Oct 15; 166 (8): 902-911. Epub 2007 Aug 9. PMID: 17690222.	Cancer excluded as outcome of interest.
Michels KB, Giovannucci E, Chan AT, Singhania R, Fuchs CS, Willett WC. Fruit and vegetable consumption and colorectal adenomas in the Nurses' Health Study. *Cancer Res*. 2006 Apr 1; 66 (7): 3, 942-3, 953. PMID: 16585224.	Cancer excluded as outcome of interest.

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Mikkelsen TB, Osler M, Orozova-Bekkevold I, Knudsen VK, Olsen SF. Association between fruit and vegetable consumption and birth weight: A prospective study among 43, 585 Danish women. *Scand J Public Health*. 2006; 34 (6): 616-622. PMID: 17132595.	Does not answer question: addresses vegetable and fruit intake during pregnancy and birth weight.
Millen AE, Subar AF, Graubard BI, Peters U, Hayes RB, Weissfeld JL, Yokochi LA, Ziegler RG; PLCO Cancer Screening Trial Project Team. Fruit and vegetable intake and prevalence of colorectal adenoma in a cancer screening trial. *Am J Clin Nutr*. 2007 Dec; 86 (6): 1, 754-1, 764. PMID: 18065596.	Cancer excluded as outcome of interest.
Mommers M, Schouten LJ, Goldbohm RA, van den Brandt PA. Consumption of vegetables and fruits and risk of ovarian carcinoma. *Cancer*. 2005 Oct 1; 104 (7): 1, 512-1, 519. PMID: 16104037.	Cancer excluded as outcome of interest.
Nomura AM, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Pike MC, Kolonel LN. Association of vegetable, fruit, and grain intakes with colorectal cancer: The Multiethnic Cohort Study. *Am J Clin Nutr*. 2008 Sep; 88 (3): 730-737. PMID: 18779290.	Cancer excluded as outcome of interest.
Nöthlings U, Schulze MB, Weikert C, Boeing H, van der Schouw YT, Bamia C, Benetou V, Lagiou P, Krogh V, Beulens JW, Peeters PH, Halkjaer J, Tjønneland A, Tumino R, Panico S, Masala G, Clavel-Chapelon F, de Lauzon B, Boutron-Ruault MC, Vercambre MN, Kaaks R, Linseisen J, Overvad K, Arriola L, Ardanaz E, Gonzalez CA, Tormo MJ, Bingham S, Khaw KT, Key TJ, Vineis P, Riboli E, Ferrari P, Boffetta P, Bueno-de-Mesquita HB, van der A DL, Berglund G, Wirfält E, Hallmans G, Johansson I, Lund E, Trichopoulo A. Intake of vegetables, legumes, and fruit, and risk for all-cause, cardiovascular and cancer mortality in a European diabetic population. *J Nutr*. 2008 Apr; 138 (4): 775-781. PMID: 18356334.	Participants were diagnosed with diabetes.
Nöthlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN. Vegetable intake and pancreatic cancer risk: The multiethnic cohort study. *Am J Epidemiol*. 2007 Jan 15; 165 (2): 138-147. Epub 2006 Oct 26. PMID: 17068094.	Cancer excluded as outcome of interest.

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Nouraie M, Pietinen P, Kamangar F, Dawsey SM, Abnet CC, Albanes D, Virtamo J, Taylor PR. Fruits, vegetables, and antioxidants and risk of gastric cancer among male smokers. *Cancer Epidemiol Biomarkers Prev*. 2005 Sep; 14 (9): 2, 087-2, 092. PMID: 16172214.	Cancer excluded as outcome of interest.
Orjuela MA, Titievsky L, Liu X, Ramirez-Ortiz M, Ponce-Castaneda V, Lecona E, Molina E, Beaverson K, Abramson DH, Mueller NE. Fruit and vegetable intake during pregnancy and risk for development of sporadic retinoblastoma. *Cancer Epidemiol Biomarkers Prev*. 2005 Jun; 14 (6): 1, 433-1, 440. PMID: 15941952.	Does not answer question: does not address outcomes of interest (examines retinoblastoma).
Papanikolaou Y, Fulgoni VL 3rd. Bean consumption is associated with greater nutrient intake, reduced systolic blood pressure, lower body weight and a smaller waist circumference in adults: Results from the National Health and Nutrition Examination Survey 1999-2002.*J Am Coll Nutr*. 2008 Oct; 27 (5): 569-576. PMID: 18845707.	Beans considered in separate question on cooked dry beans and peas and selected health outcomes.
Pavia M, Pileggi C, Nobile CG, Angelillo IF. Association between fruit and vegetable consumption and oral cancer: A meta-analysis of observational studies. *Am J Clin Nutr*. 2006 May; 83 (5): 1, 126-1, 134. PMID: 16685056.	Cancer excluded as outcome of interest.
Pham TM, Fujino Y, Ide R, Kubo T, Shirane K, Tokui N, Mizoue T, Ogimoto I, Matsuda S, Yoshimura T. Prospective study of vegetable consumption and liver cancer in Japan. *Int J Cancer.* 2006 Nov 15; 119 (10): 2, 408-2, 411. PMID: 16894561.	Cancer excluded as outcome of interest.
Pomerleau J, Lock K, Knai C, McKee M. Interventions designed to increase adult fruit and vegetable intake can be effective: A systematic review of the literature. *J Nutr*. 2005 Oct; 135 (10): 2, 486-2, 495. Review. PMID: 16177217.	Does not answer question: Evaluates interventions to increase fruit and vegetable intake.
Prynne CJ, Mishra GD, O'Connell MA, Muniz G, Laskey MA, Yan L, Prentice A, Ginty F. Fruit and vegetable intakes and bone mineral status: A cross sectional study in five age and sex cohorts. *Am J Clin Nutr*. 2006 Jun; 83 (6): 1, 420-1, 428. PMID: 16789345.	Does not answer question: Does not address outcomes of interest.

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Rai A, Mohapatra SC, Shukla HS. Correlates between vegetable consumption and gallbladder cancer. Eu*r J Cancer Prev*. 2006 Apr; 15 (2): 134-137. PMID: 16523010.	Participants diagnosed with gallbladder cancer or gallstone disease.
Ramón R, Ballester F, Iñiguez C, Rebagliato M, Murcia M, Esplugues A, Marco A, García de la Hera M, Vioque J. Vegetable but not fruit intake during pregnancy is associated with newborn anthropometric measures. *J Nutr*. 2009 Mar; 139 (3): 561-567. Epub 2009 Jan 21. PMID: 19158218.	Does not answer question: Addresses fruit and vegetable intake during pregnancy and birth outcomes.
Rashidkhani B, Lindblad P, Wolk A. Fruits, vegetables and risk of renal cell carcinoma: a prospective study of Swedish women. *Int J Cancer*. 2005 Jan 20; 113 (3): 451-455. PMID: 15455348.	Cancer excluded as outcome of interest.
Rodríguez MC, Parra MD, Marques-Lopes I, De Morentin BE, González A, Martínez JA. Effects of two energy-restricted diets containing different fruit amounts on body weight loss and macronutrient oxidation. *Plant Foods Hum Nutr*. 2005 Dec; 60 (4): 219-224. PMID: 16395633.	Does not meet inclusion criteria for sample size.
Romieu I, Varraso R, Avenel V, Leynaert B, Kauffmann F, Clavel-Chapelon F. Fruit and vegetable intakes and asthma in the E3N study. *Thorax.* 2006 Mar; 61 (3): 209-215. Epub 2006 Jan 5. PMID: 16396945; PMCID: PMC1974844.	Does not answer question: Does not measure an identified outcome of interest.
Sandoval M, Font R, Mañós M, Dicenta M, Quintana MJ, Bosch FX, Castellsagué X. The role of vegetable and fruit consumption and other habits on survival following the diagnosis of oral cancer: A prospective study in Spain. *Int J Oral Maxillofac Surg*. 2009 Jan; 38 (1): 31-39. Epub 2008 Oct 31. PubMed PMID: 18951763.	Participants diagnosed with oral cancer.
Sartorelli DS, Franco LJ, Cardoso MA. High intake of fruits and vegetables predicts weight loss in Brazilian overweight adults. *Nutr Res*. 2008 Apr; 28 (4): 233-238. PMID: 19083413.	Dropout rate higher than inclusion criteria.

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Sato K, Kawakami N, Ohtsu T, Tsutsumi A, Miyazaki S, Masumoto T, Horie S, Haratani T, Kobayashi F, Araki S. Broccoli consumption and chronic atrophic gastritis among Japanese males: An epidemiological investigation. *Acta Med Okayama*. 2004 Jun; 58 (3): 127-133. PMID: 15471434.	Does not answer question: Does not include outcome of interest (measured chronic atrophic gastritis).
Sato Y, Tsubono Y, Nakaya N, Ogawa K, Kurashima K, Kuriyama S, Hozawa A, Nishino Y, Shibuya D, Tsuji I. Fruit and vegetable consumption and risk of colorectal cancer in Japan: The Miyagi Cohort Study. *Public Health Nutr.* 2005 May; 8 (3): 309-314. PMID: 15918928.	Cancer excluded as outcome of interest.
Schnäbele K, Briviba K, Bub A, Roser S, Pool-Zobel BL, Rechkemmer G. Effects of carrot and tomato juice consumption on faecal markers relevant to colon carcinogenesis in humans.*Br J Nutr*. 2008 Mar; 99 (3): 606-613. PMID: 18254985.	Does not answer question: Does not include outcome of interest.
Schulz M, Lahmann PH, Boeing H, Hoffmann K, Allen N, Key TJ, Bingham S, Wirfält E, Berglund G, Lundin E, Hallmans G, Lukanova A, Martínez Garcia C, González CA, Tormo MJ, Quirós JR, Ardanaz E, Larrañaga N, Lund E, Gram IT, Skeie G, Peeters PH, van Gils CH, Bueno-de-Mesquita HB, Büchner FL, Pasanisi P, Galasso R, Palli D, Tumino R, Vineis P, Trichopoulou A, Kalapothaki V, Trichopoulos D, Chang-Claude J, Linseisen J, Boutron-Ruault MC, Touillaud M, Clavel-Chapelon F, Olsen A, Tjønneland A, Overvad K, Tetsche M, Jenab M, Norat T, Kaaks R, Riboli E. Fruit and vegetable consumption and risk of epithelial ovarian cancer: The European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiol Biomarkers Prev*. 2005 Nov; 14 (11 Pt 1): 2, 531-2, 535. PMID: 16284374.	Cancer excluded as outcome of interest.
Setiawan VW, Yu GP, Lu QY, Lu ML, Yu SZ, Mu L, Zhang JG, Kurtz RC, Cai L, Hsieh CC, Zhang ZF. Allium vegetables and stomach cancer risk in China. *Asian Pac J Cancer Prev.* 2005 Jul-Sep; 6 (3): 387-395. PMID: 16236005.	Cancer excluded as outcome of interest.

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Shi Z, Hu X, Yuan B, Hu G, Pan X, Dai Y, Byles JE, Holmboe-Ottesen G. Vegetable-rich food pattern is related to obesity in China. *Int J Obes* (Lond). 2008 Jun; 32 (6): 975-984. Epub 2008 Mar 4. PMID: 18317472.	Includes fruits, vegetables, and whole grains as part of vegetable-rich food pattern. Does not evaluate vegetable and fruit and health outcomes specifically.
Skuladottir H, Tjoenneland A, Overvad K, Stripp C, Olsen JH. Does high intake of fruit and vegetables improve lung cancer survival? *Lung Cancer*. 2006 Mar; 51 (3): 267-273. Epub 2006 Feb 15. PMID: 16469411.	Participants diagnosed with lung cancer.
Stoner GD, Wang LS, Casto BC. Laboratory and clinical studies of cancer chemoprevention by antioxidants in berries. *Carcinogenesis*. 2008 Sep; 29 (9): 1, 665-1, 674. Epub 2008 Jun 9. Review. PMID: 18544560.	Study design is narrative review.
Sunny L. A low fat diet rich in fruits and vegetables may reduce the risk of developing prostate cancer. *Asian Pac J Cancer Prev*. 2005 Oct-Dec; 6 (4): 490-496. PMID: 16435998.	Cancer excluded as outcome of interest.
Tang L, Zirpoli GR, Guru K, Moysich KB, Zhang Y, Ambrosone CB, McCann SE. Consumption of raw cruciferous vegetables is inversely associated with bladder cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2008 Apr; 17 (4): 938-944. PMID: 18398034.	Cancer excluded as outcome of interest.
Tao MH, Xu WH, Zheng W, Gao YT, Ruan ZX, Cheng JR, Xiang YB, Shu XO. A case-control study in Shanghai of fruit and vegetable intake and endometrial cancer. *Br J Cancer*. 2005 Jun 6; 92 (11): 2, 059-2, 064. PMID: 15886701.	Cancer excluded as outcome of interest.
te Velde SJ, Twisk JW, Brug J. Tracking of fruit and vegetable consumption from adolescence into adulthood and its longitudinal association with overweight. *Br J Nutr*. 2007 Aug; 98 (2): 431-438. Epub 2007 Apr 16. Erratum in: *Br J Nutr.* 2007 Oct; 98 (4): 871. PMID: 17433126.	Adolescents considered in the Energy Balance section.

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Thomson CA, Rock CL, Giuliano AR, Newton TR, Cui H, Reid PM, Green TL, Alberts DS; Women's Healthy Eating & Living Study Group. Longitudinal changes in body weight and body composition among women previously treated for breast cancer consuming a high-vegetable, fruit and fiber, low-fat diet. *Eur J Nutr*. 2005 Feb; 44 (1): 18-25. Epub 2004 Mar 5. PMID: 15309460.	Participants were women who had been treated for breast cancer.
Tobias M, Turley M, Stefanogiannis N, Vander Hoorn S, Lawes C, Mhurchu CN, Rodgers A. Vegetable and fruit intake and mortality from chronic disease in New Zealand. *Aust N Z J Public Health.* 2006 Feb; 30 (1): 26-31. PMID: 16502948.	Does not answer question: Does not examine relationship between vegetable and fruit intake and disease.
Tohill BC, Seymour J, Serdula M, Kettel-Khan L, Rolls BJ. What epidemiologic studies tell us about the relationship between fruit and vegetable consumption and body weight. *Nutr Rev*. 2004 Oct; 62 (10): 365-374. Review. PMID: 15508906.	Study design is narrative review.
Traka M, Gasper AV, Melchini A, Bacon JR, Needs PW, Frost V, Chantry A, Jones AM, Ortori CA, Barrett DA, Ball RY, Mills RD, Mithen RF. Broccoli consumption interacts with GSTM1 to perturb oncogenic signaling pathways in the prostate. *PLoS One*. 2008 Jul 2; 3 (7): e2568. PMID: 18596959; PMCID: PMC2430620.	Does not answer question: Does not include outcome of interest.
Tsubono Y, Otani T, Kobayashi M, Yamamoto S, Sobue T, Tsugane S; JPHC Study Group. No association between fruit or vegetable consumption and the risk of colorectal cancer in Japan.*Br J Cancer*. 2005 May 9; 92 (9): 1, 782-1, 784. PMID: 15856039.	Cancer excluded as outcome of interest.
Turner F, Smith G, Sachse C, Lightfoot T, Garner RC, Wolf CR, Forman D, Bishop DT, Barrett JH. Vegetable, fruit and meat consumption and potential risk modifying genes in relation to colorectal cancer. *Int J Cancer*. 2004 Nov 1; 112 (2): 259-264. PMID: 15352038.	Cancer excluded as outcome of interest.
van Dijk BA, Schouten LJ, Kiemeney LA, Goldbohm RA, van den Brandt PA. Vegetable and fruit consumption and risk of renal cell carcinoma: Results from the Netherlands cohort study. *Int J Cancer*. 2005 Nov 20; 117 (4): 648-654. PMID: 15929109.	Cancer excluded as outcome of interest.

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van Duijnhoven FJ, Bueno-De-Mesquita HB, Ferrari P, Jenab M, Boshuizen HC, Ros MM, Casagrande C, Tjønneland A, Olsen A, Overvad K, Thorlacius-Ussing O, Clavel-Chapelon F, Boutron-Ruault MC, Morois S, Kaaks R, Linseisen J, Boeing H, Nöthlings U, Trichopoulou A, Trichopoulos D, Misirli G, Palli D, Sieri S, Panico S, Tumino R, Vineis P, Peeters PH, van Gils CH, Ocké MC, Lund E, Engeset D, Skeie G, Suárez LR, González CA, Sánchez MJ, Dorronsoro M, Navarro C, Barricarte A, Berglund G, Manjer J, Hallmans G, Palmqvist R, Bingham SA, Khaw KT, Key TJ, Allen NE, Boffetta P, Slimani N, Rinaldi S, Gallo V, Norat T, Riboli E. Fruit, vegetables and colorectal cancer risk: The European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr*. 2009 May; 89 (5): 1, 441-1, 452. Epub 2009 Apr 1. PMID: 19339391.	Cancer excluded as outcome of interest.
van Gils CH, Peeters PH, Bueno-de-Mesquita HB, Boshuizen HC, Lahmann PH, Clavel-Chapelon F, Thiébaut A, Kesse E, Sieri S, Palli D, Tumino R, Panico S, Vineis P, Gonzalez CA, Ardanaz E, Sánchez MJ, Amiano P, Navarro C, Quirós JR, Key TJ, Allen N, Khaw KT, Bingham SA, Psaltopoulou T, Koliva M, Trichopoulou A, Nagel G, Linseisen J, Boeing H, Berglund G, Wirfält E, Hallmans G, Lenner P, Overvad K, Tjønneland A, Olsen A, Lund E, Engeset D, Alsaker E, Norat T, Kaaks R, Slimani N, Riboli E. Consumption of vegetables and fruits and risk of breast cancer. *JAMA*. 2005 Jan 12; 293 (2): 183-193. PMID: 15644545.	Cancer excluded as outcome of interest.
Wakita Asano A, Miyoshi M, Arai Y, Yoshita K, Yamamoto S, Yoshiike N. Association between vegetable intake and dietary quality in Japanese adults: A secondary analysis from the National Health and Nutrition Survey, 2003.*J Nutr Sci Vitaminol* (Tokyo). 2008 Oct; 54 (5): 384-391. PMID: 19001770.	Does not answer question: Does not examine the relationship between vegetables and fruits and health outcomes.
Wang LI, Giovannucci EL, Hunter D, Neuberg D, Su L, Christiani DC. Dietary intake of Cruciferous vegetables, Glutathione S-transferase (GST) polymorphisms and lung cancer risk in a Caucasian population. *Cancer Causes Control*. 2004 Dec; 15 (10): 977-985. PMID: 15801482.	Cancer excluded as outcome of interest.

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Wark PA, Grubben MJ, Peters WH, Nagengast FM, Kampman E, Kok FJ, van 't Veer P. Habitual consumption of fruits and vegetables: associations with human rectal glutathione S-transferase. *Carcinogenesis*. 2004 Nov; 25 (11): 2, 135-2, 142. Epub 2004 Jul 29. PMID: 15284178.	Does not answer question: Does not include outcome of interest.
Wark PA, Weijenberg MP, van 't Veer P, van Wijhe G, Lüchtenborg M, van Muijen GN, de Goeij AF, Goldbohm RA, van den Brandt PA. Fruits, vegetables, and hMLH1 protein-deficient and -proficient colon cancer: The Netherlands cohort study. *Cancer Epidemiol Biomarkers Prev*. 2005 Jul; 14 (7): 1, 619-1, 625. PMID: 16030092.	Cancer excluded as outcome of interest.
Weikert S, Boeing H, Pischon T, Olsen A, Tjonneland A, Overvad K, Becker N, Linseisen J, Lahmann PH, Arvaniti A, Kassapa C, Trichoupoulou A, Sieri S, Palli D, Tumino R, Vineis P, Panico S, van Gils CH, Peeters PH, Bueno-de-Mesquita HB, Büchner FL, Ljungberg B, Hallmans G, Berglund G, Wirfält E, Pera G, Dorronsoro M, Gurrea AB, Navarro C, Martinez C, Quirós JR, Allen N, Roddam A, Bingham S, Jenab M, Slimani N, Norat T, Riboli E. Fruits and vegetables and renal cell carcinoma: findings from the European prospective investigation into cancer and nutrition (EPIC).*Int J Cancer.* 2006 Jun 15; 118 (12): 3, 133-3, 139. PMID: 16425278.	Cancer excluded as outcome of interest.
Whybrow S, Harrison CL, Mayer C, James Stubbs R. Effects of added fruits and vegetables on dietary intakes and body weight in Scottish adults.*Br J Nutr*. 2006 Mar; 95 (3): 496-503. PMID: 16512935.	Does not answer question: Includes supplements, not food, in analyses.
Williams MT, Hord NG. The role of dietary factors in cancer prevention: Beyond fruits and vegetables. *Nutr Clin Pract.* 2005 Aug; 20 (4): 451-459. Review. PMID: 16207684.	Study design is narrative review.
Wright ME, Park Y, Subar AF, Freedman ND, Albanes D, Hollenbeck A, Leitzmann MF, Schatzkin A. Intakes of fruit, vegetables and specific botanical groups in relation to lung cancer risk in the NIH-AARP Diet and Health Study. *Am J Epidemiol*. 2008 Nov 1; 168 (9): 1, 024-1, 034. Epub 2008 Sep 12. PMID: 18791192; PMCID: PMC2631557.	Cancer excluded as outcome of interest.

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Wu H, Dai Q, Shrubsole MJ, Ness RM, Schlundt D, Smalley WE, Chen H, Li M, Shyr Y, Zheng W. Fruit and vegetable intakes are associated with lower risk of colorectal adenomas. *J Nutr.* 2009 Feb; 139 (2): 340-344. Epub 2008 Dec 17. PMID: 19091801; PMCID: PMC2646202.	Cancer excluded as outcome of interest.
Yamaji T, Inoue M, Sasazuki S, Iwasaki M, Kurahashi N, Shimazu T, Tsugane S; Japan Public Health Center-based Prospective Study Group. Fruit and vegetable consumption and squamous cell carcinoma of the esophagus in Japan: The JPHC study. *Int J Cancer*. 2008 Oct 15; 123 (8): 1, 935-1, 940. PMID: 18688852.	Cancer excluded as outcome of interest.
Yeh M, Moysich KB, Jayaprakash V, Rodabaugh KJ, Graham S, Brasure JR, McCann SE. Higher intakes of vegetables and vegetable-related nutrients are associated with lower endometrial cancer risks. *J Nutr*. 2009 Feb; 139 (2): 317-322. Epub 2008 Dec 11. PMID: 19074206.	Cancer excluded as outcome of interest.
Zhang CX, Ho SC, Chen YM, Fu JH, Cheng SZ, Lin FY. Greater vegetable and fruit intake is associated with a lower risk of breast cancer among Chinese women.*Int J Cancer*. 2009 Jul 1; 125 (1): 181-188. PMID: 19358284.	Cancer excluded as outcome of interest.

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CHAPTER 12. VEGETABLES AND FRUITS – TYPE 2 DIABETES

IN ADULTS, WHAT IS THE RELATIONSHIP BETWEEN THE INTAKE OF VEGETABLES AND FRUITS, NOT INCLUDING JUICE, AND TYPE 2 DIABETES?

Conclusion statement

Limited and inconsistent evidence suggests an inverse association between total vegetable and fruit consumption and the development of type 2 diabetes.

Grade

Limited

Evidence summary overview

In a review of five articles describing prospective cohort studies published since 2004, the evidence is inconsistent but suggests an inverse association between the development of type 2 diabetes (T2D) and total vegetable and fruit consumption (Liu, 2004), a direct association with potato (French fry) consumption (Halton, 2006), and no significant (NS) effect of tomato-based products (Wang, 2006). Another study indicated that total vegetables as well as vegetable subgroups, but not fruit, may have a preventive effect (Villegas, 2008). Conversely, the Nurses' Health Study (Bazzano, 2008) indicated no association between T2D risk and total vegetable and fruit consumption, but total fruit and green leafy vegetables were inversely associated. The number of vegetable and fruit servings in these five studies ranged from about 2.5 servings to more than 10 servings per day and sample sizes were large in all five cohort studies ranging from 35,000 to 84,000 participants (Bazzano, 2008; Halton, 2006; Liu, 2004; Villegas, 2008; Wang, 2006). The effect size was variable ranging from a multivariate relative risk (RR) of 0.82 (Bazzano, 2008) to 1.04 (Wang, 2006) and 1.21 (Halton, 2006) when comparing lowest quintiles to highest quintiles. However, the evidence is insufficiently strong to draw firm conclusions.

Evidence summary paragraphs

Bazzano et al, 2008 (positive quality), a prospective cohort study (Nurses' Health Study) in the US, examined the association between fruit, vegetable and fruit juice intake and self-reported T2D. A total of 71,346 female registered nurses were included in the analysis; Food-frequency questionnaires (FFQs) were completed every four years. Over 18 years of follow-up, 4,529 cases of T2D were documented. There was no association between total fruit and vegetable intake in the adjusted models; however, intake of total fruit and green leafy vegetables were inversely associated with development of T2D. For an increase of three servings per day in whole fruit consumption, the multivariate-adjusted HR was 0.82 (95% CI: 0.72, 0.94) and for an increase of one serving per day of green leafy vegetables, the multivariate-adjusted HR was 0.91 (95% CI: 0.84, 0.98).

Halton et al, 2006 (positive quality), a prospective cohort study (Nurses' Health Study) in the US, examined the association between potato and French fry consumption and self-reported T2D. A total of 84,555 female registered nurses were included in the analysis; FFQs were completed every four years. Over 20 years of follow-up, 4,496 cases of T2D were documented. The multivariate RR of T2D in a

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comparison between the highest and lowest quintiles (median = 0.63 vs. 0.07 servings per day) of potato intake was 1.14 (95% CI: 1.02, 1.26; P for trend = 0.009). The multivariate RR of T2D in a comparison between the highest and lowest quintiles (median = 0.14 vs. 0 servings per day) of French fry intake was 1.21 (95% CI: 1.09, 1.33; P for trend <0.0001). The association between potato consumption and risk of T2D was more pronounced in obese women.

Liu et al, 2004 (positive quality), a prospective cohort study (Women's Health Study) conducted in the US, evaluated the hypothesis that a high intake of fruits and vegetables protects against the incidence of T2D and explored whether specific subgroups of fruits and vegetables differentially affected diabetes risk. A total of 38,018 female health professionals completed a FFQ at baseline and were included in the analysis. During an average of 8.8 years of follow-up, 1,614 self-reported cases of T2D were documented. Median intake of total fruits and vegetables ranged from 2.5 servings per day in the lowest quintile to more than 10 servings per day in the highest quintile. In models adjusted for age, total calories and smoking, significant inverse relationships were observed with diabetes risk for total fruit and vegetable intake, fruits, citrus fruits, green leafy vegetables and dark yellow vegetables and a significant positive association with intake of potatoes. However, after adjusting for known diabetes risk factors, none of these associations remained statistically significant. When stratified by body mass index (BMI) (less than 25 and 25kg/m^2 or more), no significant (NS) findings were observed in the lower BMI group. Among women with BMI higher than 25kg/m^2, higher intake of green leafy or dark yellow vegetables was significantly associated with reduced risk of T2D (P for trend = 0.02 for both). However, after fully adjusting for BMI, the inverse associations of green leafy and dark yellow vegetables were still observed among overweight women, although the trends were not statistically significant.

Wang et al, 2006 (positive quality), a prospective cohort study (Women's Health Study) conducted in the US, examined the association between intake of lycopene and tomato-based products and the development of T2D. A total of 35,783 women were included in the analyses. During a median follow-up of 10.2 years, 1,544 self-reported cases of T2D were documented. Average (SD) intake of tomato-based food products was 4.33 (3.22) servings per week. Women who consumed more tomato-based food products had neither significantly decreased nor increased risk of T2D. Compared with women who consumed less than 1.5 servings per week of tomato-based foods, women who consumed 10 or more servings per week had a multivariate RR of 1.04 (95% CI: 0.80, 1.36; P for trend = 0.54).

Villegas et al, 2008 (positive quality), a prospective cohort study (Shanghai Women's Health Study) examined the association between fruit and vegetable intake and the self-reported incidence of T2D in 64,191 Chinese women. During 4.6 years of follow-up, 1,608 cases of T2D were documented. Median intake of fruits was 239.4g per day and median intake of vegetables was 236.0g per day. Quintiles of vegetable intake and T2D were inversely associated; in multivariate analyses, the RR for T2D for the upper quintile (428.0g per day) relative to the lowest quintile (121.5g per day) of vegetable intake was 0.72 (95% CI: 0.61, 0.85; P<0.001). Individual vegetable subgroups (cruciferous, green leafy, yellow, allium, tomatoes and other) were all significantly, inversely associated with risk of T2D. Fruit intake was not associated with the incidence of T2D.

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Overview table

Study	Study Type	Association: Pos, Neg, None
Bazzano et al, 2008 Positive Quality	Prospective cohort study Nurses' Health Study, US	T2D: Ø vegetable and fruit; (-) fruit; ( ) green leafy vegetables
Halton et al, 2006 Positive Quality	Prospective cohort study Nurses' Health Study, US	T2D: (+) potato, (+) potato French fries
Liu et al, 2004 Positive Quality	Prospective cohort study Women's Health Study, US	T2D: Ø vegetable, Ø fruit, Ø subgroups in fully adjusted models
Wang et al, 2006 Positive Quality	Prospective cohort study Women's Health Study, US	T2D: Ø tomato-based products
Villegas et al, 2008 Positive Quality	Prospective cohort study Shanghai Women's Health Study, China	T2D: (-) vegetable, Ø fruit, (-) with each vegetable subgroup (cruciferous, green leafy, yellow, allium, tomatoes and other)

Search plan and results

Inclusion criteria

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

Exclusion criteria

- Studies that only consider cancer outcomes
- Studies that considered vegetables and fruits as part of a larger dietary pattern
- Medical treatment/therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Study population not from a developed country as defined by the Human

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

Search terms and electronic databases used

- PubMed

  ("Fruit"[majr:NoExp] OR fruit OR "Vegetables"[majr]) AND ("Adiposity"[majr] OR "Overweight"[majr] OR "Obesity"[majr] OR "Weight Gain"[majr] OR "Body Weights and Measures"[Majr] OR "body mass index"[majr] OR "body composition"[majr] OR "energy intake"[majr] OR caloric intake*)

  ("Fruit"[majr:NoExp] OR "Vegetables"[majr]) AND ("Diabetes Mellitus, Type 2"[majr] OR "metabolic syndrome X"[majr] OR "hypertension"[majr] OR "dyslipidemias"[MeSH Terms] OR "cardiovascular diseases"[majr] OR "heart diseases"[majr] OR "chronic disease"[mh] OR "Neoplasms"[majr])

Date searched: 07/23/2009

Summary of articles identified to review

- Total hits from all electronic database searches: 626
- Total articles identified to review from electronic databases: 143
- Articles identified via handsearch or other means: 1
- Number of Primary Articles Identified: 29
- Number of Review Articles Identified: 4
- Total Number of Articles Identified: 33
- Number of Articles Reviewed but Excluded: 111

Included articles (References)

In adults, what is the relationship between the intake of vegetables and fruits, not including juice and cardiovascular disease?

Systematic Reviews/Meta-analyses

1. Dauchet L, Amouyel P, Hercberg S, Dallongeville J. Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. *J Nutr.* 2006 Oct; 136 (10): 2, 588-2, 593. PMID: 16988131.
2. Dauchet L, Amouyel P, Dallongeville J. Fruit and vegetable consumption and risk of stroke: A meta-analysis of cohort studies. *Neurology*. 2005 Oct 25; 65 (8): 1, 193-1, 197. PMID: 16247045.
3. He FJ, Nowson CA, Lucas M, MacGregor GA. Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: Meta-analysis of cohort studies. *J Hum Hypertens.* 2007 Sep; 21 (9): 717-728. Epub 2007 Apr 19. PMID: 17443205.
4. He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: Meta-analysis of cohort studies. *Lancet.* 2006 Jan 28; 367 (9507): 320-326. Review. PMID: 16443039.

Primary Citations

1. Galeone C, Tavani A, Pelucchi C, Negri E, La Vecchia C. Allium vegetable

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intake and risk of acute myocardial infarction in Italy. *Eur J Nutr*. 2009 Mar; 48 (2): 120-123. Epub 2009 Jan 13. PMID: 19142565.
2. Genkinger JM, Platz EA, Hoffman SC, Comstock GW, Helzlsouer KJ. Fruit, vegetable and antioxidant intake and all-cause, cancer and cardiovascular disease mortality in a community-dwelling population in Washington County, Maryland. *Am J Epidemiol*. 2004 Dec 15; 160 (12): 1, 223-1, 233. PMID: 15583375.
3. Hung HC, Joshipura KJ, Jiang R, Hu FB, Hunter D, Smith-Warner SA, Colditz GA, Rosner B, Spiegelman D, Willett WC. Fruit and vegetable intake and risk of major chronic disease. *J Natl Cancer Inst*. 2004 Nov 3; 96 (21): 1, 577-1, 584. PMID: 15523086.
4. Joshipura KJ, Hung HC, Li TY, Hu FB, Rimm EB, Stampfer MJ, Colditz G, Willett WC. Intakes of fruits, vegetables and carbohydrate and the risk of CVD. *Public Health Nutr*. 2009 Jan; 12 (1): 115-121. Epub 2008 Apr 15. PMID: 18410704.
5. Nakamura K, Nagata C, Oba S, Takatsuka N, Shimizu H. Fruit and vegetable intake and mortality from cardiovascular disease are inversely associated in Japanese women but not in men. *J Nutr*. 2008 Jun; 138 (6): 1, 129-1, 134. PMID: 18492845.
6. Nikolic M, Nikic D, Petrovic B. Fruit and vegetable intake and the risk for developing coronary heart disease. *Cent Eur J Public Health*. 2008 Mar; 16 (1): 17-20. PMID: 18459474.
7. Takachi R, Inoue M, Ishihara J, Kurahashi N, Iwasaki M, Sasazuki S, Iso H, Tsubono Y, Tsugane S; JPHC Study Group. Fruit and vegetable intake and risk of total cancer and cardiovascular disease: Japan Public Health Center-Based Prospective Study. *Am J Epidemiol.* 2008 Jan 1; 167 (1): 59-70. Epub 2007 Oct 10. PMID: 17928402.
8. Tucker KL, Hallfrisch J, Qiao N, Muller D, Andres R, Fleg JL; Baltimore Longitudinal Study of Aging. The combination of high fruit and vegetable and low saturated fat intakes is more protective against mortality in aging men than is either alone: The Baltimore Longitudinal Study of Aging. *J Nutr*. 2005 Mar; 135 (3): 556-561. PMID: 15735093.

Blood Pressure/Hypertension

1. Mirmiran P, Noori N, Zavareh MB, Azizi F. Fruit and vegetable consumption and risk factors for cardiovascular disease. *Metabolism*. 2009 Apr; 58 (4): 460-468. PMID: 19303965.
2. Nuñez-Cordoba JM, Alonso A, Beunza JJ, Palma S, Gomez-Gracia E, Martinez-Gonzalez MA. Role of vegetables and fruits in Mediterranean diets to prevent hypertension. *Eur J Clin Nutr*. 2009 May; 63 (5): 605-612. Epub 2008 Feb 27. PMID: 18301434.
3. Radhika G, Sudha V, Mohan Sathya R, Ganesan A, Mohan V. Association of fruit and vegetable intake with cardiovascular risk factors in urban south Indians. *Br J Nutr.* 2008 Feb; 99 (2): 398-405. Epub 2007 Aug 3. PMID: 17678569.
4. Utsugi MT, Ohkubo T, Kikuya M, Kurimoto A, Sato RI, Suzuki K, Metoki H, Hara A, Tsubono Y, Imai Y. Fruit and vegetable consumption and the risk of hypertension determined by self measurement of blood pressure at home: The Ohasama study. *Hypertens Res.* 2008 Jul; 31 (7): 1, 435-1, 443. PMID: 18957815.

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5. Wang YF, Yancy WS Jr, Yu D, Champagne C, Appel LJ, Lin PH. The relationship between dietary protein intake and blood pressure: Results from the PREMIER study. *J Hum Hypertens*. 2008 Nov; 22 (11): 745-754. Epub 2008 Jun 26. PMID: 18580887. (Hand search)

Blood Lipids

1. Kelley DS, Rasooly R, Jacob RA, Kader AA, Mackey BE. Consumption of Bing sweet cherries lowers circulating concentrations of inflammation markers in healthy men and women. *J Nutr*. 2006 Apr; 136 (4): 981-986. PMID: 16549461.
2. Mirmiran P, Noori N, Zavareh MB, Azizi F. Fruit and vegetable consumption and risk factors for cardiovascular disease. *Metabolism*. 2009 Apr; 58 (4): 460-468. PMID: 19303965.
3. Radhika G, Sudha V, Mohan Sathya R, Ganesan A, Mohan V. Association of fruit and vegetable intake with cardiovascular risk factors in urban south Indians. *Br J Nutr.* 2008 Feb; 99 (2): 398-405. Epub 2007 Aug 3. PMID: 17678569.

In adults, what is the relationship between the intake of vegetables and fruits, not including juice and body weight?

1. Bes-Rastrollo M, Martínez-González MA, Sánchez-Villegas A, de la Fuente Arrillaga C, Martínez JA. Association of fiber intake and fruit/vegetable consumption with weight gain in a Mediterranean population. *Nutrition*. 2006 May; 22 (5): 504-511. Epub 2006 Feb 24. PMID: 16500082.
2. Buijsse B, Feskens EJ, Schulze MB, Forouhi NG, Wareham NJ, Sharp S, Palli D, Tognon G, Halkjaer J, Tjønneland A, Jakobsen MU, Overvad K, van der A DL, Du H, Sørensen TI, Boeing H. Fruit and vegetable intakes and subsequent changes in body weight in European populations: Results from the project on Diet, Obesity and Genes (DiOGenes). *Am J Clin Nutr.* 2009 Jul; 90 (1): 202-209. Epub 2009 May 20. PMID: 19458016.
3. Davis JN, Hodges VA, Gillham MB. Normal-weight adults consume more fiber and fruit than their age- and height-matched overweight/obese counterparts. *J Am Diet Assoc.* 2006 Jun; 106 (6): 833-840. PMID: 16720124.
4. Fujioka K, Greenway F, Sheard J, Ying Y. The effects of grapefruit on weight and insulin resistance: Relationship to the metabolic syndrome. *J Med Food*. 2006 Spring; 9 (1): 49-54. PMID: 16579728.
5. Goss J, Grubbs L. Comparative analysis of body mass index, consumption of fruits and vegetables, smoking and physical activity among Florida residents. *J Community Health Nurs.* 2005 Spring; 22(1): 37-46. PMID: 15695195.
6. He K, Hu FB, Colditz GA, Manson JE, Willett WC, Liu S. Changes in intake of fruits and vegetables in relation to risk of obesity and weight gain among middle-aged women. *Int J Obes Relat Metab Disord*. 2004 Dec; 28 (12): 1, 569-1, 574. PMID: 15467774.
7. Ortega RM, Rodríguez-Rodríguez E, Aparicio A, Marín-Arias LI, López-Sobaler AM. Responses to two weight-loss programs based on approximating the diet to the ideal: Differences associated with increased cereal or vegetable consumption. *Int J Vitam Nutr Res*. 2006 Nov; 76 (6): 367-376. PMID: 17607956.

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8. Radhika G, Sudha V, Mohan Sathya R, Ganesan A, Mohan V. Association of fruit and vegetable intake with cardiovascular risk factors in urban south Indians. *Br J Nutr*. 2008 Feb; 99 (2): 398-405. Epub 2007 Aug 3. PMID: 17678569.
9. Tanumihardjo SA, Valentine AR, Zhang Z, Whigham LD, Lai HJ, Atkinson RL. Strategies to increase vegetable or reduce energy and fat intake induce weight loss in adults. *Exp Biol Med* (Maywood). 2009 May; 234 (5): 542-552. Epub 2009 Feb 20. PMID: 19234056.
10. Vioque J, Weinbrenner T, Castelló A, Asensio L, Garcia de la Hera M. Intake of fruits and vegetables in relation to 10-year weight gain among Spanish adults. *Obesity* (Silver Spring). 2008 Mar; 16 (3): 664-670. Epub 2008 Jan 17. PMID: 18239583.
11. Xu F, Yin XM, Tong SL. Association between excess bodyweight and intake of red meat and vegetables among urban and rural adult Chinese in Nanjing, China. *Asia Pac J Public Health*. 2007;19 (3): 3-9. PMID: 18330398.

In adults, what is the relationship between the intake of vegetables and fruits, not including juice and type 2 diabetes?

1. Bazzano LA, Li TY, Joshipura KJ, Hu FB. Intake of fruit, vegetables, and fruit juices and risk of diabetes in women. *Diabetes Care*. 2008 Jul; 31 (7): 1, 311-1, 317. Epub 2008 Apr 4. PMID: 18390796; PMCID: PMC2453647.
2. Halton TL, Willett WC, Liu S, Manson JE, Stampfer MJ, Hu FB. Potato and French fry consumption and risk of type 2 diabetes in women. *Am J Clin Nutr*. 2006 Feb; 83 (2): 284-290. PMID: 16469985.
3. Liu S, Serdula M, Janket SJ, Cook NR, Sesso HD, Willett WC, Manson JE, Buring JE. A prospective study of fruit and vegetable intake and the risk of type 2 diabetes in women. *Diabetes Care.* 2004 Dec; 27 (12): 2, 993-2, 996. PMID: 15562224.
4. Villegas R, Shu XO, Gao YT, Yang G, Elasy T, Li H, Zheng W. Vegetable but not fruit consumption reduces the risk of type 2 diabetes in Chinese women. *J Nutr*. 2008 Mar; 138 (3): 574-580. PMID: 18287369; PMCID: PMC2615491.
5. Wang L, Liu S, Manson JE, Gaziano JM, Buring JE, Sesso HD. The consumption of lycopene and tomato-based food products is not associated with the risk of type 2 diabetes in women. *J Nutr*. 2006 Mar; 136 (3): 620-625. PMID: 16484534.

Excluded articles

Article	Reason for Exclusion
Alonso A, de la Fuente C, Martín-Arnau AM, de Irala J, Martínez JA, Martínez-González MA. Fruit and vegetable consumption is inversely associated with blood pressure in a Mediterranean population with a high vegetable-fat intake: The Seguimiento Universidad de Navarra (SUN) Study.*Br J Nutr.* 2004 Aug; 92 (2): 311-319. PMID: 15333163.	Results reported based on the same dataset as Nunez-Cordoba, 2009.

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Austin GL, Adair LS, Galanko JA, Martin CF, Satia JA, Sandler RS. A diet high in fruits and low in meats reduces the risk of colorectal adenomas. *J Nutr.* 2007 Apr; 137 (4): 999-1, 004. PMID: 17374667.	Cancer excluded as outcome of interest.
Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Fruits and vegetables and endometrial cancer risk: A systematic literature review and meta-analysis. *Nutr Cancer.* 2007; 58 (1): 6-21. Review. PMID: 17571962.	Cancer excluded as outcome of interest.
Barros R, Moreira A, Fonseca J, de Oliveira JF, Delgado L, Castel-Branco MG, Haahtela T, Lopes C, Moreira P. Adherence to the Mediterranean diet and fresh fruit intake are associated with improved asthma control. *Allergy*. 2008 Jul; 63 (7): 917-923. PMID: 18588559.	Participants were diagnosed with asthma.
Benetou V, Orfanos P, Lagiou P, Trichopoulos D, Boffetta P, Trichopoulou A. Vegetables and fruits in relation to cancer risk: evidence from the Greek EPIC cohort study. *Cancer Epidemiol Biomarkers Prev.* 2008 Feb; 17 (2): 387-392. PMID: 18268122.	Cancer excluded as outcome of interest.
Boeing H, Dietrich T, Hoffmann K, Pischon T, Ferrari P, Lahmann PH, Boutron-Ruault MC, Clavel-Chapelon F, Allen N, Key T, Skeie G, Lund E, Olsen A, Tjonneland A, Overvad K, Jensen MK, Rohrmann S, Linseisen J, Trichopoulou A, Bamia C, Psaltopoulou T, Weinehall L, Johansson I, Sánchez MJ, Jakszyn P, Ardanaz E, Amiano P, Chirlaque MD, Quirós JR, Wirfalt E, Berglund G, Peeters PH, van Gils CH, Bueno-de-Mesquita HB, Büchner FL, Berrino F, Palli D, Sacerdote C, Tumino R, Panico S, Bingham S, Khaw KT, Slimani N, Norat T, Jenab M, Riboli E. Intake of fruits and vegetables and risk of cancer of the upper aero-digestive tract: The prospective EPIC-study. *Cancer Causes Control.* 2006 Sep; 17 (7): 957-969. PMID: 16841263.	Cancer excluded as outcome of interest.
Chan JM, Wang F, Holly EA. Vegetable and fruit intake and pancreatic cancer in a population-based case-control study in the San Francisco bay area. *Cancer Epidemiol Biomarkers Prev*. 2005 Sep; 14 (9): 2, 093-2, 097. PMID: 16172215.	Cancer excluded as outcome of interest.

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Chen G, Heilbrun LK, Venkatramanamoorthy R, Maranci V, Redd JN, Klurfeld DM, Djuric Z. Effects of low-fat and/or high-fruit-and-vegetable diets on plasma levels of 8-isoprostane-F2alpha in the Nutrition and Breast Health study. *Nutr Cancer.* 2004; 50 (2): 155-160. PMID: 15623461.	Does not include breast cancer incidence in analyses: Measured intermediate outcome (8-isoprostane-F2alpha).
Crujeiras AB, Parra MD, Rodríguez MC, Martínez de Morentin BE, Martínez JA. A role for fruit content in energy-restricted diets in improving antioxidant status in obese women during weight loss. *Nutrition.* 2006 Jun; 22 (6): 593-599. PMID: 16704952.	Sample size less than inclusion criteria.
Darmon N, Darmon M, Maillot M, Drewnowski A. A nutrient density standard for vegetables and fruits: Nutrients per calorie and nutrients per unit cost. *J Am Diet Assoc.* 2005 Dec; 105 (12): 1, 881-1, 887. PMID: 16321593.	Does not answer question: Does not examine the relationship between vegetables and fruits and health outcomes.
Dauchet L, Ferrières J, Arveiler D, Yarnell JW, Gey F, Ducimetière P, Ruidavets JB, Haas B, Evans A, Bingham A, Amouyel P, Dallongeville J. Frequency of fruit and vegetable consumption and coronary heart disease in France and Northern Ireland: The PRIME study.*Br J Nutr.* 2004 Dec; 92 (6): 963-972. PMID: 15613259.	Included in He, 2006.
de Oliveira MC, Sichieri R, Venturim Mozzer R. A low-energy-dense diet adding fruit reduces weight and energy intake in women. *Appetite.* 2008 Sep; 51 (2): 291-295. Epub 2008 Mar 7. PMID: 18439712.	Dropout rate higher than inclusion criteria.
De Stefani E, Boffetta P, Deneo-Pellegrini H, Ronco AL, Correa P, Mendilaharsu M. The role of vegetable and fruit consumption in the aetiology of squamous cell carcinoma of the oesophagus: A case-control study in Uruguay. *Int J Cancer*. 2005 Aug 10; 116 (1): 130-135. PMID: 15756680.	Cancer excluded as outcome of interest.
Do MH, Lee SS, Kim JY, Jung PJ, Lee MH. Fruits, vegetables, soy foods and breast cancer in pre- and postmenopausal Korean women: A case-control study. *Int J Vitam Nutr Res*. 2007 Mar; 77 (2): 130-141. PMID: 17896586.	Cancer excluded as outcome of interest.

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Dosil-Díaz O, Ruano-Ravina A, Gestal-Otero JJ, Barros-Dios JM. Consumption of fruit and vegetables and risk of lung cancer: A case-control study in Galicia, Spain. *Nutrition*. 2008 May; 24 (5): 407-413. Epub 2008 Mar 7. PMID: 18314310.	Cancer excluded as outcome of interest.
Dove ER, Hodgson JM, Puddey IB, Beilin LJ, Lee YP, Mori TA. Skim milk compared with a fruit drink acutely reduces appetite and energy intake in overweight men and women. *Am J Clin Nutr.* 2009 Jul; 90 (1): 70-75. Epub 2009 May 27. PMID: 19474132.	Does not include body weight in analyses.
Dubowitz T, Heron M, Bird CE, Lurie N, Finch BK, Basurto-Dávila R, Hale L, Escarce JJ. Neighborhood socioeconomic status and fruit and vegetable intake among whites, blacks and Mexican Americans in the United States. *Am J Clin Nutr*. 2008 Jun; 87 (6): 1, 883-1, 891. PMID: 18541581.	Does not answer question: Does not examine the relationship between vegetables and fruits and health outcomes.
Ellinger S, Ellinger J, Stehle P. Tomatoes, tomato products and lycopene in the prevention and treatment of prostate cancer: Do we have the evidence from intervention studies? *Curr Opin Clin Nutr Metab Care.* 2006 Nov; 9 (6): 722-727. Review. PMID: 17053426.	Study design is narrative review.
Ellingsen I, Hjerkinn EM, Seljeflot I, Arnesen H, Tonstad S. Consumption of fruit and berries is inversely associated with carotid atherosclerosis in elderly men.*Br J Nutr*. 2008 Mar; 99 (3): 674-681. Epub 2007 Sep 26. Erratum in: *Br J Nutr*. 2008 Mar; 99 (3): 697. PMID: 17894919.	Does not answer question: Does not include selected health outcome of interest.
Etminan M, Takkouche B, Caamaño-Isorna F. The role of tomato products and lycopene in the prevention of prostate cancer: A meta-analysis of observational studies. *Cancer Epidemiol Biomarkers Prev.* 2004 Mar; 13 (3): 340-345. PMID: 15006906.	Cancer excluded as outcome of interest.
Freedman ND, Park Y, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC. Fruit and vegetable intake and esophageal cancer in a large prospective cohort study. *Int J Cancer.* 2007 Dec 15; 121 (12): 2, 753-2, 760. PMID: 17691111.	Cancer excluded as outcome of interest.

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Freedman ND, Park Y, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC. Fruit and vegetable intake and head and neck cancer risk in a large United States prospective cohort study. *Int J Cancer*. 2008 May 15; 122 (10): 2, 330-2, 336. PMID: 18092323.	Cancer excluded as outcome of interest.
Freedman ND, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC. Fruit and vegetable intake and gastric cancer risk in a large United States prospective cohort study. *Cancer Causes Control.* 2008 Jun; 19 (5): 459-467. Epub 2008 Jan 1. PMID: 18166992.	Cancer excluded as outcome of interest.
Galeone C, Negri E, Pelucchi C, La Vecchia C, Bosetti C, Hu J. Dietary intake of fruit and vegetable and lung cancer risk: A case-control study in Harbin, northeast China. *Ann Oncol.* 2007 Feb; 18 (2): 388-392. Epub 2006 Oct 23. PMID: 17060488.	Cancer excluded as outcome of interest.
Gallicchio L, Matanoski G, Tao XG, Chen L, Lam TK, Boyd K, Robinson KA, Balick L, Mickelson S, Caulfield LE, Herman JG, Guallar E, Alberg AJ. Adulthood consumption of preserved and non-preserved vegetables and the risk of nasopharyngeal carcinoma: A systematic review. *Int J Cancer*. 2006 Sep 1;119 (5): 1, 125-1, 135. Review. PubMed PMID: 16570274.	Cancer excluded as outcome of interest.
George SM, Park Y, Leitzmann MF, Freedman ND, Dowling EC, Reedy J, Schatzkin A, Hollenbeck A, Subar AF. Fruit and vegetable intake and risk of cancer: a prospective cohort study. *Am J Clin Nutr.* 2009 Jan; 89 (1): 347-353. Epub 2008 Dec 3. PMID: 19056579; Central PMCID: PMC2647712.	Cancer excluded as outcome of interest.
Giammarioli S, Filesi C, Vitale B, Cantagallo A, Dragoni F, Sanzini E. Effect of high intakes of fruit and vegetables on redox status in type 2 onset diabetes: A pilot study. *Int J Vitam Nutr Res.* 2004 Sep; 74 (5): 313-320. PMID: 15628668.	Participants diagnosed with type 2 diabetes.

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González CA, Pera G, Agudo A, Bueno-de-Mesquita HB, Ceroti M, Boeing H, Schulz M, Del Giudice G, Plebani M, Carneiro F, Berrino F, Sacerdote C, Tumino R, Panico S, Berglund G, Simán H, Hallmans G, Stenling R, Martinez C, Dorronsoro M, Barricarte A, Navarro C, Quiros JR, Allen N, Key TJ, Bingham S, Day NE, Linseisen J, Nagel G, Overvad K, Jensen MK, Olsen A, Tjønneland A, Büchner FL, Peeters PH, Numans ME, Clavel-Chapelon F, Boutron-Ruault MC, Roukos D, Trichopoulou A, Psaltopoulou T, Lund E, Casagrande C, Slimani N, Jenab M, Riboli E. Fruit and vegetable intake and the risk of stomach and oesophagus adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST).*Int J Cancer*. 2006 May 15; 118 (10): 2, 559-2, 566. PMID: 16380980.	Cancer excluded as outcome of interest.
Gorinstein S, Caspi A, Libman I, Lerner HT, Huang D, Leontowicz H, Leontowicz M, Tashma Z, Katrich E, Feng S, Trakhtenberg S. Red grapefruit positively influences serum triglyceride level in patients suffering from coronary atherosclerosis: Studies in vitro and in humans. *J Agric Food Chem*. 2006 Mar 8; 54 (5): 1, 887-1, 892. PubMed PMID: 16506849.	Participants diagnosed with hyperlipidemia and had received coronary bypass surgery.
Holick CN, De Vivo I, Feskanich D, Giovannucci E, Stampfer M, Michaud DS. Intake of fruits and vegetables, carotenoids, folate and vitamins A, C, E and risk of bladder cancer among women (United States).Cancer Causes Control. 2005 Dec; 16 (10): 1, 135-1, 145. PMID: 16215863.	Cancer excluded as outcome of interest.
Holick CN, Giovannucci EL, Rosner B, Stampfer MJ, Michaud DS. Prospective study of intake of fruit, vegetables and carotenoids and the risk of adult glioma. *Am J Clin Nutr.* 2007 Mar; 85 (3): 877-886. PMID: 17344512.	Cancer excluded as outcome of interest.
Jansen MC, Bueno-de-Mesquita HB, Feskens EJ, Streppel MT, Kok FJ, Kromhout D. Quantity and variety of fruit and vegetable consumption and cancer risk. *Nutr Cancer.* 2004; 48 (2): 142-148. PMID: 15231448.	Cancer excluded as outcome of interest.
Johnsen SP. Intake of fruit and vegetables and risk of stroke: An overview. *Curr Opin Clin Nutr Metab Care*. 2004 Nov; 7 (6): 665-670. Review. PMID: 15534435.	Study design is narrative review.

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Kavanaugh CJ, Trumbo PR, Ellwood KC. The U.S. Food and Drug Administration's evidence-based review for qualified health claims: Tomatoes, lycopene and cancer. *J Natl Cancer Inst.* 2007 Jul 18; 99 (14): 1, 074-1, 085. Epub 2007 Jul 10. Review. PMID: 17623802.	Cancer excluded as outcome of interest.
Kellen E, Zeegers M, Paulussen A, Van Dongen M, Buntinx F. Fruit consumption reduces the effect of smoking on bladder cancer risk. The Belgian case control study on bladder cancer. *Int J Cancer.* 2006 May 15; 118 (10): 2, 572-2, 578. PMID: 16380991.	Cancer excluded as outcome of interest.
Kim SY, Yoon S, Kwon SM, Park KS, Lee-Kim YC. Kale juice improves coronary artery disease risk factors in hypercholesterolemic men. *Biomed Environ Sci.* 2008 Apr; 21 (2): 91-97. PMID: 18548846.	Participants diagnosed with hypercholesterolemia.
Kirsh VA, Mayne ST, Peters U, Chatterjee N, Leitzmann MF, Dixon LB, Urban DA, Crawford ED, Hayes RB. A prospective study of lycopene and tomato product intake and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2006 Jan; 15 (1): 92-98. PMID: 16434593.	Cancer excluded as outcome of interest.
Kirsh VA, Peters U, Mayne ST, Subar AF, Chatterjee N, Johnson CC, Hayes RB; Prospective study of fruit and vegetable intake and risk of prostate cancer. Prospective study of fruit and vegetable intake and risk of prostate cancer. *J Natl Cancer Inst*. 2007 Aug 1; 99 (15): 1, 200-1, 209. Epub 2007 Jul 24. PMID: 17652276.	Cancer excluded as outcome of interest.
Klassen AC, Garrett-Mayer E, Houts PS, Shankar S, Torio CM. The relationship of body size to participation and success in a fruits and vegetables intervention among low-income women. *J Community Health*. 2008 Apr; 33 (2): 78-89. PMID: 18074208.	Does not answer question: Does not examine the relationship between vegetables and fruits and health outcomes.

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

Koushik A, Hunter DJ, Spiegelman D, Anderson KE, Arslan AA, Beeson WL, van den Brandt PA, Buring JE, Cerhan JR, Colditz GA, Fraser GE, Freudenheim JL, Genkinger JM, Goldbohm RA, Hankinson SE, Koenig KL, Larsson SC, Leitzmann M, McCullough ML, Miller AB, Patel A, Rohan TE, Schatzkin A, Smit E, Willett WC, Wolk A, Zhang SM, Smith-Warner SA. Fruits and vegetables and ovarian cancer risk in a pooled analysis of 12 cohort studies. *Cancer Epidemiol Biomarkers Prev.* 2005 Sep; 14 (9): 2, 160-2, 167. PMID: 16172226.	Cancer excluded as outcome of interest.
Koushik A, Hunter DJ, Spiegelman D, Beeson WL, van den Brandt PA, Buring JE, Calle EE, Cho E, Fraser GE, Freudenheim JL, Fuchs CS, Giovannucci EL, Goldbohm RA, Harnack L, Jacobs DR Jr, Kato I, Krogh V, Larsson SC, Leitzmann MF, Marshall JR, McCullough ML, Miller AB, Pietinen P, Rohan TE, Schatzkin A, Sieri S, Virtanen MJ, Wolk A, Zeleniuch-Jacquotte A, Zhang SM, Smith-Warner SA. Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies. *J Natl Cancer Inst*. 2007 Oct 3; 99 (19): 1, 471-1, 483. Epub 2007 Sep 25. PMID: 17895473.	Cancer excluded as outcome of interest.
Kurahashi N, Inoue M, Iwasaki M, Tanaka Y, Mizokami M, Tsugane S; JPHC Study Group. Vegetable, fruit and antioxidant nutrient consumption and subsequent risk of hepatocellular carcinoma: A prospective cohort study in Japan. *Br J Cancer*. 2009 Jan 13; 100 (1): 181-184. PMID: 19127270.	Cancer excluded as outcome of interest.
Lam TK, Gallicchio L, Lindsley K, Shiels M, Hammond E, Tao XG, Chen L, Robinson KA, Caulfield LE, Herman JG, Guallar E, Alberg AJ. Cruciferous vegetable consumption and lung cancer risk: a systematic review. *Cancer Epidemiol Biomarkers Prev.* 2009 Jan; 18 (1): 184-195. Review. PMID: 19124497.	Cancer excluded as outcome of interest.
Larsson SC, Andersson SO, Johansson JE, Wolk A. Fruit and vegetable consumption and risk of bladder cancer: A prospective cohort study. *Cancer Epidemiol Biomarkers Prev*. 2008 Sep; 17 (9): 2, 519-2, 522. PMID: 18768526.	Cancer excluded as outcome of interest.

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

Larsson SC, Bergkvist L, Wolk A. Fruit and vegetable consumption and incidence of gastric cancer: a prospective study. *Cancer Epidemiol Biomarkers Prev*. 2006 Oct; 15 (10): 1, 998-2, 001. PMID: 17035412.	Cancer excluded as outcome of interest.
Larsson SC, Håkansson N, Näslund I, Bergkvist L, Wolk A. Fruit and vegetable consumption in relation to pancreatic cancer risk: A prospective study. *Cancer Epidemiol Biomarkers Prev*. 2006 Feb; 15 (2): 301-305. PMID: 16492919.	Cancer excluded as outcome of interest.
Larsson SC, Holmberg L, Wolk A. Fruit and vegetable consumption in relation to ovarian cancer incidence: The Swedish Mammography Cohort. *Br J Cancer*. 2004 Jun 1; 90 (11): 2, 167-2, 170. PMID: 15150575.	Cancer excluded as outcome of interest.
Lee JE, Giovannucci E, Smith-Warner SA, Spiegelman D, Willett WC, Curhan GC. Intakes of fruits, vegetables, vitamins A, C, and E and carotenoids and risk of renal cell cancer. *Cancer Epidemiol Biomarkers Prev*. 2006 Dec; 15 (12): 2, 445-2, 452. PMID: 17164369.	Cancer excluded as outcome of interest.
Lin J, Zhang SM, Cook NR, Rexrode KM, Liu S, Manson JE, Lee IM, Buring JE. Dietary intakes of fruit, vegetables, and fiber and risk of colorectal cancer in a prospective cohort of women (United States).*Cancer Causes Control*. 2005 Apr; 16 (3): 225-233. PMID: 15947874.	Cancer excluded as outcome of interest.
Liu Y, Sobue T, Otani T, Tsugane S. Vegetables, fruit consumption and risk of lung cancer among middle-aged Japanese men and women: JPHC study. *Cancer Causes Control*. 2004 May; 15 (4): 349-357. PMID: 15141136.	Cancer excluded as outcome of interest.
Longo-Mbenza B, Tshimanga KB, Buassa-bu-Tsumbu B, Kabangu MJ. Diets rich in vegetables and physical activity are associated with a decreased risk of pregnancy induced hypertension among rural women from Kimpese, DR Congo. *Niger J Med*. 2008 Jul-Aug; 17 (3): 265-269. PMID: 18788250.	Study population not from a developed country as defined by the Human Development Index.
Lunet N, Lacerda-Vieira A, Barros H. Fruit and vegetables consumption and gastric cancer: a systematic review and meta-analysis of cohort studies. *Nutr Cancer*. 2005; 53 (1): 1-10. Review. PMID: 16351501.	Cancer excluded as outcome of interest.

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

Lunet N, Valbuena C, Vieira AL, Lopes C, Lopes C, David L, Carneiro F, Barros H. Fruit and vegetable consumption and gastric cancer by location and histological type: Case-control and meta-analysis. *Eur J Cancer Prev*. 2007 Aug; 16 (4): 312-327. PMID: 17554204.	Cancer excluded as outcome of interest.
Masala G, Ceroti M, Pala V, Krogh V, Vineis P, Sacerdote C, Saieva C, Salvini S, Sieri S, Berrino F, Panico S, Mattiello A, Tumino R, Giurdanella MC, Bamia C, Trichopoulou A, Riboli E, Palli D.A dietary pattern rich in olive oil and raw vegetables is associated with lower mortality in Italian elderly subjects.*Br J Nutr*. 2007 Aug; 98 (2): 406-415. Epub 2007 Apr 3. PMID: 17403268.	Does not answer question: Discusses vegetables and fruits as part of dietary pattern.
Maserejian NN, Giovannucci E, Rosner B, Zavras A, Joshipura K. Prospective study of fruits and vegetables and risk of oral premalignant lesions in men. *Am J Epidemiol*. 2006 Sep 15; 164 (6): 556-566. Epub 2006 Jul 17. PMID: 16847039.	Cancer excluded as outcome of interest.
McCall DO, McGartland CP, McKinley MC, Patterson CC, Sharpe P, McCance DR, Young IS, Woodside JV. Dietary intake of fruits and vegetables improves microvascular function in hypertensive subjects in a dose-dependent manner. *Circulation*. 2009 Apr 28; 119 (16): 2, 153-2, 160. Epub 2009 Apr 13. PMID: 19364976.	Participants diagnosed with hypertension, and study did not measure identified outcome of interest.
McCullough ML, Bandera EV, Patel R, Patel AV, Gansler T, Kushi LH, Thun MJ, Calle EE. A prospective study of fruits, vegetables and risk of endometrial cancer. *Am J Epidemiol.* 2007 Oct 15; 166 (8): 902-911. Epub 2007 Aug 9. PMID: 17690222.	Cancer excluded as outcome of interest.
Michels KB, Giovannucci E, Chan AT, Singhania R, Fuchs CS, Willett WC. Fruit and vegetable consumption and colorectal adenomas in the Nurses' Health Study. *Cancer Res*. 2006 Apr 1; 66 (7): 3, 942-3, 953. PMID: 16585224.	Cancer excluded as outcome of interest.
Mikkelsen TB, Osler M, Orozova-Bekkevold I, Knudsen VK, Olsen SF. Association between fruit and vegetable consumption and birth weight: A prospective study among 43, 585 Danish women. *Scand J Public Health*. 2006; 34 (6): 616-622. PMID: 17132595.	Does not answer question: addresses vegetable and fruit intake during pregnancy and birth weight.

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Millen AE, Subar AF, Graubard BI, Peters U, Hayes RB, Weissfeld JL, Yokochi LA, Ziegler RG; PLCO Cancer Screening Trial Project Team. Fruit and vegetable intake and prevalence of colorectal adenoma in a cancer screening trial. *Am J Clin Nutr*. 2007 Dec; 86 (6): 1, 754-1, 764. PMID: 18065596.	Cancer excluded as outcome of interest.
Mommers M, Schouten LJ, Goldbohm RA, van den Brandt PA. Consumption of vegetables and fruits and risk of ovarian carcinoma. *Cancer*. 2005 Oct 1; 104 (7): 1, 512-1, 519. PMID: 16104037.	Cancer excluded as outcome of interest.
Nomura AM, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Pike MC, Kolonel LN. Association of vegetable, fruit, and grain intakes with colorectal cancer: The Multiethnic Cohort Study. *Am J Clin Nutr*. 2008 Sep; 88 (3): 730-737. PMID: 18779290.	Cancer excluded as outcome of interest.
Nöthlings U, Schulze MB, Weikert C, Boeing H, van der Schouw YT, Bamia C, Benetou V, Lagiou P, Krogh V, Beulens JW, Peeters PH, Halkjaer J, Tjønneland A, Tumino R, Panico S, Masala G, Clavel-Chapelon F, de Lauzon B, Boutron-Ruault MC, Vercambre MN, Kaaks R, Linseisen J, Overvad K, Arriola L, Ardanaz E, Gonzalez CA, Tormo MJ, Bingham S, Khaw KT, Key TJ, Vineis P, Riboli E, Ferrari P, Boffetta P, Bueno-de-Mesquita HB, van der A DL, Berglund G, Wirfält E, Hallmans G, Johansson I, Lund E, Trichopoulo A. Intake of vegetables, legumes, and fruit, and risk for all-cause, cardiovascular and cancer mortality in a European diabetic population. *J Nutr*. 2008 Apr; 138 (4): 775-781. PMID: 18356334.	Participants were diagnosed with diabetes.
Nöthlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN. Vegetable intake and pancreatic cancer risk: The multiethnic cohort study. *Am J Epidemiol*. 2007 Jan 15; 165 (2): 138-147. Epub 2006 Oct 26. PMID: 17068094.	Cancer excluded as outcome of interest.
Nouraie M, Pietinen P, Kamangar F, Dawsey SM, Abnet CC, Albanes D, Virtamo J, Taylor PR. Fruits, vegetables, and antioxidants and risk of gastric cancer among male smokers. *Cancer Epidemiol Biomarkers Prev*. 2005 Sep; 14 (9): 2, 087-2, 092. PMID: 16172214.	Cancer excluded as outcome of interest.

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Orjuela MA, Titievsky L, Liu X, Ramirez-Ortiz M, Ponce-Castaneda V, Lecona E, Molina E, Beaverson K, Abramson DH, Mueller NE. Fruit and vegetable intake during pregnancy and risk for development of sporadic retinoblastoma. *Cancer Epidemiol Biomarkers Prev*. 2005 Jun; 14 (6): 1, 433-1, 440. PMID: 15941952.	Does not answer question: does not address outcomes of interest (examines retinoblastoma).
Papanikolaou Y, Fulgoni VL 3rd. Bean consumption is associated with greater nutrient intake, reduced systolic blood pressure, lower body weight and a smaller waist circumference in adults: Results from the National Health and Nutrition Examination Survey 1999-2002. *J Am Coll Nutr*. 2008 Oct; 27 (5): 569-576. PMID: 18845707.	Beans considered in separate question on cooked dry beans and peas and selected health outcomes.
Pavia M, Pileggi C, Nobile CG, Angelillo IF. Association between fruit and vegetable consumption and oral cancer: A meta-analysis of observational studies. *Am J Clin Nutr*. 2006 May; 83 (5): 1, 126-1, 134. PMID: 16685056.	Cancer excluded as outcome of interest.
Pham TM, Fujino Y, Ide R, Kubo T, Shirane K, Tokui N, Mizoue T, Ogimoto I, Matsuda S, Yoshimura T. Prospective study of vegetable consumption and liver cancer in Japan. *Int J Cancer.* 2006 Nov 15; 119 (10): 2, 408-2, 411. PMID: 16894561.	Cancer excluded as outcome of interest.
Pomerleau J, Lock K, Knai C, McKee M. Interventions designed to increase adult fruit and vegetable intake can be effective: A systematic review of the literature. *J Nutr*. 2005 Oct; 135 (10): 2, 486-2, 495. Review. PMID: 16177217.	Does not answer question: Evaluates interventions to increase fruit and vegetable intake.
Prynne CJ, Mishra GD, O'Connell MA, Muniz G, Laskey MA, Yan L, Prentice A, Ginty F. Fruit and vegetable intakes and bone mineral status: A cross sectional study in five age and sex cohorts. *Am J Clin Nutr*. 2006 Jun; 83 (6): 1, 420-1, 428. PMID: 16789345.	Does not answer question: Does not address outcomes of interest.
Rai A, Mohapatra SC, Shukla HS. Correlates between vegetable consumption and gallbladder cancer. Eu*r J Cancer Prev*. 2006 Apr; 15 (2): 134-137. PMID: 16523010.	Participants diagnosed with gallbladder cancer or gallstone disease.

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Ramón R, Ballester F, Iñiguez C, Rebagliato M, Murcia M, Esplugues A, Marco A, García de la Hera M, Vioque J. Vegetable but not fruit intake during pregnancy is associated with newborn anthropometric measures. *J Nutr*. 2009 Mar; 139 (3): 561-567. Epub 2009 Jan 21. PMID: 19158218.	Does not answer question: Addresses fruit and vegetable intake during pregnancy and birth outcomes.
Rashidkhani B, Lindblad P, Wolk A. Fruits, vegetables and risk of renal cell carcinoma: a prospective study of Swedish women.*Int J Cancer*. 2005 Jan 20; 113 (3): 451-455. PMID: 15455348.	Cancer excluded as outcome of interest.
Rodríguez MC, Parra MD, Marques-Lopes I, De Morentin BE, González A, Martínez JA. Effects of two energy-restricted diets containing different fruit amounts on body weight loss and macronutrient oxidation. *Plant Foods Hum Nutr*. 2005 Dec; 60 (4): 219-224. PMID: 16395633.	Does not meet inclusion criteria for sample size.
Romieu I, Varraso R, Avenel V, Leynaert B, Kauffmann F, Clavel-Chapelon F. Fruit and vegetable intakes and asthma in the E3N study. *Thorax.* 2006 Mar; 61 (3): 209-215. Epub 2006 Jan 5. PMID: 16396945; PMCID: PMC1974844.	Does not answer question: Does not measure an identified outcome of interest.
Sandoval M, Font R, Mañós M, Dicenta M, Quintana MJ, Bosch FX, Castellsagué X. The role of vegetable and fruit consumption and other habits on survival following the diagnosis of oral cancer: A prospective study in Spain. *Int J Oral Maxillofac Surg*. 2009 Jan; 38 (1): 31-39. Epub 2008 Oct 31. PubMed PMID: 18951763.	Participants diagnosed with oral cancer.
Sartorelli DS, Franco LJ, Cardoso MA. High intake of fruits and vegetables predicts weight loss in Brazilian overweight adults. *Nutr Res*. 2008 Apr; 28 (4): 233-238. PMID: 19083413.	Dropout rate higher than inclusion criteria.
Sato K, Kawakami N, Ohtsu T, Tsutsumi A, Miyazaki S, Masumoto T, Horie S, Haratani T, Kobayashi F, Araki S. Broccoli consumption and chronic atrophic gastritis among Japanese males: An epidemiological investigation. *Acta Med Okayama*. 2004 Jun; 58 (3): 127-133. PMID: 15471434.	Does not answer question: Does not include outcome of interest (measured chronic atrophic gastritis).

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Sato Y, Tsubono Y, Nakaya N, Ogawa K, Kurashima K, Kuriyama S, Hozawa A, Nishino Y, Shibuya D, Tsuji I. Fruit and vegetable consumption and risk of colorectal cancer in Japan: The Miyagi Cohort Study. *Public Health Nutr.* 2005 May; 8 (3): 309-314. PMID: 15918928.	Cancer excluded as outcome of interest.
Schnäbele K, Briviba K, Bub A, Roser S, Pool-Zobel BL, Rechkemmer G. Effects of carrot and tomato juice consumption on faecal markers relevant to colon carcinogenesis in humans. *Br J Nutr*. 2008 Mar; 99 (3): 606-613. PMID: 18254985.	Does not answer question: Does not include outcome of interest.
Schulz M, Lahmann PH, Boeing H, Hoffmann K, Allen N, Key TJ, Bingham S, Wirfält E, Berglund G, Lundin E, Hallmans G, Lukanova A, Martínez Garcia C, González CA, Tormo MJ, Quirós JR, Ardanaz E, Larrañaga N, Lund E, Gram IT, Skeie G, Peeters PH, van Gils CH, Bueno-de-Mesquita HB, Büchner FL, Pasanisi P, Galasso R, Palli D, Tumino R, Vineis P, Trichopoulou A, Kalapothaki V, Trichopoulos D, Chang-Claude J, Linseisen J, Boutron-Ruault MC, Touillaud M, Clavel-Chapelon F, Olsen A, Tjønneland A, Overvad K, Tetsche M, Jenab M, Norat T, Kaaks R, Riboli E. Fruit and vegetable consumption and risk of epithelial ovarian cancer: The European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiol Biomarkers Prev*. 2005 Nov; 14 (11 Pt 1): 2, 531-2, 535. PMID: 16284374.	Cancer excluded as outcome of interest.
Setiawan VW, Yu GP, Lu QY, Lu ML, Yu SZ, Mu L, Zhang JG, Kurtz RC, Cai L, Hsieh CC, Zhang ZF. Allium vegetables and stomach cancer risk in China. *Asian Pac J Cancer Prev.* 2005 Jul-Sep; 6 (3): 387-395. PMID: 16236005.	Cancer excluded as outcome of interest.
Shi Z, Hu X, Yuan B, Hu G, Pan X, Dai Y, Byles JE, Holmboe-Ottesen G. Vegetable-rich food pattern is related to obesity in China. *Int J Obes* (Lond). 2008 Jun; 32 (6): 975-984. Epub 2008 Mar 4. PMID: 18317472.	Includes fruits, vegetables, and whole grains as part of vegetable-rich food pattern. Does not evaluate vegetable and fruit and health outcomes specifically.
Skuladottir H, Tjoenneland A, Overvad K, Stripp C, Olsen JH. Does high intake of fruit and vegetables improve lung cancer survival? *Lung Cancer*. 2006 Mar; 51 (3): 267-273. Epub 2006 Feb 15. PMID: 16469411.	Participants diagnosed with lung cancer.

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Stoner GD, Wang LS, Casto BC. Laboratory and clinical studies of cancer chemoprevention by antioxidants in berries. *Carcinogenesis*. 2008 Sep; 29 (9): 1, 665-1, 674. Epub 2008 Jun 9. Review. PMID: 18544560.	Study design is narrative review.
Sunny L. A low fat diet rich in fruits and vegetables may reduce the risk of developing prostate cancer. *Asian Pac J Cancer Prev*. 2005 Oct-Dec; 6 (4): 490-496. PMID: 16435998.	Cancer excluded as outcome of interest.
Tang L, Zirpoli GR, Guru K, Moysich KB, Zhang Y, Ambrosone CB, McCann SE. Consumption of raw cruciferous vegetables is inversely associated with bladder cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2008 Apr; 17 (4): 938-944. PMID: 18398034.	Cancer excluded as outcome of interest.
Tao MH, Xu WH, Zheng W, Gao YT, Ruan ZX, Cheng JR, Xiang YB, Shu XO. A case-control study in Shanghai of fruit and vegetable intake and endometrial cancer. *Br J Cancer*. 2005 Jun 6; 92 (11): 2, 059-2, 064. PMID: 15886701.	Cancer excluded as outcome of interest.
te Velde SJ, Twisk JW, Brug J. Tracking of fruit and vegetable consumption from adolescence into adulthood and its longitudinal association with overweight. *Br J Nutr*. 2007 Aug; 98 (2): 431-438. Epub 2007 Apr 16. Erratum in: *Br J Nutr.* 2007 Oct; 98 (4): 871. PMID: 17433126.	Adolescents considered in the Energy Balance section.
Thomson CA, Rock CL, Giuliano AR, Newton TR, Cui H, Reid PM, Green TL, Alberts DS; Women's Healthy Eating & Living Study Group. Longitudinal changes in body weight and body composition among women previously treated for breast cancer consuming a high-vegetable, fruit and fiber, low-fat diet. *Eur J Nutr*. 2005 Feb; 44 (1): 18-25. Epub 2004 Mar 5. PMID: 15309460.	Participants were women who had been treated for breast cancer.
Tobias M, Turley M, Stefanogiannis N, Vander Hoorn S, Lawes C, Mhurchu CN, Rodgers A. Vegetable and fruit intake and mortality from chronic disease in New Zealand. *Aust N Z J Public Health.* 2006 Feb; 30 (1): 26-31. PMID: 16502948.	Does not answer question: Does not examine relationship between vegetable and fruit intake and disease.

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

Tohill BC, Seymour J, Serdula M, Kettel-Khan L, Rolls BJ. What epidemiologic studies tell us about the relationship between fruit and vegetable consumption and body weight. *Nutr Rev*. 2004 Oct; 62 (10): 365-374. Review. PMID: 15508906.	Study design is narrative review.
Traka M, Gasper AV, Melchini A, Bacon JR, Needs PW, Frost V, Chantry A, Jones AM, Ortori CA, Barrett DA, Ball RY, Mills RD, Mithen RF. Broccoli consumption interacts with GSTM1 to perturb oncogenic signaling pathways in the prostate. *PLoS One*. 2008 Jul 2; 3 (7): e2568. PMID: 18596959; PMCID: PMC2430620.	Does not answer question: Does not include outcome of interest.
Tsubono Y, Otani T, Kobayashi M, Yamamoto S, Sobue T, Tsugane S; JPHC Study Group. No association between fruit or vegetable consumption and the risk of colorectal cancer in Japan.*Br J Cancer*. 2005 May 9; 92 (9): 1, 782-1, 784. PMID: 15856039.	Cancer excluded as outcome of interest.
Turner F, Smith G, Sachse C, Lightfoot T, Garner RC, Wolf CR, Forman D, Bishop DT, Barrett JH. Vegetable, fruit and meat consumption and potential risk modifying genes in relation to colorectal cancer. *Int J Cancer*. 2004 Nov 1; 112 (2): 259-264. PMID: 15352038.	Cancer excluded as outcome of interest.
van Dijk BA, Schouten LJ, Kiemeney LA, Goldbohm RA, van den Brandt PA. Vegetable and fruit consumption and risk of renal cell carcinoma: Results from the Netherlands cohort study. *Int J Cancer*. 2005 Nov 20; 117 (4): 648-654. PMID: 15929109.	Cancer excluded as outcome of interest.
van Duijnhoven FJ, Bueno-De-Mesquita HB, Ferrari P, Jenab M, Boshuizen HC, Ros MM, Casagrande C, Tjønneland A, Olsen A, Overvad K, Thorlacius-Ussing O, Clavel-Chapelon F, Boutron-Ruault MC, Morois S, Kaaks R, Linseisen J, Boeing H, Nöthlings U, Trichopoulou A, Trichopoulos D, Misirli G, Palli D, Sieri S, Panico S, Tumino R, Vineis P, Peeters PH, van Gils CH, Ocké MC, Lund E, Engeset D, Skeie G, Suárez LR, González CA, Sánchez MJ, Dorronsoro M, Navarro C, Barricarte A, Berglund G, Manjer J, Hallmans G, Palmqvist R, Bingham SA, Khaw KT, Key TJ, Allen NE, Boffetta P, Slimani N, Rinaldi S, Gallo V, Norat T, Riboli E. Fruit, vegetables and colorectal cancer risk: The European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr*. 2009 May; 89 (5): 1, 441-1, 452. Epub 2009 Apr 1. PMID: 19339391.	Cancer excluded as outcome of interest.

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van Gils CH, Peeters PH, Bueno-de-Mesquita HB, Boshuizen HC, Lahmann PH, Clavel-Chapelon F, Thiébaut A, Kesse E, Sieri S, Palli D, Tumino R, Panico S, Vineis P, Gonzalez CA, Ardanaz E, Sánchez MJ, Amiano P, Navarro C, Quirós JR, Key TJ, Allen N, Khaw KT, Bingham SA, Psaltopoulou T, Koliva M, Trichopoulou A, Nagel G, Linseisen J, Boeing H, Berglund G, Wirfält E, Hallmans G, Lenner P, Overvad K, Tjønneland A, Olsen A, Lund E, Engeset D, Alsaker E, Norat T, Kaaks R, Slimani N, Riboli E. Consumption of vegetables and fruits and risk of breast cancer. *JAMA*. 2005 Jan 12; 293 (2): 183-193. PMID: 15644545.	Cancer excluded as outcome of interest.
Wakita Asano A, Miyoshi M, Arai Y, Yoshita K, Yamamoto S, Yoshiike N. Association between vegetable intake and dietary quality in Japanese adults: A secondary analysis from the National Health and Nutrition Survey, 2003. *J Nutr Sci Vitaminol* (Tokyo). 2008 Oct; 54 (5): 384-391. PMID: 19001770.	Does not answer question: Does not examine the relationship between vegetables and fruits and health outcomes.
Wang LI, Giovannucci EL, Hunter D, Neuberg D, Su L, Christiani DC. Dietary intake of Cruciferous vegetables, Glutathione S-transferase (GST) polymorphisms and lung cancer risk in a Caucasian population. *Cancer Causes Control*. 2004 Dec; 15 (10): 977-985. PMID: 15801482.	Cancer excluded as outcome of interest.
Wark PA, Grubben MJ, Peters WH, Nagengast FM, Kampman E, Kok FJ, van 't Veer P. Habitual consumption of fruits and vegetables: associations with human rectal glutathione S-transferase. *Carcinogenesis*. 2004 Nov; 25 (11): 2, 135-2, 142. Epub 2004 Jul 29. PMID: 15284178.	Does not answer question: Does not include outcome of interest.
Wark PA, Weijenberg MP, van 't Veer P, van Wijhe G, Lüchtenborg M, van Muijen GN, de Goeij AF, Goldbohm RA, van den Brandt PA. Fruits, vegetables, and hMLH1 protein-deficient and -proficient colon cancer: The Netherlands cohort study. *Cancer Epidemiol Biomarkers Prev*. 2005 Jul; 14 (7): 1, 619-1, 625. PMID: 16030092.	Cancer excluded as outcome of interest.

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Weikert S, Boeing H, Pischon T, Olsen A, Tjonneland A, Overvad K, Becker N, Linseisen J, Lahmann PH, Arvaniti A, Kassapa C, Trichoupoulou A, Sieri S, Palli D, Tumino R, Vineis P, Panico S, van Gils CH, Peeters PH, Bueno-de-Mesquita HB, Büchner FL, Ljungberg B, Hallmans G, Berglund G, Wirfält E, Pera G, Dorronsoro M, Gurrea AB, Navarro C, Martinez C, Quirós JR, Allen N, Roddam A, Bingham S, Jenab M, Slimani N, Norat T, Riboli E. Fruits and vegetables and renal cell carcinoma: findings from the European prospective investigation into cancer and nutrition (EPIC).*Int J Cancer.* 2006 Jun 15; 118 (12): 3, 133-3, 139. PMID: 16425278.	Cancer excluded as outcome of interest.
Whybrow S, Harrison CL, Mayer C, James Stubbs R. Effects of added fruits and vegetables on dietary intakes and body weight in Scottish adults.*Br J Nutr*. 2006 Mar; 95 (3): 496-503. PMID: 16512935.	Does not answer question: Includes supplements, not food, in analyses.
Williams MT, Hord NG. The role of dietary factors in cancer prevention: Beyond fruits and vegetables. *Nutr Clin Pract.* 2005 Aug; 20 (4): 451-459. Review. PMID: 16207684.	Study design is narrative review.
Wright ME, Park Y, Subar AF, Freedman ND, Albanes D, Hollenbeck A, Leitzmann MF, Schatzkin A. Intakes of fruit, vegetables and specific botanical groups in relation to lung cancer risk in the NIH-AARP Diet and Health Study. *Am J Epidemiol*. 2008 Nov 1; 168 (9): 1, 024-1, 034. Epub 2008 Sep 12. PMID: 18791192; PMCID: PMC2631557.	Cancer excluded as outcome of interest.
Wu H, Dai Q, Shrubsole MJ, Ness RM, Schlundt D, Smalley WE, Chen H, Li M, Shyr Y, Zheng W. Fruit and vegetable intakes are associated with lower risk of colorectal adenomas. *J Nutr.* 2009 Feb; 139 (2): 340-344. Epub 2008 Dec 17. PMID: 19091801; PMCID: PMC2646202.	Cancer excluded as outcome of interest.
Yamaji T, Inoue M, Sasazuki S, Iwasaki M, Kurahashi N, Shimazu T, Tsugane S; Japan Public Health Center-based Prospective Study Group. Fruit and vegetable consumption and squamous cell carcinoma of the esophagus in Japan: The JPHC study. *Int J Cancer*. 2008 Oct 15; 123 (8): 1, 935-1, 940. PMID: 18688852.	Cancer excluded as outcome of interest.

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Yeh M, Moysich KB, Jayaprakash V, Rodabaugh KJ, Graham S, Brasure JR, McCann SE. Higher intakes of vegetables and vegetable-related nutrients are associated with lower endometrial cancer risks. *J Nutr*. 2009 Feb; 139 (2): 317-322. Epub 2008 Dec 11. PMID: 19074206.	Cancer excluded as outcome of interest.
Zhang CX, Ho SC, Chen YM, Fu JH, Cheng SZ, Lin FY. Greater vegetable and fruit intake is associated with a lower risk of breast cancer among Chinese women.*Int J Cancer*. 2009 Jul 1; 125 (1): 181-188. PMID: 19358284.	Cancer excluded as outcome of interest.

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CHAPTER 13. WHOLE GRAINS – BODY WEIGHT

WHAT IS THE RELATIONSHIP BETWEEN WHOLE GRAIN INTAKE AND BODY WEIGHT?

Conclusion statement

Moderate evidence shows that intake of whole grains and grain fiber is associated with lower body weight.

Grade

Moderate

Evidence summary overview

Seven articles met the inclusion criteria and were reviewed to determine the effect of whole grain consumption on body weight, body mass index (BMI) and measures of adiposity. Of these studies, one was a systematic review (Williams PG et al, 2008), one was a systematic review/meta-analysis (Harland JI and Garton LE, 2007), two were RCTs (Behall KM et al, 2006; Katcher HI et al, 2008) and three were cross-sectional studies. Of the seven articles, five were of positive quality (Behall KM et al, 2006; Harland JI and Garton LE, 2007; Lutsey PL et al, 2007; Van de Vijver LP et al, 2009; Williams PG et al, 2008) and two were of neutral quality (Katcher HI et al, 2008; McKeown NM et al, 2009).

Both systematic reviews found that whole grains were associated with lower BMI and protected against weight gain and adiposity. Harland and Garton (2007) reviewed 15 observational trials that included a total of 119,829 subjects. Pooled analysis of high vs. low whole grain intake, using a random-effects model, found a combined and weighted mean difference in BMI of 0.630kg/m^2 ($P<0.0001$). They also found reduced waist circumference ($P=0.03$) and lower waist:hip ratio ($P=0.0001$) with higher whole grain intakes. The authors concluded that a higher intake of whole grains (approximately three servings per day) was associated with lower BMI and central adiposity. Williams PG et al, (2008) found that 10 of 11 studies of dietary patterns reported that diets including higher whole grain intakes were associated with lower measures of obesity; two RCTs found greater weight loss with the whole grain intervention, while three RCTs showed significant weight loss in both interventions; three out of four observational studies reported greater weight loss with higher whole grain intake. The authors concluded that there was strong evidence that a diet high in whole grains was associated with lower BMI, smaller waist circumference and reduced risk of being overweight.

The randomized controlled feeding trial (Behall KM et al, 2006) compared the effects of three whole grain diets on blood pressure with weight as an ancillary outcome. Subjects (N= 25) consumed a controlled Step I diet for two weeks after which approximately 20% of energy was replaced with whole wheat or brown rice, barley or half wheat-rice and half barley, for five weeks each. Subjects lost approximately 1kg during the study ($P<0.01$). In the RCT by Katcher et al (2008), subjects were told either to avoid whole grains foods or obtain all of their grain servings from whole grains for 12 weeks. Body weight, waist circumference and percentage body fat decreased significantly in both groups over the study period,

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but there was a significantly greater decrease in percentage body fat in the abdominal region in the whole grain group compared to the refined grain group.

The three cross-sectional studies consistently found that whole grain intakes were associated with lower BMI and adiposity. Analysis of a MESA study cohort of 5,496 men and women comparing the extreme quintiles of whole grain intake found a mean difference in BMI of 0.6kg/m^2 (P<0.0001) (Lutsey et al, 2007). Similarly, McKeown et al (2009) found that in older adults, after multivariate adjustment comparing the extreme quartiles of consumption, whole grain intake was inversely associated with BMI (P=0.08), percent body fat (P=0.02) and percent trunk fat mass (P=0.02) measured by whole-body dual-energy X-ray absorptiometry. In the Netherlands, Van de Vijver et al (2009) assessed the association of whole grain and cereal fiber intake with BMI and the risk of being overweight in older adults. They reported an inverse association between whole grain consumption and BMI. Fiber and cereal fiber intake were inversely associated with BMI in men only.

Evidence summary paragraphs

Systematic Reviews (2)

Harland JI and Garton LE, 2007 (positive quality), a systematic review and meta-analysis conducted in the United Kingdom, examined the relationship between whole grain consumption and body weight. The review included 15 observational trials published between 1990 and 2006 that reported whole grain consumption, an appropriate control group and measures of body weight and adiposity. Subjects included a total of 119,829 males and females, aged 13 years or older. Pooled analysis of high vs. low whole grain intake, using a random-effects model, found a combined and weighted mean difference in BMI of 0.630kg/m^2 (95% CI: 0.460, 0.800kg/m^2; P<0.0001). In subjects with higher whole grain intakes (six data sets, N=4,178), waist circumference was reduced by 2.7cm (95% CI: 0.2, 5.2, P=0.03). In four data sets (N=20.417), higher whole grain intake was associated with a lower waist:hip ratio of 0.023 (95% CI: 0.016, 0.030, P=0.0001). The authors concluded that a higher intake of whole grains (approximately three servings per day) was associated with lower BMI and central adiposity.

Williams PG et al, 2008 (positive quality), a systematic review conducted in Australia, evaluated existing evidence regarding the role of cereal grains and legumes in the prevention or management of overweight and obesity. A total of 53 studies met the inclusion criteria for review; 20 examined whole grain intake. Of those, 10 of 11 studies of dietary patterns found that diets that included higher whole grain intakes were associated with lower measures of obesity. Of five RCTs that included a whole grain were reviewed and results were mixed with two studies reporting greater weight loss in the whole grain intervention and three studies showing significant weight loss in both interventions. Three of four observational studies reported greater weight loss with higher whole grain intake. The authors concluded that there was strong evidence that a diet high in whole grains was associated with lower BMI, smaller waist circumference and reduced risk of being overweight.

Randomized Controlled Trials (2)

Behall KM et al, 2006 (positive quality), a randomized, controlled crossover feeding trial conducted in the United States, compared the effects of three whole grain interventions on blood pressure. Weight was an ancillary outcome. Subjects

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(N=25; seven males, nine premenopausal and nine postmenopausal women) consumed a controlled Step I diet for two weeks after which approximately 20% of energy was replaced with whole wheat and brown rice, barley, or half wheat-rice and half barley for five weeks each. Blood pressure was measured weekly and weight taken daily before breakfast. Replacing refined grain foods with whole wheat, barley or brown rice products lowered blood pressure and maintained or lowered body weight while increasing energy intakes (P<0.0138) in overweight or obese subjects. Although the energy intakes were adjusted weekly to maintain weight, subjects lost about 1kg during the study (P<0.01). The authors concluded that increasing whole grain foods may help to control weight.

Katcher HI et al, 2008 (neutral-quality), an RCT conducted in the United States, examined 50 obese men and women with metabolic syndrome who received dietary advice either to avoid whole grain foods or obtain all of their grain servings from whole grains for 12 weeks. All participants were given the same dietary advice in other respects for weight loss. Forty-seven subjects completed the study (94%). Body weight, waist circumference and percent body fat decreased significantly in both groups over the study period (P<0.001), but there was a significantly greater decrease in percentage body fat in the abdominal region in the whole grain group (P=0.03). Total, LDL and HDL-cholesterol decreased in both diet groups (P<0.05).

Cross-sectional Studies (3)

Lutsey PL et al, 2007 (positive quality), a cross-sectional study conducted in the United States, examined the association between whole grain intake and obesity, selected CVD risk factors and measures of subclinical atherosclerosis using baseline data from the Multi-Ethnic Study of Atherosclerosis (MESA Study). Subjects included 5,496 men and women free of CHD and previously known diabetes. A 127-item FFQ was used to obtain dietary information, including whole grain intake. Mean whole grain intake was 0.5 servings per day. After multivariate adjustment, the mean difference in BMI for the extreme quintiles of whole grain intake was 0.6kg/m^2 (P<0.0001). The authors concluded that there were strong cross-sectional associations between whole grain consumption and BMI.

McKeown NM et al, 2009 (neutral quality), a cross-sectional study conducted in the United States, examined the associations between whole and refined grain intake, dietary fiber and fiber sources, and body fat among older adults. Subjects included 434 free-living adults (177 men, 257 women) aged 60 to 80 years. Dietary intake was estimated from a 126-item semi-quantitative FFQ. Percent body fat and percent trunk fat mass were measured by whole-body dual-energy X-ray absorptiometry (DXA). After multivariate adjustment comparing the extreme quartiles of consumption, whole grain intake was inversely associated with BMI (26.8kg/m^2 vs. 25.8 kg/m^2; P=0.08), percent body fat (34.5% vs. 32.1%; P=0.02) and percent trunk fat mass (43.0% vs. 39.4%; P=0.02). Cereal fiber was also inversely associated with BMI, body fat and trunk fat mass. The authors concluded that higher consumption of whole grains, and consequently cereal fiber, was associated in a dose-dependent manner with a significantly lower BMI and percentage of abdominal fat as determined by DXA.

Van de Vijver LP et al, 2009 (positive quality), a cross-sectional study conducted in the Netherlands, examined the associations between whole grain and cereal fiber intake with BMI and the risk of overweight or obesity (BMI higher than

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25 to 30kg/m^2). The study included 4,237 subjects (2,078 men and 2,159 women) aged 55 to 99 years. Multivariate regression analysis found an inverse association between whole grain consumption and BMI, as well as with the risk of overweight and obesity. The associations were stronger in men than in women. For each additional gram of (dry) whole grain intake, obesity risk was 10% lower for men and 4% lower for women. Fiber and cereal fiber intake were inversely associated with BMI in men only. The authors concluded that whole grain consumption might be protective against overweight or obesity, although the cross-sectional study design did not allow conclusions about the causality of the association.

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Overview table

Author, Year, Study Design, Class, Rating	Participants, Duration and Location	Description of Study Design	Outcomes	Whole Grain Definition
Behall KM, Scholfield DJ et al, 2006 Study Design: Non-Randomized Crossover Trial Class: A Positive Quality	N = 25; seven males, nine pre- and nine post-menopausal women. Location: United States.	Examined the effects of three whole grain feeding interventions on blood pressure (BP). Subjects consumed a controlled Step I AHA diet for two weeks after which refined grains (approximately 20% of energy) were replaced with whole wheat or brown rice, barley, or half whole wheat-rice and half barley, for five weeks each. BP was measured weekly and weight taken daily before breakfast.	Weight loss approximately 1kg during whole grain interventions ($P<0.01$). Energy intakes were significantly ↑ (average 100kcal) with the three whole grain diets than with the Step I diet. ($P <0.036$). *Note: Fiber was not examined.*	Planned dietary interventions with whole wheat, whole barley or brown rice products.

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Harland JI and Garton LE, 2008 Study Design: Meta-analysis or Systematic Review Class: M Positive Quality	N=15 observational trials. Pooled analysis. N=119,829 males and females. Age: 13+ years. Location: United Kingdom.	Review and pooled analysis of whole-grain intake and body weight. Search dates: 1990 to 2006. Included observational trials that reported whole-grain consumption, an appropriate control group and measures using a random-effects model.	Combined and weighted mean difference in BMI = 0.630kg/m^2(95% CI: 0.460, 0.800kg/m2; P <0.0001). Waist circumference reduced by 2.7cm (95% CI: 0.2, 5.2, P=0.03) in subjects with higher whole grain intakes (six data sets, N=4,178). Waist:hip ratio ↓ by 0.023 (95% CI: 0.016, 0.030; P=0.0001). *Note: Fiber was not examined relative to outcomes. Authors stated that it's not clear if whole grain mechanism is fiber or a micro-component, such as lignin or phytosterol.*	Varied by study; most used the Jacob algorithm (Jacobs, 1998) to classify foods as whole or refined grain. Brand of cereals consumed resulted in classification of whole grain or refined grain. Breakfast cereals containing at least 25% whole grain.

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Katcher HI, Legro RS et al, 2008 Study Design: Randomized Controlled Trial Class: A Positive Quality	N=50 obese men and women with metabolic syndrome. Ages 20 to 65 year. 47 subjects completed the study (94%). Location: United States.	Subjects received dietary advice to avoid whole grain foods or obtain all of their grain servings from whole grains for 12 weeks. All participants were given the same dietary advice in other respects for weight loss.	Body weight, waist circumference and percent body fat ↓ significantly in both groups from baseline (P<0.001). Percent abdominal body fat ↓ in whole grain compared to refined grain intervention (P=0.03). *Note: In addition to whole grains, the associated components - fiber and magnesium intake - differed significantly between the whole grain and refined grain groups. The authors did not draw conclusions related to these factors.*	Whole grain group consumed approximately five servings per day. Whole grains were defined as "whole grain was first item on ingredient list."
Lutsey PL et al 2007 Study Design: Cross sectional study Class: D Positive Quality	N=5,496 men and women. Location: United States.	Examined association between whole grain intake and obesity using baseline data from the Multi-Ethnic Study of Atherosclerosis (MESA Study). A 127-item FFQ was used to obtain dietary information, including whole grain intake.	The highest quintile of whole grain intake consumed 1.39 servings per day; the lowest quintile consumed 0.02 servings per day. Multivariate adjusted mean difference in BMI for the extreme quintiles of whole grain intake was 0.6kg/m^2 (P<0.0001). *Note: Fiber not examined.*	Whole grains included whole grain breakfast cereal, oatmeal, dark bread, bran muffins, brown or wild rice.

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McKeown NM, Yoshida M et al, 2009 Study Design: Cross-sectional study Class: D Neutral Quality	N=434 free-living adults (177 men, 257 women). Age: 60 to 80 years. Location: United States.	Examined association between whole and refined grain intake, dietary fiber and fiber sources and body fat among older adults. Semi-quantitative FFQ (126-item) used to estimate intake levels. Percent body fat and trunk fat mass measured with whole-body DEXA.	After adjustment for covariates, whole-grain intake was inversely associated with: BMI: 25.8kg/m^2 (95% CI: 24.6 to 27.1; P=0.08) Percent body fat: 32.1% (95% CI: 30.1 to 34.1%; P=0.02) Percent trunk fat mass: 39.4% (95% CI: 36.7 to 42.1; P=0.02). *Note: Cereal fiber was also inversely associated with BMI. Total fiber was not.*	Whole grain estimated as grams per day using a food composition database for whole grains. Whole grains included cooked and cold breakfast cereals, dark bread, brown rice, popcorn and other grains (e.g., bulgur, kasha and couscous). Breakfast cereal was considered whole grain if it contained 25% or more whole grain or bran by weight.

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van de Vijver LP et al 2009 Study Design: Cross-sectional Class: D Positive Quality	N=4,237 subjects (2,078 men and 2,159 women). Age: 55 to 69 years. Location: Netherlands.	Examined associations between whole-grain and cereal fiber intake with BMI and the risk of overweight or obesity (BMI of 25 to 30kg/m^2 or more) using multivariate regression analysis. Whole grain intake calculated in mean daily intake (grams per day).	Obesity risk for each additional 1g intake of whole grain intake (dry weight): Men: OR=0.90; 95% CI: 0.84, 0.98; P<0.01. Women: OR=0.96; 95% CI: 0.93, 0.99; P<0.01. Each SD ↓ in BMI corresponded to a 33g per day increase in whole grain intake (dry weight). *Note: Fiber and cereal fiber intake were inversely associated with BMI in men only.*	The variable 'all grain' calculated as sum of bran, wheat germs, muesli, porridge (oats or whole wheat), brown rice and cooked grains. Dry weight of porridge, brown rice and cooked grains calculated to prevent unbalanced weighting to the sum score. 'Whole grain' variable did not include bran and wheat germ.

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Williams PG et al 2008 Study Design: Systematic Review Class: M Positive Quality	N=53 studies; only 20 studies examined whole grain intake. Location: Australia.	Examined existing research to assess the role of cereal grains and legumes in the prevention or management of overweight and obesity. Search date: 1980 to 2005. Limited to English language and studies that reported anthropometric outcome measures. European Heart Network criteria used to assess scientific quality.	Ten of 11 studies of dietary patterns found that diets that included higher whole grain intakes were associated with lower measures of obesity. Five RCTs with a whole grain intervention were reviewed. Results were mixed: Two studies reported greater weight loss in the whole grain intervention; three studies reported significant weight loss in both interventions. Three of four observational studies reported greater weight loss with higher whole grain intake. *Note: Authors stated that while dietary fiber appears strongly inversely associated with body weight and weight gain, not all of the effect of whole grains may be explained by their fiber content.*	Varied by study; most used the Jacob algorithm (Jacobs, 1998) or FDA health claim criteria to classify foods as whole or refined grain.

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Search plan and results

Inclusion criteria

- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* <20% per intervention arm; preference for smaller dropout rates
- *Ages:* Children, two to 18 years; adults, 19 years and older
- *Populations:* Healthy
- *Study design:* Systematic review, meta-analysis, clinical trial, prospective cohort. Cross-sectional studies were included for weight question.

Exclusion criteria

- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Malnourished or third-world populations or disease incidence not relative to US population (e.g., malaria)
- Animal studies
- In vitro studies
- *Study design:* Cross-sectional, case control
- Articles not peer reviewed (web sites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed

  (Whole grain* OR cereal[mh] OR amaranth OR barley OR buckwheat OR corn OR maize OR millet OR oats OR quinoa OR rice OR rye OR sorghum OR teff OR triticale OR wheat OR spelta OR emmer OR ferro OR einhorn OR kamut OR durum OR bran) AND ("CARDIOVASCULAR DISEASES"[mesh] OR "Diabetes Mellitus OR "Type 2"[Mesh]) NOT (Editorial[ptyp] OR Letter[ptyp])

  Whole grain* OR cereal[mh]) AND (("overweight"[mh] OR "Body Weights and Measures"[mh])

  Whole grain* AND (intake or consumption) AND "published last 10 years"[Filter] AND "english and humans"[Filter]

  (Whole grain* OR cereal[mh] OR amaranth OR barley OR buckwheat OR corn OR maize OR millet OR oats OR quinoa OR rice OR rye OR sorghum OR teff OR triticale OR wheat OR spelta OR emmer OR ferro OR einhorn OR kamut OR durum OR bran) AND ("CARDIOVASCULAR DISEASES"[mesh] OR "Diabetes Mellitus, Type 2"[Mesh]) AND (systematic[sb] OR Meta-Analysis[ptyp] OR"Trial"[Mesh] OR "Cohort Studies"[Mesh]) NOT (Editorial[ptyp] OR Letter[ptyp]).

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Date searched: July 2009, September 2009, November 2009

Summary of articles identified to review

- Total hits from all electronic database searches: 888
- Total articles identified to review from electronic databases: 89
- Articles identified via handsearch or other means: 1
- Number of Primary Articles Identified: 11
- Number of Review Articles Identified: 7
- Total Number of Articles Identified: 18
- Number of Articles Reviewed but Excluded: 72

Included articles (References)

Cardiovascular Disease

Systematic Reviews and Meta-analyses:

1. De Moura FF, Lewis KD, Falk MC. Applying the FDA definition of whole grains to the evidence for cardiovascular disease health claims. *J Nutr.* 2009 Nov; 139 (11): 2, 220S-2, 226S. Epub 2009 Sep 23. PMID: 19776180.
2. Kelly SA, Summerbell CD, Brynes A, Whittaker V, Frost G. Wholegrain cereals for coronary heart disease. *Cochrane Database Syst Rev.* 2007 Apr 18; (2): CD005051. Review. PMID: 17443567.
3. Mellen PB, Walsh TF, Herrington DM. Whole grain intake and cardiovascular disease: A meta-analysis. *Nutr Metab Cardiovasc Dis.* 2008 May; 18 (4): 283-290. Epub 2007 Apr 20. PMID: 17449231.

Primary Citations:

1. Brownlee IA, Moore C, Chatfield M, Richardson DP, Ashby P, Kuznesof SA, Jebb SA, Seal CJ. Markers of cardiovascular risk are not changed by increased whole-grain intake: The WHOLEheart study, a randomised, controlled dietary intervention. *Br J Nutr.* 2010 Mar 23 :1-10. PMID: 20307353. (Hand Search)
2. Djoussé L, Gaziano JM. Breakfast cereals and risk of heart failure in the Physicians' Health Study I. *Arch Intern Med.* 2007 Oct 22; 167 (19): 2, 080-2, 085. PMID: 17954802.
3. Flint AJ, Hu FB, Glynn RJ, Jensen MK, Franz M, Sampson L, Rimm EB. Whole grains and incident hypertension in men. *Am J Clin Nutr.* 2009 Sep; 90 (3): 493-498. Epub 2009 Jul 1. PMID: 19571218.
4. Nettleton JA, Steffen LM, Loehr LR, Rosamond WD, Folsom AR. Incident heart failure is associated with lower whole-grain intake and greater high-fat dairy and egg intake in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Diet Assoc.* 2008 Nov; 108 (11): 1, 881-1, 887. PMID: 18954578; PMCID: PMC2650810.

Type 2 Diabetes

Systematic Reviews and Meta-analyses:

1. de Munter JS, Hu FB, Spiegelman D, Franz M, van Dam RM. Whole grain, bran, and germ intake and risk of type 2 diabetes: A prospective cohort study and systematic review. *PLoS Med.* 2007 Aug; 4 (8): e261. PMID: 17760498; PMCID: PMC1952203.
2. Priebe MG, van Binsbergen JJ, de Vos R, Vonk RJ. Whole grain foods for the

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prevention of type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2008 Jan 23; (1): CD006061. Review. PMID: 18254091.

Primary Studies:

1. Brownlee IA, Moore C, Chatfield M, Richardson DP, Ashby P, Kuznesof SA, Jebb SA, Seal CJ. Markers of cardiovascular risk are not changed by increased whole-grain intake: The WHOLEheart study, a randomised, controlled dietary intervention. *Br J Nutr.* 2010 Mar 23: 1-10. PMID: 20307353. (Hand Search)
2. Kochar J, Djoussé L, Gaziano JM. Breakfast cereals and risk of type 2 diabetes in the Physicians' Health Study I. *Obesity (Silver Spring).* 2007 Dec; 15 (12): 3, 039-3, 044. PMID:18198313.

Weight, Adiposity and Obesity

Systematic Reviews and Meta-analyses:

1. Harland JI, Garton LE. Whole-grain intake as a marker of healthy body weight and adiposity. Whole-grain intake as a marker of healthy body weight and adiposity. *Public Health Nutrition.* 2008 Jun; 11(6): 554-563. Epub 2007 Nov 16. PMID: 18005489.
2. Williams PG, Grafenauer SJ, O'Shea JE. Cereal grains, legumes and weight management: A comprehensive review of the scientific evidence. *Nutr Rev.* 2008 Apr; 66 (4): 171-182. Review. PMID: 18366531.

Primary Studies:

1. Behall KM, Scholfield DJ, Hallfrisch J. Whole-grain diets reduce blood pressure in mildly hypercholesterolemic men and women. *J Am Diet Assoc.* 2006 Sep; 106 (9): 1, 445-1, 449. PMID: 16963350.
2. Katcher HI, Legro RS, Kunselman AR, Gillies PJ, Demers LM, Bagshaw DM, Kris-Etherton PM. The effects of a whole grain-enriched hypocaloric diet on cardiovascular disease risk factors in men and women with metabolic syndrome. *Am J Clin Nutr.* 2008 Jan; 87 (1): 79-90. PMID: 18175740.
3. Lutsey PL, Jacobs DR Jr, Kori S, Mayer-Davis E, Shea S, Steffen LM, Szklo M, Tracy R. Whole grain intake and its cross-sectional association with obesity, insulin resistance, inflammation, diabetes and subclinical CVD: The MESA Study. *Br J Nutr.* 2007 Aug; 98 (2): 397-405. Epub 2007 Mar 29. PMID: 17391554.
4. McKeown NM, Yoshida M, Shea MK, Jacques PF, Lichtenstein AH, Rogers G, Booth SL, Saltzman E. Whole-grain intake and cereal fiber are associated with lower abdominal adiposity in older adults. *J Nutr.* 2009 Oct; 139 (10): 1, 950-1, 955. Epub 2009 Sep 2.
5. van de Vijver LP, van den Bosch LM, van den Brandt PA, Goldbohm RA. Whole-grain consumption, dietary fibre intake and body mass index in the Netherlands cohort study. *Eur J Clin Nutr.* 2009 Jan; 63 (1): 31-38. Epub 2007 Sep 26. PMID: 17895913.

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Excluded articles

Article	Reason for Exclusion
Alminger M, Eklund-Jonsson C. Whole-grain cereal products based on a high-fibre barley or oat genotype lower post-prandial glucose and insulin responses in healthy humans. *Eur J Nutr.* 2008 Sep; 47 (6): 294-300. Epub 2008 Jul 16.	Does not answer questions. Measures postprandial response.
Alonso A, Beunza JJ, Bes-Rastrollo M, Pajares RM, Martínez-González MA. Vegetable protein and fiber from cereal are inversely associated with the risk of hypertension in a Spanish cohort. *Arch Med Res.* 2006 Aug; 37 (6): 778-786. PMID: 16824939.	Does not include whole grain in analyses.
Anderson JW, Hanna TJ, Peng X, Kryscio RJ. Whole grain foods and heart disease risk. *J Am Coll Nutr.* 2000 Jun; 19 (3 Suppl): 291S-299S. PMID: 10875600.	Publication is a narrative review.
Bazzano LA, Song Y, Bubes V, Good CK, Manson JE, Liu S. Dietary intake of whole and refined grain breakfast cereals and weight gain in men. *Obes Res.* 2005 Nov; 13 (11): 1, 952-1, 960. PMID: 1633912.	Included in Harland/Garton 2007 systematic review for weight question. Does not include CVD or T2D in analyses.
Behall KM, Scholfield DJ, Hallfrisch J. Comparison of hormone and glucose responses of overweight women to barley and oats. *J Am Coll Nutr.* 2005 Jun; 24 (3): 182-188.	Does not answer questions. Measures postprandial response to whole grain intake.
Behall KM, Scholfield DJ, Hallfrisch J. Diets containing barley significantly reduce lipids in mildly hypercholesterolemic men and women. *Am J Clin* Nutr. 2004 Nov; 80 (5): 1, 185-1, 193.	Study subjects had hypercholesterolemia.
Behall KM, Scholfield DJ, Hallfrisch J. Whole-grain diets reduce blood pressure in mildly hypercholesterolemic men and women. *J Am Diet* Assoc. 2006 Sep; 106 (9): 1, 445-1, 449.	Participants had hypercholesterolemia. However, for CVD question was included in De Moura, 2009.

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Davy BM, Melby CL, Beske SD, Ho RC, Davrath LR, Davy KP. Oat consumption does not affect resting casual and ambulatory 24-hour arterial blood pressure in men with high-normal blood pressure to stage I hypertension. *J Nutr.* 2002 Mar; 132 (3): 394-398. PMID: 11880561.	For CVD question: Included in De Moura, 2009. Does not include T2D or weight in analyses.
Erkkilä AT, Herrington DM, Mozaffarian D, Lichtenstein AH. Cereal fiber and whole-grain intake are associated with reduced progression of coronary-artery atherosclerosis in postmenopausal women with coronary artery disease. *Am Heart J.* 2005 Jul; 150 (1): 94-101.	Study subjects had coronary artery disease.
Flight I, Clifton P. Cereal grains and legumes in the prevention of coronary heart disease and stroke: A review of the literature. *Eur J Clin Nutr.* 2006 Oct; 60 (10): 1, 145-1, 159. Epub 2006 May 3. Review. PMID: 16670693.	Publication is a narrative review; the literature search was systematic.
Fung TT, Hu FB, Pereira MA, Liu S, Stampfer MJ, Colditz GA, Willett WC. Whole-grain intake and the risk of type 2 diabetes: A prospective study in men. *Am J Clin Nutr.* 2002 Sep; 76 (3): 535-540. PMID: 12197996.	For T2D question: Included in systematic reviews de Munter, 2007 and Priebe, 2008. Does not include CVD or weight in analyses.
Giacco R, Brighenti F, Parillo M, Capuano M, Ciardullo AV, Rivieccio A, Rivellese AA, Riccardi G. Characteristics of some wheat-based foods of the Italian diet in relation to their influence on postprandial glucose metabolism in patients with type 2 diabetes. *Br J Nutr.* 2001 Jan; 85 (1): 33-40. PMID: 11227031.	Study subjects were type 2 diabetics.
Good CK, Holschuh N, Albertson AM, Eldridge AL. Whole grain consumption and body mass index in adult women: An analysis of NHANES 1999-2000 and the USDA pyramid servings database. *J Am Coll Nutr.* 2008 Feb; 27 (1): 80-87. PMID: 18460485.	For weight question, included in Harland/Garton 2007 systematic review. Does not include CVD or weight in analyses.
Granfeldt Y, Nyberg L, BjörckI. Muesli with 4g oat beta-glucans lowers glucose and insulin responses after a bread meal in healthy subjects. *Eur J Clin Nutr.* 2008 May; 62 (5): 600-607. Epub 2007 Apr 4.	Does not include outcomes of interest analyses. Measures postprandial response.

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Harder H, Tetens I, Let MB, Meyer AS. Rye bran bread intake elevates urinary excretion of ferulic acid in humans, but does not affect the susceptibility of LDL to oxidation ex vivo. *Eur J Nutr.* 2004 Aug; 43 (4): 230-236. Epub 2004 Jan 6.	Does not include outcomes of interest in analyses.
Hsu TF, Kise M, Wang MF, Ito Y, Yang MD, Aoto H, Yoshihara R, Yokoyama J, Kunii D, Yamamoto S. Effects of pre-germinated brown rice on blood glucose and lipid levels in free-living patients with impaired fasting glucose or type 2 diabetes. *J Nutr Sci Vitaminol* (Tokyo). 2008 Apr; 54 (2): 163-168.	Study subjects had impaired fasting glucose or T2D.
Jacobs DR Jr, Gallaher DD. Whole grain intake and cardiovascular disease: A review. *Curr Atheroscler Rep*. 2004 Nov; 6 (6): 415-423.	Publication is a narrative review.
Jacobs DR Jr, Meyer KA, Kushi LH, Folsom AR. Is whole grain intake associated with reduced total and cause-specific death rates in older women? The Iowa Women's Health Study. *Am J Public Health.* 1999 Mar; 89 (3): 322-329. PMID:10076480; PMCID: PMC1508593.	For CVD question: included in De Moura, 2009. Does not include T2D or weight in analyses.
Jacobs DR Jr, Meyer KA, Kushi LH, Folsom AR. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: The Iowa Women's Health Study. *Am J Clin Nutr.* 1998 Aug; 68 (2): 248-257. PMID: 9701180.	For CVD question: Included in De Moura, 2009. Does not include T2D or weight in analyses.
Jacobs DR Jr, Meyer HE, Solvoll K. Reduced mortality among whole grain bread eaters in men and women in the Norwegian County Study. *Eur J Clin Nutr.* 2001 Feb; 55 (2): 137-143. PMID:11305627.	Does not include outcomes of interest in analyses.
Jenkins DJ, Kendall CW, McKeown-Eyssen G, Josse RG, Silverberg J, Booth GL, Vidgen E, Josse AR, Nguyen TH, Corrigan S, Banach MS, Ares S, Mitchell S, Emam A, Augustin LS, Parker TL, Leiter LA. Effect of a low-glycemic index or a high-cereal fiber diet on type 2 diabetes: A randomized trial. *JAMA*. 2008 Dec 17; 300 (23): 2, 742-2, 753. PMID: 19088352.	Study subjects had T2D.
Jensen MK, Koh-Banerjee P, Hu FB, Franz M, Sampson L, Grønbaek M, Rimm EB. Intakes of whole grains, bran, and germ and the risk of coronary heart disease in men. *Am J Clin Nutr.* 2004 Dec; 80(6): 1, 492-1, 499.	For CVD question: Included in De Moura, 2009. Does not include T2D or weight in analyses.

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Johnsen NF, Hausner H, Olsen A, Tetens I, Christensen J, Knudsen KE, Overvad K, Tjønneland A. Intake of whole grains and vegetables determines the plasma enterolactone concentration of Danish women. J *Nutr.* 2004 Oct; 134 (10): 2, 691-2, 697.	Study design is cross-sectional.
Katcher HI, Legro RS, Kunselman AR, Gillies PJ, Demers LM, Bagshaw DM, Kris-Etherton PM. The effects of a whole grain-enriched hypocaloric diet on cardiovascular disease risk factors in men and women with metabolic syndrome. *Am J Clin Nutr.* 2008 Jan; 87(1): 79-90.	Study subjects had hyperlipidemia.
Katz DL, Evans MA, Chan W, Nawaz H, Comerford BP, Hoxley ML, Njike VY, Sarrel PM. Oats, antioxidants and endothelial function in overweight, dyslipidemic adults. *J Am Coll Nutr*. 2004 Oct; 23 (5): 397-403.	Study subjects had hyperlipidemia.
Koh-Banerjee P, Franz M, Sampson L, Liu S, Jacobs DR Jr, Spiegelman D, Willett W, Rimm E. Changes in whole-grain, bran, and cereal fiber consumption in relation to 8-year weight gain among men. *Am J Clin Nutr.* 2004 Nov; 80 (5): 1, 237-1, 245.	Does not include CHD or T2D in analyses. For weight question, included in systematic review, Williams, 2008.
Kuriyan R, Gopinath N, Vaz M, Kurpad AV. Use of rice bran oil in patients with hyperlipidaemia. *Natl Med J India*. 2005 Nov-Dec; 18 (6): 292-296.	Does not include whole grain in analyses. Study subjects had hyperlipidemia.
Lairon D, Arnault N, Bertrais S, Planells R, Clero E, Hercberg S, Boutron-Ruault MC. Dietary fiber intake and risk factors for cardiovascular disease in French adults. *Am J Clin Nutr*. 2005 Dec; 82 (6): 1, 185-1, 194.	Does not include whole grain in analyses.
Lammert A, Kratzsch J, Selhorst J, Humpert PM, Bierhaus A, Birck R, Kusterer K, Hammes HP. Clinical benefit of a short term dietary oatmeal intervention in patients with type 2 diabetes and severe insulin resistance: A pilot study. *Exp Clin Endocrinol Diabetes.* 2008 Feb; 116 (2): 132-134. Epub 2007 Dec 20. PMID: 18095234.	Study subjects had T2D.

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Landberg R, Kamal-Eldin A, Andersson A, Vessby B, Aman P. Alkylresorcinols as biomarkers of whole-grain wheat and rye intake: Plasma concentration and intake estimated from dietary records. *Am J Clin Nutr*. 2008 Apr; 87 (4): 832-838.	Does not answer questions. Examined biomarkers of whole grain wheat and rye intake.
Lee KW, Song KE, Lee HS, Kim YK, Lee SW, Kim DJ, Hwang WS, Choe SJ, Kim YS, Kim TY. The effects of Goami No. 2 rice, a natural fiber-rich rice, on body weight and lipid metabolism. *Obesity* (Silver Spring). 2006 Mar; 14(3): 423-430.	Does not include incident T2D or T2D in analyses. Examined experimental Goami rice.
Linko AM, Juntunen KS, Mykkänen HM, Adlercreutz H. Whole-grain rye bread consumption by women correlates with plasma alkylresorcinols and increases their concentration compared with low-fiber wheat bread. *J Nutr.* 2005 Mar; 135 (3): 580-583.	Does not answer questions. Examined biomarkers of whole grain wheat and rye intake.
Linko-Parvinen AM, Landberg R, Tikkanen MJ, Adlercreutz H, Peñalvo JL. Alkylresorcinols from whole-grain wheat and rye are transported in human plasma lipoproteins. *J Nutr*. 2007 May; 137 (5): 1, 137-1, 142.	Does not answer questions. Examined biomarkers of whole-grain wheat and rye intake.
Liu S, Manson JE, Stampfer MJ, Hu FB, Giovannucci E, Colditz GA, Hennekens CH, Willett WC. A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. *Am J Public Health.* 2000 Sep; 90 (9): 1, 409-1, 415. PMID: 10983198; PMCID: PMC1447620.	Included in systematic reviews: For CVD question: DeMoura, 2009. For T2D Question: de Munter, 2007 and Priebe, 2008.
Liu S, Sesso HD, Manson JE, Willett WC, Buring JE. Is intake of breakfast cereals related to total and cause-specific mortality in men? *Am J Clin Nutr.* 2003 Mar; 77 (3): 594-599. PMID: 12600848.	Does not include T2D or weight in analyses. For CVD question: Included in DeMoura, 2009 systematic review.
Liu S, Stampfer MJ, Hu FB, Giovannucci E, Rimm E, Manson JE, Hennekens CH, Willett WC. Whole-grain consumption and risk of coronary heart disease: Results from the Nurses' Health Study. *Am J Clin Nutr.* 1999 Sep; 70 (3): 412-419.	For CVD question: Included in DeMoura, 2009 systematic review. Does not include T2D or weight in analyses.

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Lu Z, Kou W, Du B, Wu Y, Zhao S, Brusco OA, Morgan JM, Capuzzi DM; Chinese Coronary Secondary Prevention Study Group, Li S. Effect of Xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction. *Am J Cardiol.* 2008 Jun 15; 101 (12): 1, 689-1, 693. Epub 2008 Apr 11.	Does not answer questions. examined the effects of an Study subjects were post myocardial infarction.
Maki KC, Davidson MH, Witchger MS, Dicklin MR, Subbaiah PV. Effects of high-fiber oat and wheat cereals on postprandial glucose and lipid responses in healthy men. *Int J Vitam Nutr Res.* 2007 Sep; 77 (5): 347-356	Does not answer questions. Measured postpr andial response.
McKeown NM. Whole grain intake and insulin sensitivity: evidence from observational studies. *Nutr Rev.* 2004 Jul; 62 (7 Pt 1): 286-291. Review.	Publication is a narrative review.
Melanson KJ, Angelopoulos TJ, Nguyen VT, Martini M, Zukley L, Lowndes J, Dube TJ, Fiutem JJ, Yount BW, Rippe JM. Consumption of whole-grain cereals during weight loss: Effects on dietary quality, dietary fiber, magnesium, vitamin B-6, and obesity. *J Am Diet Assoc.* 2006 Sep; 106 (9): 1, 380-1, 388; quiz 1, 389-1, 390.	Does not examine incident T2D or CHD. Examined weight loss. Included in Harland/Garton 2007 systematic review for weight question.
Mellen PB, Liese AD, Tooze JA, Vitolins MZ, Wagenknecht LE, Herrington DM. Whole-grain intake and carotid artery atherosclerosis in a multiethnic cohort: The Insulin Resistance Atherosclerosis Study. *Am J Clin Nutr.* 2007 Jun; 85 (6): 1, 495-1, 502.	Does not examine incident T2D or weight. Study examined carotid intimal medial thickness, not CVD outcome of interest.
Merchant AT, Pitiphat W, Franz M, Joshipura KJ. Whole-grain and fiber intakes and periodontitis risk in men. *Am J Clin Nutr.* 2006 Jun; 83 (6):1395-400.	Does not examine outcomes of interest. Study examines periodontitis.
Mesci B, Oguz A, Sagun HG, Uzunlulu M, Keskin EB, Coksert D. Dietary breads: Myth or reality? *Diabetes Res Clin Pract*. 2008 Jul; 81 (1): 68-71. Epub 2008 Mar 26.	Study subjects were type 2 diabetics.
Meyer KA, Kushi LH, Jacobs DR Jr, Slavin J, Sellers TA, Folsom AR. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr.* 2000 Apr; 71 (4): 921-930. PMID:10731498.	For T2D question, included in systematic reviews, de Munter, 2007 and Priebe, 2008. Does not include CHD or weight in analyses.

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Montonen J, Knekt P, Järvinen R, Aromaa A, Reunanen A. Whole-grain and fiber intake and the incidence of type 2 diabetes. *Am J Clin Nutr.* 2003 Mar; 77 (3): 622-629. PMID: 12600852	For T2D question, included in systematic reviews, de Munter, 2007 and Priebe, 2008. Does not include CHD or weight in analyses.
Mozaffarian D, Kumanyika SK, Lemaitre RN, Olson JL, Burke GL, Siscovick DS. Cereal, fruit, and vegetable fiber intake and the risk of cardiovascular disease in elderly individuals. *JAMA*. 2003 Apr 2; 289 (13): 1, 659-1, 666. PMID: 12672734.	Did include whole grain intake in analyses.
Murtaugh MA, Jacobs DR Jr, Jacob B, Steffen LM, Marquart L. Epidemiological support for the protection of whole grains against diabetes. *Proc Nutr Soc.* 2003 Feb; 62 (1): 143-149. Review. PMID: 12740069.	Publication is a narrative review.
Newby PK, Maras J, Bakun P, Muller D, Ferrucci L, Tucker KL. Intake of whole grains, refined grains, and cereal fiber measured with seven-day diet records and associations with risk factors for chronic disease. *Am J Clin Nutr.* 2007 Dec; 86 (6): 1, 745-1, 753. PMID: 18065595; PMCID: PMC2646086.	Included in systematic reviews: For weight question, Williams, 2008; for CHD, DeMoura, 2009.
Nilsson AC, Ostman EM, Granfeldt Y, Björck IM. Effect of cereal test breakfasts differing in glycemic index and content of indigestible carbohydrates on daylong glucose tolerance in healthy subjects. *Am J Clin Nutr*. 2008 Mar; 87(3): 645-654. PMID: 18326603.	Does not examine incident T2D. Measures glucose tolerance following 24-hour intervention.
Nilsson AC, Ostman EM, Holst JJ, Björck IM. Including indigestible carbohydrates in the evening meal of healthy subjects improves glucose tolerance, lowers inflammatory markers, and increases satiety after a subsequent standardized breakfast. *J Nutr*. 2008 Apr; 138 (4): 732-739.	Does not examine incident T2D. Measures postprandial response.
Panahi S, Ezatagha A, Temelli F, Vasanthan T, Vuksan V. Beta-glucan from two sources of oat concentrates affect postprandial glycemia in relation to the level of viscosity. *J Am Coll Nutr.* 2007 Dec; 26(6): 639-644.	Does not examine incident T2D, CVD or weight. Postprandial study.
Panlasigui LN, Thompson LU. Blood glucose lowering effects of brown rice in normal and diabetic subjects. *Int J Food Sci Nutr.* 2006 May-Jun; 57(3-4): 151-158.	Does not include incident T2D, CVD or weight in analyses.

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Qi L, Hu FB. Dietary glycemic load, whole grains, and systemic inflammation in diabetes: The epidemiological evidence. *Curr Opin Lipidol.* 2007 Feb; 18 (1): 3-8.	Publication is a narrative review.
Qi L, van Dam RM, Liu S, Franz M, Mantzoros C, Hu FB. Whole-grain, bran, and cereal fiber intakes and markers of systemic inflammation in diabetic women. *Diabetes Care.* 2006 Feb; 29 (2): 207-211.	Study design is cross-sectional. Study subjects had T2D.
Rave K, Roggen K, Dellweg S, Heise T, tom Dieck H. Improvement of insulin resistance after diet with a whole-grain based dietary product: Results of a randomized, controlled cross-over study in obese subjects with elevated fasting blood glucose. *Br J Nutr*. 2007 Nov; 98 (5): 929-936. Epub 2007 Jun 12.	Study subjects had elevated fasting blood glucose.
Sadiq Butt M, Tahir-Nadeem M, Khan MK, Shabir R, Butt MS. Oat: unique among the cereals. *Eur J Nutr.* 2008 Mar; 47 (2): 68-79. Epub 2008 Feb 26.	Publication is a narrative review.
Sahyoun NR, Jacques PF, Zhang XL, Juan W, McKeown NM. Whole-grain intake is inversely associated with the metabolic syndrome and mortality in older adults. *Am J Clin Nutr.* 2006 Jan; 83 (1): 124-131.	Study design is cross-sectional.
Seal CJ, Brownleel A, Jones AR. Grains and health: the "whole" picture. *Quintessence Int.* 2007 Jun; 38 (6): 498-503. PMID: 17625633.	Publication is a narrative review.
Seal CJ. Whole grains and CVD risk. *Proc Nutr Soc.* 2006 Feb; 65 (1): 24-34. Review. PMID: 16441941.	Publication is a narrative review.
Shimizu C, Kihara M, Aoe S, Araki S, Ito K, Hayashi K, Watari J, Sakata Y, Ikegami S. Effect of high beta-glucan barley on serum cholesterol concentrations and visceral fat area in Japanese men: A randomized, double-blinded, placebo-controlled trial. *Plant Foods Hum Nutr.* 2008 Mar; 63 (1): 21-25. Epub 2007 Dec 12.	Study subjects had hypercholesterolemia.

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Smith KN, Queenan KM, Thomas W, Fulcher RG, Slavin JL. Physiological effects of concentrated barley beta-glucan in mildly hypercholesterolemic adults. *J Am Coll Nutr.* 2008 Jun; 27 (3): 434-440. PMID: 18838533.	Study subjects had hypercholesterolemia.
Steffen LM, Jacobs DR Jr, Stevens J, Shahar E, Carithers T, Folsom AR. Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke: The Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr*. 2003 Sep; 78 (3): 383-390.	Included in systematic reviews: For CVD question DeMoura, 2009. For Weight question Harland/Garton 2007. Does not include T2D in analyses.
Thane CW, Jones AR, Stephen AM, Seal CJ, Jebb SA. Comparative whole-grain intake of British adults in 1986-1987 and 2000-2001. *Br J Nutr.* 2007 May; 97 (5): 987-992.	Does not answer questions. Study reports dietary intake of whole grains.
Thane CW, Jones AR, Stephen AM, Seal CJ, Jebb SA. Whole-grain intake of British young people aged four-18 years. *Br J Nutr*. 2005 Nov; 94 (5): 825-831.	Study design is cross-sectional. Does not answer questions. Reports dietary intake of whole grains.
Thane CW, Stephen AM, Jebb SA. Whole grains and adiposity: Little association among British adults. *Eur J Clin Nutr*. 2009 Feb; 63 (2): 229-237. Epub 2007 Sep 19. PMID: 17882134.	Included in systematic review for weight: Harland/Garton 2007. Does not include CVD or T2D in analyses.
Theuwissen E, Plat J, Mensink RP. Consumption of oat beta-glucan with or without plant stanols did not influence inflammatory markers in hypercholesterolemic subjects. *Mol Nutr Food Res.* 2009 Mar; 53 (3): 370-376. PMID: 18979504.	Study subjects had hypercholesterolemia.
van Dam RM, Hu FB, Rosenberg L, Krishnan S, Palmer JR. Dietary calcium and magnesium, major food sources, and risk of type 2 diabetes in US black women. *Diabetes Care.* 2006 Oct; 29 (10): 2, 238-2, 243. Erratum in: *Diabetes Care.* 2008 Oct; 31(10): 2, 077. PMID: 17003299.	Included in systematic reviews for T2D: de Munter, 2007 and Priebe, 2008. Does not include CVD or weight in analyses.

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Vuksan V, Whitham D, Sievenpiper JL, Jenkins AL, Rogovik AL, Bazinet RP, Vidgen E, Hanna A. Supplementation of conventional therapy with the novel grain Salba (Salvia hispanica L.) improves major and emerging cardiovascular risk factors in type 2 diabetes: Results of a randomized controlled trial. *Diabetes Care*. 2007 Nov; 30 (11): 2, 804-2, 810. Epub 2007 Aug 8.	Study subjects diagnosed with T2D.
Wang L, Gaziano JM, Liu S, Manson JE, Buring JE, Sesso HD. Whole- and refined-grain intakes and the risk of hypertension in women. *Am J Clin Nutr.* 2007 Aug; 86 (2): 472-479. PMID: 17684221.	Included in systematic review for CVD question: DeMoura, 2009. Does not include T2D or weight in analyses.
Weickert MO, Möhlig M, Schöfl C, Arafat AM, Otto B, Viehoff H, Koebnick C, Kohl A, Spranger J, Pfeiffer AF. Cereal fiber improves whole-body insulin sensitivity in overweight and obese women. 2006 Apr; 29 (4): 775-780.	Study examines effect of cereal fiber intake, not whole grain.
Yannakoulia M, Yiannakouris N, Melistas L, Kontogianni MD, Malagaris I, Mantzoros CS. A dietary pattern characterized by high consumption of whole-grain cereals and low-fat dairy products and low consumption of refined cereals is positively associated with plasma adiponectin levels in healthy women. *Metabolism.* 2008 Jun; 57 (6): 824-830.	Study design is cross-sectional. Outcome was adiponectin.
Zhang HW, Zhang YH, Lu MJ, Tong WJ, Cao GW. Comparison of hypertension, dyslipidaemia and hyperglycaemia between buckwheat seed-consuming and non-consuming Mongolian-Chinese populations in Inner Mongolia, China. *Clin Exp Pharmacol Physiol.* 2007 Sep; 34 (9): 838-844. PMID: 17645626.	Study design was cross-sectional.

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CHAPTER 14. WHOLE GRAINS – CARDIOVASCULAR DISEASE

WHAT IS THE RELATIONSHIP BETWEEN WHOLE GRAIN INTAKE AND CARDIOVASCULAR DISEASE?

Conclusion statement

A moderate body of evidence from large prospective cohort studies shows that whole grain intake, which includes cereal fiber, protects against cardiovascular disease.

Grade

Moderate

Evidence summary overview

Seven articles (one systematic review, two meta-analyses, one randomized controlled trial (RCT) and three prospective cohorts that were published after the systematic reviews) met the inclusion criteria and were reviewed to determine the effect of whole grain consumption on cardiovascular disease. Of the seven articles, four were of positive quality (Flint, 2009; Kelly, 2007; Mellen, 2008; Nettleton, 2008) and three were of neutral quality (Brownlee, 2010; DeMoura, 2009; Djousse, 2007.

The importance of agreed upon definitions for whole grains was noted in the DeMoura et al, (2009) review. Their initial inclusion criteria required studies to explicitly state the use of the Food and Drug Administration (FDA) definition for whole grains, 51% of weight being whole grains, to be eligible for review. Using this standard, only two RCTs, one prospective, cohort study and one cross-sectional study were identified for review. A second, broader set of inclusion criteria used a minimum level of 25% of whole grain by dry weight to assign values for whole grains and added bran or germ along with whole grains. It is important to note that RCTs conducted with individual whole grains, such as whole grain barley, oats, and rye, were included in the broader definition group, for which a total of 29 studies (15 intervention and 14 observational) were deemed eligible for review. All of the observational studies found a protective association between whole grain intake and cardiovascular disease (CVD) risk. Six RCTs found a beneficial effect of oats on CVD outcomes; five showed no effect. The positive studies had a longer intervention periods (six to eight weeks vs. three weeks). Four RCTs with barley showed reduction in plasma total cholesterol (TC) (20-15%) and LDL cholesterol (LDL-C) (21%) levels across diverse populations. The authors concluded that, for the restricted assessment, while two observational studies found a significant reduction in CVD-related surrogate end-points, there were not supporting intervention studies, thus there was not sufficient evidence to support a whole grain health claim for CVD risk reduction. Using the broader definition, the authors concluded that the evidence supported a whole-grain health claim for reduced risk of CVD.

Two meta-analyses of whole grains and CVD found a protective effect of whole grains on CVD. Kelly et al, (2007), a systematic review and meta-analysis of nine RCTs (eight oat, one rye), reported a significantly lower TC and LDL-C with higher whole grain intake. Mellen et al, (2008), a meta-

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analysis of seven prospective cohort studies, conducted pooled analysis and found that greater whole grain intake (pooled average 2.5 servings per day vs. 0.2 servings per day) was associated with a 21% lower risk of CVD events (OR 0.79; 95% CI: 0.73-0.85). Similar estimates were noted for other CVD outcomes, including incident coronary heart disease (CHD), stroke and fatality. The authors' concluded that evidence from prospective cohort studies consistently showed an inverse association between dietary whole grains and incident CVD.

One RCT (Brownlee et al, 2010) examined markers of cardiovascular risk in a large (N=266) intervention study with high risk (BMI>25kg/m^2) subjects. Subjects who routinely consumed few whole grain products were randomized to control group, 60g whole grains per day for eight weeks, or 60g per day for eight weeks then 120g per day for eight more weeks. Cardiovascular disease biomarkers were measured at baseline, eight and 16 weeks. There were no differences in BMI, percentage body fat, waist circumference, fasting plasma lipid profile, glucose or insulin.

Three prospective cohort studies examined whole grain intake and cardiovascular outcomes. Flint et al, (2009), 18-year follow-up of the Health Professional's Study, quantified whole grain intake in grams and found that whole grain intake was inversely associated with risk of hypertension (HTN) (RR=0.81; P<0.0001). The RR for total bran was 0.85 (P=0.002). The authors concluded that there was an independent inverse association between whole grain intake and incident HTN in men. Bran, an integral component of whole grains, may play an important role in this association.

Djousse and Graziano, (2007) concluded that there was an inverse association between whole grain breakfast cereal consumption and the risk of heart failure (HF). Similarly, Nettleton et al, (2008) concluded that in their large population-based cohort of the ARIC study (N=14,153 African-American and white adults) whole grain intake was associated with lower HF risk. The multivariate-adjusted heart failure risk for whole grain intake was 0.93 (P<0.05) for each one serving per day increase in whole grain consumption.

Evidence summary paragraphs

Systematic Reviews/Meta-analyses

De Moura et al, 2009 (neutral quality) a systematic review, conducted in the United States, evaluated the strength of scientific evidence in support of health claims for risk reduction of cardiovascular disease (CVD) when applying the FDA whole grain definition vs. applying a broader whole grain definition that is more commonly used in scientific studies. The restricted analysis was limited to studies that explicitly defined grains according to the FDA definition of whole grains, "intact, ground, cracked or flaked fruit of the grains whose principal components, the starchy endosperm, germ and bran are present in the same relative proportions as they exist in intact grain." Four studies (two RCTs, one prospective cohort, one cross-sectional study) met the criteria and were included in the restricted analysis. The two RCTs did not find significant differences for surrogate CVD endpoints such as TC, LDL-C and blood pressure (BP). The prospective cohort study reported a reduced relative risk of coronary heart disease (CHD) in men when comparing the highest to the lowest quintiles of whole grain intake (P for trend=0.01). The cross-sectional study observed a decrease in total cholesterol of 0.16mmol/L when comparing the extreme quintiles of whole grain intake (P for trend=0.02). The

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expanded analysis included a broader definition that added bran or germ along with whole grains, as well as studies that were conducted with individual whole oat and rye grains. A total of 29 studies (15 intervention and 14 observational) were included. All of the observational studies found a protective association between whole grain intake and CVD risk. Six RCTs found a beneficial effect of oats on CVD outcomes; four found a significant positive effect (P<0.05), and one showed no effect. The positive studies had a longer intervention periods (six to eight weeks vs. three weeks). Four RCTs with barley showed reduction in plasma TC (20-15%) and LDL-C (21%) levels across diverse populations. The authors concluded that, for the restricted analysis, while two observational studies found a significant reduction in CVD-related surrogate endpoints, there were not supporting intervention studies, thus there was not sufficient evidence to support a whole grain health claim for CVD risk reduction. Using the broader definition, the authors concluded that the evidence supported a whole-grain health claim for reduced risk of CVD.

Kelly SAM et al, 2007 (positive quality) a Cochrane systematic review, conducted in the United Kingdom, examined RCTs that studied the effect of whole-grain consumption on CHD risk factors, morbidity and mortality, in subjects with existing CHD risk factors or previously diagnosed with CHD. Ten trials met the criteria for review, including minimum study duration of four weeks. Nine of the 10 trials, reported the effect of whole-grain foods or diets on risk factors for CHD; no studies examining the effect of whole-grains on CHD events or mortality were found. Eight studies examined the effect of an oat intervention; seven of them reported lower TC and LDL-C compared to the controls. Meta-analysis of the eight studies found a lower total and LDL-C with oatmeal foods (-0.20mmol/L, 95% CI: -0.31 to -0.10, P=0.0001) and (0.18mmol/L, 95% CI: -0.28 to -0.09, P<0.0001), respectively. Pooling the rye study with the other data for oatmeal did not change the results. Heterogeneity was not found in the pooled analyses for TC, LDL-C, HDL cholesterol and triglycerides (TG). Overall, the authors concluded that, despite the consistency of effects seen in whole grain oat trials, there was insufficient evidence to make any conclusions about whole grain diets other than oatmeal. They also indicated that many of the trials identified were short term, of poor quality and had insufficient power. They identified the need for well-designed, adequately powered, longer term RCTs on whole grain foods and diets other than oats.

Mellen P et al, 2008 (positive quality) a meta-analysis, conducted in the United States, quantified observational evidence on whole grain intake and clinical cardiovascular events. Seven prospective cohort studies with quantitative measures of dietary whole grains and clinical cardiovascular outcomes were identified for pooled analysis. Six studies provided information for demographic adjusted analyses and seven for risk-factor-adjusted analyses. Based on event estimates adjusted for cardiovascular risk factors, greater whole grain intake (pooled average 2.5 servings per day vs. 0.2 servings per day) was associated with a 21% lower risk of CVD events (OR0.79; 95% CI: 0.73-0.85). The findings were similar when analyses were restricted to studies that provided gender-specific results for men (OR: 0.82, 95% CI: 0.73-0.92) and women (OR: 0.79, 95% CI: 0.68-0.91). Similar estimates were noted for other CVD outcomes, including incident CHD, stroke and fatal. The authors' concluded that evidence from prospective cohort studies consistently showed an inverse association between dietary whole grains and incident cardiovascular disease.

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Primary Studies

Brownlee I et al, 2010 (neutral quality) an RCT, conducted in the United Kingdom, investigated the effect of substituting whole grain for refined grains on CVD risk markers. Subjects (N=266; BMI>25kg/m^2) who routinely consumed few whole grain products were randomized to consume 60g whole grains per day for eight weeks or 60g whole grains per day for eight weeks and then 120g whole grains per day for eight more weeks. Markers of CVD risk (BMI, percent body fat, waist circumference; fasting plasma lipid profile, glucose and insulin) were measured at baseline, eight and 16 weeks. A random intercepts model with time and whole grain intake factors was used to assess differences between the control and the average of the two intervention groups. Self -reported whole grain intake was significantly increased in both intervention groups. No significant differences in CVD risk markers were found between the control and the averaged intervention groups between groups.

Djousse L and Graziano J, 2007 (neutral quality) a prospective cohort study, conducted in the United States, evaluated the association between breakfast cereal intake and incident heart failure (HF) in a cohort of the Physicians' Health Study (N=21,376 men, aged 40-86 years). Cereal consumption was estimated using a semi-quantitative food frequency questionnaire (FFQ). Incident HF was determined from annual follow-up questionnaires and validated using Framingham criteria. Cox regression models were used to estimate adjusted relative risk of HF across categories of cereal intake. During an average follow-up of 19.6 years, 1,018 incident cases of HF occurred. The multivariate adjusted RR for the extreme quintiles of average weekly whole grain cereal consumption (zero servings per week to at least seven or more servings per week was 0.72 (95% CI: 0.59-0.88); P<0.001. The association for refined cereals was not significant (NS) (P=0.70 for trend). The authors concluded that there was an inverse association between whole grain breakfast cereal consumption and the risk of heart failure.

Flint A et al, 2009 (positive quality) a prospective cohort study, conducted in the United States, examined the association between whole grain intake (grams per day) and risk of incident HTN in a cohort from the Health Professionals Follow-Up Study (N=31,684 males, baseline age 40-75 years). Whole grain intake was measured at baseline and with administration of each follow-up food frequency questionnaire. A total of 9,227 cases of incident hypertension were reported over the 18 years of follow-up. In multivariate-adjusted analyses, comparing the extreme quintiles of consumption, whole grain intake was inversely associated with risk of HTN, (RR=0.81 (95% CI: 0.75-0.87, P<0.0001). The RR for total bran was 0.85 (95% CI: 0.78, 0.92, P=0.002). The authors concluded that there was an independent inverse association between whole grain intake and incident HTN in men. Bran may play an important role in this association.

Nettleton J et al, 2008 (positive quality) a prospective cohort study, conducted in the United States, studied the relationships between incident heart failure (HF) (death or hospitalization) and consumption of seven food categories (whole grains, fruits and vegetables, fish, nuts, high-fat dairy, eggs, red meat). The subjects were a cohort of the Atherosclerosis Risk in Communities (ARIC) study (N=14,153 African-American and white adults, age 45 to 64 years). Dietary intake was assessed using a validated 66-item FFQ. During a mean follow-up period of 13 years, 1,140 cases of incident HF were identified. Heart failure hazard ratios (HR) were calculated on a

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one serving per day difference in each food group intake. The multivariate-adjusted HF risk for whole grain intake was 0.93 (95% CI: 0.87, 0.99; P<0.05) for each one serving per day difference in consumption. This association remained significant independent of intakes of the other food categories analyzed. The authors concluded that in their large, population-based sample of African-American and white adults whole grain intake was associated with lower HF risk.

Overview table

Author, Year, Study Design, Class, Rating	Participants, Duration and Location	Description of Study Design	Outcomes	Whole Grain Definition
Brownlee IA, Moore C et al, 2010 Study Design: Randomized controlled trial Class: A Neutral Quality	N=266 participants. Age: 18-65 years. BMI>25kg/m^2. Consuming <30g whole grain per day.	Examined effect of substituting whole grain for refined grains on CVD risk markers using random intercepts model Interventions: Control (no dietary Δ) Int 1: 60g whole grain per day x 16 weeks Int 2: 60g whole grain per day x eight weeks, then 120g whole grain per day for eight weeks Measures taken at zero, eight and 16 weeks. Whole grain foods were provided; intake data was self-reported on EPIC FFQ.	*Dropout rates:* Int 1=19% Int 2=23% Control=6% Int 1 and 2 outcome measures were averaged and then compared to controls. There were NS differences in any markers of CVD risk between the combined intervention groups and the control.	Selected whole grain foods were provided to free-living subjects.

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De Moura FF, Lewis KD et al, 2009 Study Design: Meta-analysis or Systematic Review Class: M Neutral Quality	Restricted analysis: N=4 studies; two RCT and two observational. Expanded analysis: N=29 studies; 15 RCT and 14 observational. Location: Most of the studies were conducted in the US (one each in China, England, Germany Iran, Japan and Sweden).	Evaluated the strength of scientific evidence in support of claims for CVD risk reduction using two whole grain definitions; the FDA definition vs. a broader definition commonly used in scientific studies. Lit search: MEDLINE for primary studies published through Feb 2008. English language only. Study quality was not assessed.	Six RCTs found a beneficial effect of oats on CVD outcomes; four found a significant positive effect (P<0.05) and one showed no effect. The positive studies had a longer intervention periods (six to eight weeks vs. three weeks). Four RCTs with barley showed reduction in plasma TC (20-15%) and LDL-C (21%) levels across diverse populations. The estimates and CIs were not reported. All of the observational studies found a protective association between whole grain intake and CVD risk.	FDA: Whole grains consist of the intact, ground, cracked or flaked fruit of the grains whose principal components-the starchy endosperm, germ and bran-are present in the same relative proportions as they exist in the intact grain. Expanded: Added bran or germ along with whole grains, as well as RCTs that were conducted with individual whole grain oats or rye.
Djousse L and Gaziano JM, 2007 Study Design: Prospective Cohort Study Class: B Neutral Quality	N=21,376 male subjects (Cohort of Physician's Health Study I). Baseline age: 40-86 years. Duration: 19.6 years of follow-up. Location: United States.	Examined the relationship between consumption of breakfast cereals and risk of heart failure (HF). Used a semi-quantitative FFQ to collect intake data. Cereal consumption obtained at baseline, 18 weeks and 24, 48, 72, 96 and 120 months after randomization. Incident HF ascertained through annual follow-up questionnaires and validated using Framingham criteria.	1,018 incident cases of heart failure occurred. Consumption of at least seven servings of whole grain breakfast cereals per week was associated with a reduced incidence of HF: RR=0.72 (95% CI: 0.59-0.88; P<0.001).	Used algorithm developed by Jacobs et al, AJCN 1998 to classify foods as whole or refined grain. One serving=One cup of cold ready-to-eat cereal. Brand of cereals consumed resulted in classification of whole grain or refined grain. Breakfast cereals containing at least 25% whole grain or bran by weight were classified as whole grain.

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Flint AJ, Hu FB et al, 2009 Study Design: Prospective Cohort Study Class: B Positive Quality	N=31,684 males, (Cohort of the Health Professional's Follow-Up Study). Baseline age: 40-75 years. Follow up duration: 18 years. Location: United States.	Examined the association between whole grain intake (grams per day) and risk of incident HTN. Semi-quantitative FFQ used to obtain whole grain intake data. This study employed a new food composition database, which allowed estimation of whole-grain intake in grams per day, is described in detail elsewhere Incident HTN was obtained by self-report on bi-ennial questionnaires. This approach was validated in this cohort.	9,227 cases of incident HTN were reported Multivariate-adjusted RR for the highest quintile of whole grain consumption (46.0g per day)=0.81 (95% CI: 0.75-0.87, P<0.0001). The RR for the highest quintile of total bran (12.0g per day)=0.85 (95% CI: 0.78, 0.92, P=0.002).	Whole grains were considered by definition to contain the expected proportion of bran, endosperm and germ for the specific grain type. Whole grains, bran and germ were calculated by determining the whole-grain content of each grain food according to the dry weight of its whole-grain ingredients. Nutrient profiles of the various grain foods were derived by using composite recipes, US Department of Agriculture nutrient data, and product labels, whereas cookbooks were used to estimate contents of home-prepared bakery items.

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Kelly et al 2007 (Cochrane) Study Design: Meta-analysis; systematic review (Cochrane) Class: M Positive Quality	10 RCT met the inclusion criteria. Duration: Four-week minimum. Subjects included adults with existing CHD or at least one CHD risk factor. Location: Nine studies were conducted in the United States and one in Finland. Literature search date ranges spanned from 1966 to 2005 and varied by database. No language restrictions were applied.	Examined the effect of whole grain food consumption on CHD risk factors, morbidity and mortality. Eight trials studied oat foods. One compared whole meal rye to refined wheat bread. One compared a whole grain diet to a refined grain diet.	Seven of eight parallel oat studies reported lower total cholesterol in the whole grain groups compared to controls. Meta-analysis (eight oat studies) found an effect on total cholesterol in the whole grain group compared to the control Group; direction favored lower total cholesterol on whole grain diets; weighted mean difference= -0.19mmol/L 95% CI -0.30 to -0.08 P=0.0005 Addition of the rye cross-over study weighted mean difference= -0.20, 95% CI -0.31 to -0.10, P=0.0001. Sensitivity analysis without the Reynolds study: -0.23 95% CI -0.33 to -0.12. Additional, removal of the Keenan study (small number of subjects) weighted mean difference: -0.22mmol/L, 95% CI -0.33 to -0.10. Sensitivity analysis: Heterogeneity was not found in the pooled analysis for total, LDL-C or HDL-C and TG. All 10 studies were graded quality level “C” based on the Cochrane criteria. Since all trials received the same quality rating, sensitivity analysis on the basis of quality was not performed.	Included foods based on milled whole grains, such as whole meal or oatmeal, where the components of the endosperm, bran and germ had not been removed.

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Mellen PB, Walsh TF & Herrington DM 2008 Study Design: Meta-analysis Class: M Positive Quality	Pooled data from seven prospective cohort studies. Total N for pooled analysis=149,000 male and female subjects. Age: 35 to 98 years. Follow up duration: Six to 15 years. Location: Six studies from the United States, one from Norway.	Evaluated the association between whole grain intake and clinical CVD events using the following criteria: The studies used self-reported quantitative measures of whole grain intake (e.g., servings per day) CVD events were ascertained prospectively Data provided was adequate to generate adjusted event rates. Literature search in MEDLINE; date range=1966 to April 2006.	Mantel-Haentzel test for heterogeneity found no evidence of significant heterogeneity, so fixed-effects models were used. Incident CVD: Demographic-adjusted CVD estimates (OR): 0 .63; 95% CI: 0.58-0.68. Risk-factor-adjusted CVD estimates: 0.79; 95% CI: 0.73-0.85. Sex-specific CVD estimate: Men: 0.82; 95% CI: 0.73-0.92; Women: 0.79; 95%CI: 0.68-0.91. Fatal CVD end-points: 0.78; 95% CI: 0.70-0.88. Incident CHD end-points: 0.76; 95% CI: 0.69-0.83. Incident stroke end-points: 0.83; 95% CI: 0.68-1.02. Funnel plots and Egger test used to evaluate publication bias.	Whole grain definition not stated. Included only studies that reported a quantitative whole-grain intake in servings per day.

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Nettleton JA, Steffen LM et al, 2008 Study Design: Prospective Cohort Study Class: B Positive Quality	N=14,153 African-American and white adults (Cohort of the Atherosclerosis Risk in Communities study). Age: 45 to 64 years. Follow up duration: 13 years. Location: United States.	Used a 66-item FFQ to examine the association between incident heart failure (HF) (death or hospitalization) and consumption of seven food categories (whole grains, fruits, vegetables, fish, nuts, high-fat dairy, eggs, red meat). Hazard ratios for HF were calculated on a one serving per day difference in each food group intake. Incident HF defined as first HF hospitalization (428, ICD-9). HF fatality based on any death certificate with an HF code (428, ICD-9 and I50, ICD-10).	1,140 cases of incident HF identified. Multivariate-adjusted HF risk for each one serving per day increase in whole-grain intake=0.93 (95% CI: 0.87, 0.99; P<0.05).	Whole grain and what constituted one serving were not defined in the manuscript. Citation for validated FFQ was Willett WC et al, *Am J Epi*, 1985

Research recommendations

1. Develop definitions for whole grain foods and criteria for whole grain foods that can be universally accepted.
    - Rationale: At present, there is no consistent way that whole grain foods are defined and determined. Without clear definitions for whole grain foods, it is difficult to compare research studies examining the effectiveness of various whole grains on biomarkers of interest in CVD, diabetes, and obesity. Clear definitions would also help consumers identify foods that can help them meet the Dietary Guidelines recommendations.

Search plan and results

Inclusion criteria

- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* <20% per intervention arm; preference for smaller dropout rates
- *Ages:* Children, two to 18 years; adults, 19 years and older
- *Populations:* Healthy

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- *Study design:* Systematic review, meta-analysis, clinical trial, prospective cohort. Cross-sectional studies were included for weight question.

Exclusion criteria

- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Malnourished or third-world populations or disease incidence not relative to US population (e.g., malaria)
- Animal studies
- In vitro studies
- *Study design:* Cross-sectional, case control
- Articles not peer reviewed (web sites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed

  (Whole grain* OR cereal[mh] OR amaranth OR barley OR buckwheat OR corn OR maize OR millet OR oats OR quinoa OR rice OR rye OR sorghum OR teff OR triticale OR wheat OR spelta OR emmer OR ferro OR einhorn OR kamut OR durum OR bran) AND ("CARDIOVASCULAR DISEASES"[mesh] OR "Diabetes Mellitus OR "Type 2"[Mesh]) NOT (Editorial[ptyp] OR Letter[ptyp])

  Whole grain* OR cereal[mh]) AND (("overweight"[mh] OR "Body Weights and Measures"[mh])

  Whole grain* AND (intake or consumption) AND "published last 10 years"[Filter] AND "english and humans"[Filter]

  (Whole grain* OR cereal[mh] OR amaranth OR barley OR buckwheat OR corn OR maize OR millet OR oats OR quinoa OR rice OR rye OR sorghum OR teff OR triticale OR wheat OR spelta OR emmer OR ferro OR einhorn OR kamut OR durum OR bran) AND ("CARDIOVASCULAR DISEASES"[mesh] OR "Diabetes Mellitus, Type 2"[Mesh]) AND (systematic[sb] OR Meta-Analysis[ptyp] OR"Trial"[Mesh] OR "Cohort Studies"[Mesh]) NOT (Editorial[ptyp] OR Letter[ptyp]).

Date searched: July 2009, September 2009, November 2009

Summary of articles identified to review

- Total hits from all electronic database searches: 888
- Total articles identified to review from electronic databases: 89
- Articles identified via handsearch or other means: 1
- Number of Primary Articles Identified: 11
- Number of Review Articles Identified: 7
- Total Number of Articles Identified: 18
- Number of Articles Reviewed but Excluded: 72

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Included articles (References)

Cardiovascular Disease

Systematic Reviews and Meta-analyses:

1. De Moura FF, Lewis KD, Falk MC. Applying the FDA definition of whole grains to the evidence for cardiovascular disease health claims. *J Nutr.* 2009 Nov; 139 (11): 2, 220S-2, 226S. Epub 2009 Sep 23. PMID: 19776180.
2. Kelly SA, Summerbell CD, Brynes A, Whittaker V, Frost G. Wholegrain cereals for coronary heart disease. *Cochrane Database Syst Rev.* 2007 Apr 18; (2): CD005051. Review. PMID: 17443567.
3. Mellen PB, Walsh TF, Herrington DM. Whole grain intake and cardiovascular disease: A meta-analysis. *Nutr Metab Cardiovasc Dis.* 2008 May; 18 (4): 283-290. Epub 2007 Apr 20. PMID: 17449231.

Primary Citations:

1. Brownlee IA, Moore C, Chatfield M, Richardson DP, Ashby P, Kuznesof SA, Jebb SA, Seal CJ. Markers of cardiovascular risk are not changed by increased whole-grain intake: The WHOLEheart study, a randomised, controlled dietary intervention. *Br J Nutr.* 2010 Mar 23 :1-10. PMID: 20307353. (Hand Search)
2. Djoussé L, Gaziano JM. Breakfast cereals and risk of heart failure in the Physicians' Health Study I. *Arch Intern Med.* 2007 Oct 22; 167 (19): 2, 080-2, 085. PMID: 17954802.
3. Flint AJ, Hu FB, Glynn RJ, Jensen MK, Franz M, Sampson L, Rimm EB. Whole grains and incident hypertension in men. *Am J Clin Nutr.* 2009 Sep; 90 (3): 493-498. Epub 2009 Jul 1. PMID: 19571218.
4. Nettleton JA, Steffen LM, Loehr LR, Rosamond WD, Folsom AR. Incident heart failure is associated with lower whole-grain intake and greater high-fat dairy and egg intake in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Diet Assoc.* 2008 Nov; 108 (11): 1, 881-1, 887. PMID: 18954578; PMCID: PMC2650810.

Type 2 Diabetes

Systematic Reviews and Meta-analyses:

1. de Munter JS, Hu FB, Spiegelman D, Franz M, van Dam RM. Whole grain, bran, and germ intake and risk of type 2 diabetes: A prospective cohort study and systematic review. *PLoS Med.* 2007 Aug; 4 (8): e261. PMID: 17760498; PMCID: PMC1952203.
2. Priebe MG, van Binsbergen JJ, de Vos R, Vonk RJ. Whole grain foods for the prevention of type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2008 Jan 23; (1): CD006061. Review. PMID: 18254091.

Primary Studies:

1. Brownlee IA, Moore C, Chatfield M, Richardson DP, Ashby P, Kuznesof SA, Jebb SA, Seal CJ. Markers of cardiovascular risk are not changed by increased whole-grain intake: The WHOLEheart study, a randomised, controlled dietary intervention. *Br J Nutr.* 2010 Mar 23: 1-10. PMID: 20307353. (Hand Search)
2. Kochar J, Djoussé L, Gaziano JM. Breakfast cereals and risk of type 2

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diabetes in the Physicians' Health Study I. *Obesity (Silver Spring).* 2007 Dec; 15 (12): 3, 039-3, 044. PMID:18198313.

Weight, Adiposity and Obesity

***Systematic Reviews and Meta-analyses**:*

1. Harland JI, Garton LE. Whole-grain intake as a marker of healthy body weight and adiposity. Whole-grain intake as a marker of healthy body weight and adiposity. *Public Helath Nutrition.* 2008 Jun; 11(6): 554-563. Epub 2007 Nov 16. PMID: 18005489.
2. Williams PG, Grafenauer SJ, O'Shea JE. Cereal grains, legumes and weight management: A comprehensive review of the scientific evidence. *Nutr Rev.* 2008 Apr; 66 (4): 171-182. Review. PMID: 18366531.

Primary Studies:

1. Behall KM, Scholfield DJ, Hallfrisch J. Whole-grain diets reduce blood pressure in mildly hypercholesterolemic men and women. *J Am Diet Assoc.* 2006 Sep; 106 (9): 1, 445-1, 449. PMID: 16963350.
2. Katcher HI, Legro RS, Kunselman AR, Gillies PJ, Demers LM, Bagshaw DM, Kris-Etherton PM. The effects of a whole grain-enriched hypocaloric diet on cardiovascular disease risk factors in men and women with metabolic syndrome. *Am J Clin Nutr.* 2008 Jan; 87 (1): 79-90. PMID: 18175740.
3. Lutsey PL, Jacobs DR Jr, Kori S, Mayer-Davis E, Shea S, Steffen LM, Szklo M, Tracy R. Whole grain intake and its cross-sectional association with obesity, insulin resistance, inflammation, diabetes and subclinical CVD: The MESA Study. *Br J Nutr.* 2007 Aug; 98 (2): 397-405. Epub 2007 Mar 29. PMID: 17391554.
4. McKeown NM, Yoshida M, Shea MK, Jacques PF, Lichtenstein AH, Rogers G, Booth SL, Saltzman E. Whole-grain intake and cereal fiber are associated with lower abdominal adiposity in older adults. *J Nutr.* 2009 Oct; 139 (10): 1, 950-1, 955. Epub 2009 Sep 2.
5. van de Vijver LP, van den Bosch LM, van den Brandt PA, Goldbohm RA. Whole-grain consumption, dietary fibre intake and body mass index in the Netherlands cohort study. *Eur J Clin Nutr.* 2009 Jan; 63 (1): 31-38. Epub 2007 Sep 26. PMID: 17895913.

Excluded articles

Article	Reason for Exclusion
Alminger M, Eklund-Jonsson C. Whole-grain cereal products based on a high-fibre barley or oat genotype lower post-prandial glucose and insulin responses in healthy humans. *Eur J Nutr.* 2008 Sep; 47 (6): 294-300. Epub 2008 Jul 16.	Does not answer questions. Measures postprandial response.

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Alonso A, Beunza JJ, Bes-Rastrollo M, Pajares RM, Martínez-González MA. Vegetable protein and fiber from cereal are inversely associated with the risk of hypertension in a Spanish cohort. *Arch Med Res.* 2006 Aug; 37 (6): 778-786. PMID: 16824939.	Does not include whole grainin analyses.
Anderson JW, Hanna TJ, Peng X, Kryscio RJ. Whole grain foods and heart disease risk. *J Am Coll Nutr.* 2000 Jun; 19 (3 Suppl): 291S-299S. PMID: 10875600.	Publication is a narrative review.
Bazzano LA, Song Y, Bubes V, Good CK, Manson JE, Liu S. Dietary intake of whole and refined grain breakfast cereals and weight gain in men. *Obes Res.* 2005 Nov; 13 (11): 1, 952-1, 960. PMID: 1633912.	Included in Harland/Garton 2007 systematic review for weight question. Does not include CVD or T2D in analyses.
Behall KM, Scholfield DJ, Hallfrisch J. Comparison of hormone and glucose responses of overweight women to barley and oats. *J Am Coll Nutr.* 2005 Jun; 24 (3): 182-188.	Does not answer questions. Measures postprandial response to whole grain intake.
Behall KM, Scholfield DJ, Hallfrisch J. Diets containing barley significantly reduce lipids in mildly hypercholesterolemic men and women. *Am J Clin* Nutr. 2004 Nov; 80 (5): 1, 185-1, 193.	Study subjects had hypercholesterolemia.
Behall KM, Scholfield DJ, Hallfrisch J. Whole-grain diets reduce blood pressure in mildly hypercholesterolemic men and women. *J Am Diet* Assoc. 2006 Sep; 106 (9): 1, 445-1, 449.	Participants had hypercholesterolemia. However, for CVD question was included in De Moura, 2009.
Davy BM, Melby CL, Beske SD, Ho RC, Davrath LR, Davy KP. Oat consumption does not affect resting casual and ambulatory 24-hour arterial blood pressure in men with high-normal blood pressure to stage I hypertension. *J Nutr.* 2002 Mar; 132 (3): 394-398. PMID: 11880561.	For CVD question: Included in De Moura, 2009. Does not include T2D or weight in analyses.
Erkkilä AT, Herrington DM, Mozaffarian D, Lichtenstein AH. Cereal fiber and whole-grain intake are associated with reduced progression of coronary-artery atherosclerosis in postmenopausal women with coronary artery disease. *Am Heart J*. 2005 Jul; 150 (1): 94-101.	Study subjects had coronary artery disease.

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Flight I, Clifton P. Cereal grains and legumes in the prevention of coronary heart disease and stroke: A review of the literature. *Eur J Clin Nutr.* 2006 Oct; 60 (10): 1, 145-1, 159. Epub 2006 May 3. Review. PMID: 16670693.	Publication is a narrative review; the literature search was systematic.
Fung TT, Hu FB, Pereira MA, Liu S, Stampfer MJ, Colditz GA, Willett WC. Whole-grain intake and the risk of type 2 diabetes: A prospective study in men. *Am J Clin Nutr.* 2002 Sep; 76 (3): 535-540. PMID: 12197996.	For T2D question: Included in systematic reviews de Munter, 2007 and Priebe, 2008. Does not include CVD or weight in analyses.
Giacco R, Brighenti F, Parillo M, Capuano M, Ciardullo AV, Rivieccio A, Rivellese AA, Riccardi G. Characteristics of some wheat-based foods of the Italian diet in relation to their influence on postprandial glucose metabolism in patients with type 2 diabetes. *Br J Nutr.* 2001 Jan; 85 (1): 33-40. PMID: 11227031.	Study subjects were type 2 diabetics.
Good CK, Holschuh N, Albertson AM, Eldridge AL. Whole grain consumption and body mass index in adult women: An analysis of NHANES 1999-2000 and the USDA pyramid servings database. *J Am Coll Nutr.* 2008 Feb; 27 (1): 80-87. PMID: 18460485.	For weight question, included in Harland/Garton 2007 systematic review. Does not include CVD or weight in analyses.
Granfeldt Y, Nyberg L, BjörckI. Muesli with 4g oat beta-glucans lowers glucose and insulin responses after a bread meal in healthy subjects. *Eur J Clin Nutr.* 2008 May; 62 (5): 600-607. Epub 2007 Apr 4.	Does not include outcomes of interest analyses. Measures postprandial response.
Harder H, Tetens I, Let MB, Meyer AS. Rye bran bread intake elevates urinary excretion of ferulic acid in humans, but does not affect the susceptibility of LDL to oxidation ex vivo. *Eur J Nutr.* 2004 Aug; 43 (4): 230-236. Epub 2004 Jan 6.	Does not include outcomes of interest in analyses.
Hsu TF, Kise M, Wang MF, Ito Y, Yang MD, Aoto H, Yoshihara R, Yokoyama J, Kunii D, Yamamoto S. Effects of pre-germinated brown rice on blood glucose and lipid levels in free-living patients with impaired fasting glucose or type 2 diabetes. *J Nutr Sci Vitaminol* (Tokyo). 2008 Apr; 54 (2): 163-168.	Study subjects had impaired fasting glucose or T2D.
Jacobs DR Jr, Gallaher DD. Whole grain intake and cardiovascular disease: A review. *Curr Atheroscler Rep*. 2004 Nov; 6 (6): 415-423.	Publication is a narrative review.

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Jacobs DR Jr, Meyer KA, Kushi LH, Folsom AR. Is whole grain intake associated with reduced total and cause-specific death rates in older women? The Iowa Women's Health Study. *Am J Public Health.* 1999 Mar; 89 (3): 322-329. PMID:10076480; PMCID: PMC1508593.	For CVD question: included in De Moura, 2009. Does not include T2D or weight in analyses.
Jacobs DR Jr, Meyer KA, Kushi LH, Folsom AR. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: The Iowa Women's Health Study. *Am J Clin Nutr.* 1998 Aug; 68 (2): 248-257. PMID: 9701180.	For CVD question: Included in De Moura, 2009. Does not include T2D or weight in analyses.
Jacobs DR Jr, Meyer HE, Solvoll K. Reduced mortality among whole grain bread eaters in men and women in the Norwegian County Study. *Eur J Clin Nutr.* 2001 Feb; 55 (2): 137-143. PMID:11305627.	Does not include outcomes of interest in analyses.
Jenkins DJ, Kendall CW, McKeown-Eyssen G, Josse RG, Silverberg J, Booth GL, Vidgen E, Josse AR, Nguyen TH, Corrigan S, Banach MS, Ares S, Mitchell S, Emam A, Augustin LS, Parker TL, Leiter LA. Effect of a low-glycemic index or a high-cereal fiber diet on type 2 diabetes: A randomized trial. *JAMA*. 2008 Dec 17; 300 (23): 2, 742-2, 753. PMID: 19088352.	Study subjects had T2D.
Jensen MK, Koh-Banerjee P, Hu FB, Franz M, Sampson L, Grønbaek M, Rimm EB. Intakes of whole grains, bran, and germ and the risk of coronary heart disease in men. *Am J Clin Nutr.* 2004 Dec; 80(6): 1, 492-1, 499.	For CVD question: Included in De Moura, 2009. Does not include T2D or weight in analyses.
Johnsen NF, Hausner H, Olsen A, Tetens I, Christensen J, Knudsen KE, Overvad K, Tjønneland A. Intake of whole grains and vegetables determines the plasma enterolactone concentration of Danish women. J *Nutr.* 2004 Oct; 134 (10): 2, 691-2, 697.	Study design is cross-sectional.
Katcher HI, Legro RS, Kunselman AR, Gillies PJ, Demers LM, Bagshaw DM, Kris-Etherton PM. The effects of a whole grain-enriched hypocaloric diet on cardiovascular disease risk factors in men and women with metabolic syndrome. *Am J Clin Nutr.* 2008 Jan; 87(1): 79-90.	Study subjects had hyperlipidemia.

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Katz DL, Evans MA, Chan W, Nawaz H, Comerford BP, Hoxley ML, Njike VY, Sarrel PM. Oats, antioxidants and endothelial function in overweight, dyslipidemic adults. *J Am Coll Nutr*. 2004 Oct; 23 (5): 397-403.	Study subjects had hyperlipidemia.
Koh-Banerjee P, Franz M, Sampson L, Liu S, Jacobs DR Jr, Spiegelman D, Willett W, Rimm E. Changes in whole-grain, bran, and cereal fiber consumption in relation to 8-year weight gain among men. *Am J Clin Nutr.* 2004 Nov; 80 (5): 1, 237-1, 245.	Does not include CHD or T2D in analyses. For weight question, included in systematic review, Williams, 2008.
Kuriyan R, Gopinath N, Vaz M, Kurpad AV. Use of rice bran oil in patients with hyperlipidaemia. *Natl Med J India*. 2005 Nov-Dec; 18 (6): 292-296.	Does not include whole grain in analyses. Study subjects had hyperlipidemia.
Lairon D, Arnault N, Bertrais S, Planells R, Clero E, Hercberg S, Boutron-Ruault MC. Dietary fiber intake and risk factors for cardiovascular disease in French adults. *Am J Clin Nutr*. 2005 Dec; 82 (6): 1, 185-1, 194.	Does not include whole grain in analyses.
Lammert A, Kratzsch J, Selhorst J, Humpert PM, Bierhaus A, Birck R, Kusterer K, Hammes HP. Clinical benefit of a short term dietary oatmeal intervention in patients with type 2 diabetes and severe insulin resistance: A pilot study. *Exp Clin Endocrinol Diabetes.* 2008 Feb; 116 (2): 132-134. Epub 2007 Dec 20. PMID: 18095234.	Study subjects had T2D.
Landberg R, Kamal-Eldin A, Andersson A, Vessby B, Aman P. Alkylresorcinols as biomarkers of whole-grain wheat and rye intake: Plasma concentration and intake estimated from dietary records. *Am J Clin Nutr*. 2008 Apr; 87 (4): 832-838.	Does not answer questions. Examined biomarkers of whole grain wheat and rye intake.
Lee KW, Song KE, Lee HS, Kim YK, Lee SW, Kim DJ, Hwang WS, Choe SJ, Kim YS, Kim TY. The effects of Goami No. 2 rice, a natural fiber-rich rice, on body weight and lipid metabolism. *Obesity* (Silver Spring). 2006 Mar; 14(3): 423-430.	Does not include incident T2D or T2D in analyses. Examined experimental Goami rice.
Linko AM, JuntunenKS, Mykkänen HM, Adlercreutz H. Whole-grain rye bread consumption by women correlates with plasma alkylresorcinols and increases their concentration compared with low-fiber wheat bread. *J Nutr.* 2005 Mar; 135 (3): 580-583.	Does not answer questions. Examined biomarkers of whole grain wheat and rye intake.

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Linko-Parvinen AM, Landberg R, Tikkanen MJ, Adlercreutz H, Peñalvo JL. Alkylresorcinols from whole-grain wheat and rye are transported in human plasma lipoproteins. *J Nutr*. 2007 May; 137 (5): 1, 137-1, 142.	Does not answer questions. Examined biomarkers of whole-grain wheat and rye intake.
Liu S, Manson JE, Stampfer MJ, Hu FB, Giovannucci E, Colditz GA, Hennekens CH, Willett WC. A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. *Am J Public Health.* 2000 Sep; 90 (9): 1, 409-1, 415. PMID: 10983198; PMCID: PMC1447620.	Included in systematic reviews: For CVD question: DeMoura, 2009. For T2D Question: de Munter, 2007 and Priebe, 2008.
Liu S, Sesso HD, Manson JE, Willett WC, Buring JE. Is intake of breakfast cereals related to total and cause-specific mortality in men? *Am J Clin Nutr.* 2003 Mar; 77 (3): 594-599. PMID: 12600848.	Does not include T2D or weight in analyses. For CVD question: Included in DeMoura, 2009 systematic review.
Liu S, Stampfer MJ, Hu FB, Giovannucci E, Rimm E, Manson JE, Hennekens CH, Willett WC. Whole-grain consumption and risk of coronary heart disease: Results from the Nurses' Health Study. *Am J Clin Nutr.* 1999 Sep; 70 (3): 412-419.	For CVD question: Included in DeMoura, 2009 systematic review. Does not include T2D or weight in analyses.
Lu Z, Kou W, Du B, Wu Y, Zhao S, Brusco OA, Morgan JM, Capuzzi DM; Chinese Coronary Secondary Prevention Study Group, Li S. Effect of Xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction. *Am J Cardiol.* 2008 Jun 15; 101 (12): 1, 689-1, 693. Epub 2008 Apr 11.	Does not answer questions. examined the effects of an Study subjects were post myocardial infarction.
Maki KC, Davidson MH, Witchger MS, Dicklin MR, Subbaiah PV. Effects of high-fiber oat and wheat cereals on postprandial glucose and lipid responses in healthy men. *Int J Vitam Nutr Res.* 2007 Sep; 77 (5): 347-356	Does not answer questions. Measured postpr andial response.
McKeown NM. Whole grain intake and insulin sensitivity: evidence from observational studies. *Nutr Rev.* 2004 Jul; 62 (7 Pt 1): 286-291. Review.	Publication is a narrative review.

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Melanson KJ, Angelopoulos TJ, Nguyen VT, Martini M, Zukley L, Lowndes J, Dube TJ, Fiutem JJ, Yount BW, Rippe JM. Consumption of whole-grain cereals during weight loss: Effects on dietary quality, dietary fiber, magnesium, vitamin B-6, and obesity. *J Am Diet Assoc.* 2006 Sep; 106 (9): 1, 380-1, 388; quiz 1, 389-1, 390.	Does not examine incident T2D or CHD. Examined weight loss. Included in Harland/Garton 2007 systematic review for weight question.
Mellen PB, Liese AD, Tooze JA, Vitolins MZ, Wagenknecht LE, Herrington DM. Whole-grain intake and carotid artery atherosclerosis in a multiethnic cohort: The Insulin Resistance Atherosclerosis Study. *Am J Clin Nutr.* 2007 Jun; 85 (6): 1, 495-1, 502.	Does not examine incident T2D or weight. Study examined carotid intimal medial thickness, not CVD outcome of interest.
Merchant AT, Pitiphat W, Franz M, Joshipura KJ. Whole-grain and fiber intakes and periodontitis risk in men. *Am J Clin Nutr.* 2006 Jun; 83 (6):1395-400.	Does not examine outcomes of interest. Study examines periodontitis.
Mesci B, Oguz A, Sagun HG, Uzunlulu M, Keskin EB, Coksert D. Dietary breads: Myth or reality? *Diabetes Res Clin Pract*. 2008 Jul; 81 (1): 68-71. Epub 2008 Mar 26.	Study subjects were type 2 diabetics.
Meyer KA, Kushi LH, Jacobs DR Jr, Slavin J, Sellers TA, Folsom AR. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr.* 2000 Apr; 71 (4): 921-930. PMID:10731498.	For T2D question, included in systematic reviews, de Munter, 2007 and Priebe, 2008. Does not include CHD or weight in analyses.
Montonen J, Knekt P, Järvinen R, Aromaa A, Reunanen A. Whole-grain and fiber intake and the incidence of type 2 diabetes. *Am J Clin Nutr.* 2003 Mar; 77 (3): 622-629. PMID: 12600852	For T2D question, included in systematic reviews, de Munter, 2007 and Priebe, 2008. Does not include CHD or weight in analyses.
Mozaffarian D, KumanyikaSK, Lemaitre RN, Olson JL, Burke GL, Siscovick DS. Cereal, fruit, and vegetable fiber intake and the risk of cardiovascular disease in elderly individuals. *JAMA*. 2003 Apr 2; 289 (13): 1, 659-1, 666. PMID: 12672734.	Did include whole grain intake in analyses.
Murtaugh MA, Jacobs DR Jr, Jacob B, Steffen LM, Marquart L. Epidemiological support for the protection of whole grains against diabetes. *Proc Nutr Soc.* 2003 Feb; 62 (1): 143-149. Review. PMID: 12740069.	Publication is a narrative review.

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Newby PK, Maras J, Bakun P, Muller D, Ferrucci L, Tucker KL. Intake of whole grains, refined grains, and cereal fiber measured with seven-day diet records and associations with risk factors for chronic disease. *Am J Clin Nutr.* 2007 Dec; 86 (6): 1, 745-1, 753. PMID: 18065595; PMCID: PMC2646086.	Included in systematic reviews: For weight question, Williams, 2008; for CHD, DeMoura, 2009.
Nilsson AC, Ostman EM, Granfeldt Y, Björck IM. Effect of cereal test breakfasts differing in glycemic index and content of indigestible carbohydrates on daylong glucose tolerance in healthy subjects. *Am J Clin Nutr*. 2008 Mar; 87(3): 645-654. PMID: 18326603.	Does not examine incident T2D. Measures glucose tolerance following 24-hour intervention.
Nilsson AC, Ostman EM, Holst JJ, Björck IM. Including indigestible carbohydrates in the evening meal of healthy subjects improves glucose tolerance, lowers inflammatory markers, and increases satiety after a subsequent standardized breakfast. *J Nutr*. 2008 Apr; 138 (4): 732-739.	Does not examine incident T2D. Measures postprandial response.
Panahi S, Ezatagha A, Temelli F, Vasanthan T, Vuksan V. Beta-glucan from two sources of oat concentrates affect postprandial glycemia in relation to the level of viscosity. *J Am Coll Nutr.* 2007 Dec; 26(6): 639-644.	Does not examine incident T2D, CVD or weight. Postprandial study.
Panlasigui LN, Thompson LU. Blood glucose lowering effects of brown rice in normal and diabetic subjects. *Int J Food Sci Nutr.* 2006 May-Jun; 57(3-4): 151-158.	Does not include incident T2D, CVD or weight in analyses.
Qi L, Hu FB. Dietary glycemic load, whole grains, and systemic inflammation in diabetes: The epidemiological evidence. *Curr Opin Lipidol.* 2007 Feb; 18 (1): 3-8.	Publication is a narrative review.
Qi L, van Dam RM, Liu S, Franz M, Mantzoros C, Hu FB. Whole-grain, bran, and cereal fiber intakes and markers of systemic inflammation in diabetic women. *Diabetes Care.* 2006 Feb; 29 (2): 207-211.	Study design is cross-sectional. Study subjects had T2D.
Rave K, Roggen K, Dellweg S, Heise T, tom Dieck H. Improvement of insulin resistance after diet with a whole-grain based dietary product: Results of a randomized, controlled cross-over study in obese subjects with elevated fasting blood glucose. *Br J Nutr*. 2007 Nov; 98 (5): 929-936. Epub 2007 Jun 12.	Study subjects had elevated fasting blood glucose.

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Sadiq Butt M, Tahir-Nadeem M, Khan MK, Shabir R, Butt MS. Oat: unique among the cereals. *Eur J Nutr.* 2008 Mar; 47 (2): 68-79. Epub 2008 Feb 26.	Publication is a narrative review.
Sahyoun NR, Jacques PF, Zhang XL, Juan W, McKeown NM. Whole-grain intake is inversely associated with the metabolic syndrome and mortality in older adults. *Am J Clin Nutr.* 2006 Jan; 83 (1): 124-131.	Study design is cross-sectional.
Seal CJ, BrownleeIA, Jones AR. Grains and health: the "whole" picture. *Quintessence Int.* 2007 Jun; 38 (6): 498-503. PMID: 17625633.	Publication is a narrative review.
Seal CJ. Whole grains and CVD risk. *Proc Nutr Soc.* 2006 Feb; 65 (1): 24-34. Review. PMID: 16441941.	Publication is a narrative review.
Shimizu C, Kihara M, Aoe S, Araki S, Ito K, Hayashi K, Watari J, Sakata Y, Ikegami S. Effect of high beta-glucan barley on serum cholesterol concentrations and visceral fat area in Japanese men: A randomized, double-blinded, placebo-controlled trial. *Plant Foods Hum Nutr.* 2008 Mar; 63 (1): 21-25. Epub 2007 Dec 12.	Study subjects had hypercholesterolemia.
Smith KN, Queenan KM, Thomas W, Fulcher RG, Slavin JL. Physiological effects of concentrated barley beta-glucan in mildly hypercholesterolemic adults. *J Am Coll Nutr.* 2008 Jun; 27 (3): 434-440. PMID: 18838533.	Study subjects had hypercholesterolemia.
Steffen LM, Jacobs DR Jr, Stevens J, Shahar E, Carithers T, Folsom AR. Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke: The Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr*. 2003 Sep; 78 (3): 383-390.	Included in systematic reviews: For CVD question DeMoura, 2009. For Weight question Harland/Garton 2007. Does not include T2D in analyses.
Thane CW, Jones AR, Stephen AM, Seal CJ, Jebb SA. Comparative whole-grain intake of British adults in 1986-1987 and 2000-2001. *Br J Nutr.* 2007 May; 97 (5): 987-992.	Does not answer questions. Study reports dietary intake of whole grains.

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Thane CW, Jones AR, Stephen AM, Seal CJ, Jebb SA. Whole-grain intake of British young people aged four-18 years. *Br J Nutr*. 2005 Nov; 94 (5): 825-831.	Study design is cross-sectional. Does not answer questions. Reports dietary intake of whole grains.
Thane CW, Stephen AM, Jebb SA. Whole grains and adiposity: Little association among British adults. *Eur J Clin Nutr*. 2009 Feb; 63 (2): 229-237. Epub 2007 Sep 19. PMID: 17882134.	Included in systematic review for weight: Harland/Garton 2007. Does not include CVD or T2D in analyses.
Theuwissen E, Plat J, Mensink RP. Consumption of oat beta-glucan with or without plant stanols did not influence inflammatory markers in hypercholesterolemic subjects. *Mol Nutr Food Res.* 2009 Mar; 53 (3): 370-376. PMID: 18979504.	Study subjects had hypercholesterolemia.
van Dam RM, Hu FB, Rosenberg L, Krishnan S, Palmer JR. Dietary calcium and magnesium, major food sources, and risk of type 2 diabetes in US black women. *Diabetes Care.* 2006 Oct; 29 (10): 2, 238-2, 243. Erratum in: *Diabetes Care.* 2008 Oct; 31(10): 2, 077. PMID: 17003299.	Included in systematic reviews for T2D: de Munter, 2007 and Priebe, 2008. Does not include CVD or weight in analyses.
Vuksan V, Whitham D, Sievenpiper JL, Jenkins AL, Rogovik AL, Bazinet RP, Vidgen E, Hanna A. Supplementation of conventional therapy with the novel grain Salba (Salvia hispanica L.) improves major and emerging cardiovascular risk factors in type 2 diabetes: Results of a randomized controlled trial. *Diabetes Care*. 2007 Nov; 30 (11): 2, 804-2, 810. Epub 2007 Aug 8.	Study subjects diagnosed with T2D.
Wang L, Gaziano JM, Liu S, Manson JE, Buring JE, Sesso HD. Whole- and refined-grain intakes and the risk of hypertension in women. *Am J Clin Nutr.* 2007 Aug; 86 (2): 472-479. PMID: 17684221.	Included in systematic review for CVD question: DeMoura, 2009. Does not include T2D or weight in analyses.
Weickert MO, Möhlig M, Schöfl C, Arafat AM, Otto B, Viehoff H, Koebnick C, Kohl A, Spranger J, Pfeiffer AF. Cereal fiber improves whole-body insulin sensitivity in overweight and obese women. 2006 Apr; 29 (4): 775-780.	Study examines effect of cereal fiber intake, not whole grain.

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Yannakoulia M, Yiannakouris N, Melistas L, Kontogianni MD, Malagaris I, Mantzoros CS. A dietary pattern characterized by high consumption of whole-grain cereals and low-fat dairy products and low consumption of refined cereals is positively associated with plasma adiponectin levels in healthy women. *Metabolism.* 2008 Jun; 57 (6): 824-830.	Study design is cross-sectional. Outcome was adiponectin.
Zhang HW, Zhang YH, Lu MJ, Tong WJ, Cao GW. Comparison of hypertension, dyslipidaemia and hyperglycaemia between buckwheat seed-consuming and non-consuming Mongolian-Chinese populations in Inner Mongolia, China. *Clin Exp Pharmacol Physiol.* 2007 Sep; 34 (9): 838-844. PMID: 17645626.	Study design was cross-sectional.

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CHAPTER 15. WHOLE GRAINS – TYPE 2 DIABETES

WHAT IS THE RELATIONSHIP BETWEEN WHOLE GRAIN INTAKE AND TYPE 2 DIABETES?

Conclusion statement

Consumption of whole grains is associated with a reduced incidence of type 2 diabetes in large prospective cohort studies.

Grade

Limited

Evidence summary overview

Four articles met the inclusion criteria and were reviewed to determine the effect of whole grain consumption on the incidence of type 2 diabetes (T2D). Of the four papers, one was a systematic review and meta-analysis of six prospective cohorts, as well as a separate prospective cohort study (de Munter et al, 2007, positive quality); one was a systematic review of 12 studies (one RCT and 11 prospective cohort studies of which five were relevant to this question) (Priebe MG et al, 2008, positive quality); one was a RCT (Brownlee et al, 2010, neutral quality) and one was a prospective cohort study (Kochar et al 2008, neutral quality).

Both systematic reviews reported that whole grain intake was inversely associated with risk of T2D. They included a common sub-set of five prospective cohorts; one conducted a pooled analysis and the other did not. The systematic review and meta-analysis (de Munter et al, 2007) pooled the data of six prospective cohort studies (N=286,125 predominantly black and white male and female subjects with 10,944 incident cases of T2D) and found that a two-serving-per-day increment in whole grain consumption was associated with a 21% decrease in risk of T2D after adjustment for potential confounders and BMI (RR=0.79; 95% CI: 0.72, 0.87; P<0.001). Priebe 2008, reported on five prospective cohort studies that examined the effect of whole grain foods and found an inverse association ranging from 0.67 (95% CI; 0.32 to 1.38) to 0.79 (95% CI; 0.65 to 0.96). After excluding of studies that did not correct for family history of diabetes (Meyer 2000; Montonen 2003) and physical activity (Montonen 2003), the observed effect in the remaining three studies was a relative risk of 0.70, 0.73 and 0.73. Priebe 2008, also reviewed one RCT of low methodological quality, which reported that, in 12 obese hyperinsulinemic subjects, a six-week feeding intervention of whole grain foods at each meal compared to refined grain foods resulted in a slight improvement of insulin sensitivity (P<0.05).

Kochar et al, 2008 examined the association between cold ready-to-eat breakfast cereal consumption (whole grain and refined) and risk of T2D in a cohort of men from the Physicians' Health Study I (N=1,270 for cereal analyses). Incident T2D was determined from 19 years of annual follow-up questionnaires. Comparing the highest and lowest category of consumption, the relative risk for T2D was 0.63 (95% CI: 0.55, to 0.72; P<0.0001). The authors noted that their simplified food frequency questionnaire (FFQ) did not collect data that would allow them to control for total energy intake and other nutrients such as fiber and magnesium.

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Brownlee IA et al, 2010 investigated the effect of substituting whole grain for refined grains on risk markers of insulin sensitivity. Subjects who routinely consumed few whole grain products were randomized to consume 60g whole grains per day for eight weeks or 60g whole grains per day for eight weeks and then 120g whole grains per day for eight more weeks. Self -reported whole grain intake by the ad libitum subjects was significantly increased in both intervention groups. No significant differences in marker of insulin sensitivity, serum glucose and insulin, were found between the control and the averaged intervention groups between groups.

Evidence summary paragraphs

Systematic Reviews

de Munter et al, 2007 (positive quality) a prospective cohort study, conducted in the United States, examined the associations between whole grain, bran, germ and risk of T2D. The authors examined this question further by conducting a systematic review and meta-analysis of six cohort studies. The prospective cohort included 161,737 women from the Nurses' Health Studies I (NHSI) (age 37-65 years) and II (26-46 years). Dietary intakes and potential confounders were assessed with regularly administered questionnaires during 12-18 years of follow-up. The median whole grain intake in the lowest and highest quintile of intake was 3.7 and 31.2 grams per day for NHSI and 6.2 and 39.9 grams per day for NHSII. After adjustment for potential confounders, the relative risks (RRs) comparing the extreme quintiles of consumption was 0.63 (95% CI0.57, 0.69) for NHSI and 0.68 (95% CI 0.57, 0.81) for NHSII (both: P<0.001). After further adjustment for body mass index (BMI), these RRs were 0.75 (95% CI 0.68, 0.83; >0.001) and 0.86 (95% CI 0.72, 1.02; >0.03), respectively. The associations for bran intake were similar to those for total whole grain intake. The association for germ intake after adjustment for bran was not significant. Systematic review and Meta-analysis: Prospective cohort studies on whole grain intake and risk of T2D were identified in searches of MEDLINE and EMBASE up to January 2007, and data were independently extracted by two reviewers. Based on pooled data for six cohort studies (conducted in the United States and Finland; the same five cohort studies as Priebe plus de Munter) including 286,125 predominantly black and white male and female subjects and 10,944 cases of type 2 diabetes, a two-serving-per-day increment in whole grain consumption was associated with a 21% (RR 0.79; 95% CI: 0.72, 0.87) decrease in risk of T2D after adjustment for potential confounders and BMI. Whole grain intake was inversely associated with risk of T2D. Additional analysis of whole grain components found that the association was stronger for bran than for germ.

Priebe MG et al, 2008 (positive quality) a Cochrane systematic review of studies conducted in Europe and the United States examined the effect of whole grain foods on prevention of type 2 diabetes (T2D). The literature search date range was all papers published prior to May 2006. Inclusion criteria for cohort studies was minimum duration of five years and evaluation of the relationship between whole-grain foods or cereal fiber intake and incidence of T2D. For RCT inclusion, the minimum study duration was six weeks and it had to assess the effect of a diet rich in whole-grain foods compared to a diet rich in refined grain foods on T2D and its major risk factors. One RCT and 11 prospective cohort studies met the inclusion criteria. Data were not pooled due to methodological differences. The one RCT studied 12 obese hyperinsulinemic subjects and found that a six-week feeding

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intervention of whole grain foods at each meal compared to refined grain foods at each meal resulted in a slight improvement of insulin sensitivity. Priebe et al obtained the insulin sensitivity measurement finding from the authors (Pereira et al, 2002) as only the mean difference was reported in the publication. Insulin sensitivity (M-value) was measured with the euglycemic hyperinsulinemic clamp test and was significantly higher after the whole grain intervention compared to the refined grain intervention ($P<0.05$). The authors deemed the RCT to be of low methodological quality, as blinding and randomization were not described and the sample size was small. Of the 11 included prospective cohort studies, three examined whole grain intake, four studied cereal fiber intake, and two studied both. The five studies that examined the effect of whole grain foods consistently found an inverse association with T2D at the higher levels of consumption. The relative risks (RR) ranged between 0.67 (95% CI 0.32 to 1.38) and 0.79 (95% CI 0.65 to 0.96). After exclusion of studies that did not correct for family history of diabetes (Meyer 2000; Montonen 2003) and physical activity(Montonen 2003), the observed effect was very similar in the rest of the studies (RR of 0.70, 0.73 and 0.73). Overall, While the results of the cohort studies were homogenous, the authors stated that evidence from only prospective cohort trials was considered to be too weak to draw a definite conclusion about the effect of whole grain foods on the development of T2D.

Primary Studies

Brownlee et al, 2010 (neutral quality) an RCT, conducted in the United Kingdom, investigated the effect of substituting whole grain for refined grains on CVD risk markers. Subjects (N=266; BMI>25kg/m^2) who routinely consumed few whole grain products were randomized to consume 60g whole grains per day for eight weeks or 60g whole grains per day for eight weeks and then 120g whole grains per day for eight more weeks. Markers of CVD risk and insulin sensitivity (BMI, percent body fat, waist circumference; fasting plasma lipid profile, glucose and insulin) were measured at baseline, eight and 16 weeks. A random intercepts model with time and whole grain intake factors was used to assess differences between the control and the average of the two intervention groups. Self-reported whole grain intake was significantly increased in both intervention groups. No significant differences in markers of insulin sensitivity were found between the control and the averaged intervention groups between groups.

Kochar et al, 2007 (neutral quality) prospective cohort study, conducted in the United States, examined the association between cold ready-to-eat breakfast cereal consumption (whole grain and refined) and risk of type 2 diabetes (T2D) in men from the Physicians' Health Study I (N=1,270 for cereal analyses). Cereal consumption was estimated using an abbreviated food questionnaire. Incident T2D was determined from 19 years of annual follow-up questionnaires. The median whole grain breakfast cereal intake in the lowest and highest category of intake was zero and at least seven cups per week, respectively. Comparing the highest and lowest category of consumption, the relative risk for T2D was 0.63 (95% CI: 0.55, to 0.72; $P<0.0001$). A limitation noted by the authors was that the simple food questionnaire for collection of dietary information did not allow controlling for total energy intake and other nutrients such as fiber and magnesium. Additionally, the study examined only one source of grain consumption; cold (ready-to-eat) breakfast cereals.

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Overview table

Author, Year, Study Design, Class, Rating	Participants, Duration, and Location	Description of Study Design	Outcomes	Whole Grain Definition
Brownlee IA, Moore C et al, 2010 Study Design: Randomized controlled trial Class: A Neutral Quality	N=266 participants. Age: 18-65 years. BMI>25kg/m^2. Consuming<30g WG per day . Location: United Kingdom.	Examined effect of substituting whole grain for refined grains on CVD risk markers using random intercepts model. Interventions: Control (no dietary Δ). Int 1: 60g WG per day x 16 weeks. Int 2: 60g WG per day x eight weeks, then 120g WG per day for eight weeks. Measures taken at zero, eight and 16 weeks. Whole-grain foods were provided; intake data was self-reported on EPIC FFQ.	Dropout rates: WG Int 1=19% WG Int 2=23% Control=6%. WG Int 1 and 2 outcome measures were averaged and then compared to controls. There were no significant differences in any markers of insulin sensitivity between the combined intervention groups and the control.	Selected whole grain foods were provided to free-living subjects.

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deMunter JSL, Hu FB et al, 2007 Study Design: Prospective cohort study; Meta-analysis Class: M Positive Quality	*Meta-analysis* N=286,125 subjects and 10,944 cases of type 2 diabetes from six cohort studies including this one. Cohorts included predominantly white or black populations of men and women. Locations: United States and Finland. *Prospective Cohort Study* N=161,737 women; 73,327 from Nurse's Health Study I (NHSI) Baseline Ages=37-65 years; starting with 1984 FFQ. 88,410 from NHSII; Baseline age=26-46 years, starting with 1991 FFQ. Duration: NHSI-18 year follow up; NHSII-12 year follow up. Location: United States.	Pooled meta-analysis of six prospective cohort studies. For each study, the RR of T2D was expressed per two serving per day increment of whole grain intake (40g). Examined association between quintiles of whole grain consumption and incidence of T2D using Cox proportional hazards analysis to estimate RR. Used whole grain food composition database to directly calculate each participant's whole grain intake in grams per day. Used National Diabetes Data Group criteria for diagnosis of T2D.	A 40g ↑ in daily whole grain intake associated with a 21% ↓ in T2D risk; RR=0.79 (95% CI=0.72, 0.87) after adjustment for potential confounders and BMI. *Note: Pooled analysis did not include fiber.* RR highest vs. lowest quintile of whole grain intake: NHSI (Q5=31.2g per day) RR=0.63 (95% CI=0.57, 0.69) NHSII (Q5=39.3g per day) RR=0.68 (95% CI 0.57, 0.81) (both: P<0.001); adjusted for potential confounders. RR after further adjustment for BMI: NHSI=0.75 (95% CI 0.68, 0.83; P<0.001) NHSII=0.86 (95% CI 0.72, 1.02; P=0.03). *Note: Associations for bran intake were similar to those for whole grain intake, association for germ intake after adjustment for bran was not significant.*	20 grams whole grain defined as one serving. For the study by Montonen, one serving was defined as 30 grams of grain. Intact and pulverized forms of whole grain containing the expected proportion of bran, germ and endosperm for the specific grain types. The following ingredients in the database were considered whole. Grains: Whole wheat and whole wheat flour, whole oats and whole oat flour, whole cornmeal and whole corn flour, brown rice and brown rice flour, whole rye and whole rye flour, whole barley, bulgur, buckwheat, popcorn, amaranth and psyllium.

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Kochar J, Djousse L et al, 2007 Study Design: Prospective cohort study Class: B Neutral Quality	N=21,152 males from the Physicians Health Study I. For the whole-grain vs. refined grain analysis, N=17,270 as 3,882 subjects were excluded for failing to specify cereal brand. Baseline age: 39.7-85.9 years (1981-1983). Duration: 19 years. Location: United States.	Consumption of cold breakfast cereals estimated using abbreviated food questionnaire. Participants reported average consumption of cold breakfast cereals (by one-cup increments) during the past year. Hot cereal consumption (e.g. oatmeal) was not assessed.	Adjusted RR of T2D was 0.63 (95% CI=0.55, 0.72) for the highest category of cold whole-grain breakfast cereal consumption (at least seven cups per week) (P for trend <0.0001). Distribution for total, whole and refined grain was skewed to the right, thus a gradient of consumption was used rather than quintiles. *Note: Fiber not a variable. Authors discussed a number of potential mechanisms for effect.*	Used algorithm developed by Jacobs et al, AJCN 1998 to classify breakfast cereals in to whole or refined grain. Cereals containing at least 25% of oat or bran were classified as whole grain.

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Priebe MG et al 2008 Study Design: Systematic Review Class: M Positive Quality	The literature search included studies published prior to May 2006. 12 studies met the inclusion criteria: 11 prospective cohort studies (minimum duration of five years); five of these examined the effect of whole grain. One RCT (minimum duration of each intervention arm was six weeks). N=12 obese hyperinsulinemic subjects. Study locations: Europe and the US.	Examined the effect of whole grain foods on prevention of type 2 diabetes (T2D). Five prospective cohort studies examined the effect of whole grain foods. The RCT examined the effect of a diet rich in whole-grain foods compared to a diet rich in refined grain foods on T2D and its major risk factors. Data were not pooled due to methodological differences.	Five cohort studies found an inverse association with T2D and whole grain consumption: RR=0.67 (95% CI 0.32 to 1.38) to 0.79 (95% CI 0.65 to 0.96). Following exclusion of studies that did not correct for family history of diabetes (Meyer 2000; Montonen 2003) and physical activity (Montonen 2003), the observed effect in the remaining thee studies was similar RR=0.70, 0.73 and 0.73). RCT: Insulin sensitivity (M-value) measured with euglycemic hyperinsulinemic clamp test: Whole grain intervention (0.396 x 10-4±0.131 x 10-4mmol/kg/one minute; 1 per pmol/L) Refined grain intervention (0.323 x 10-4±0.043 x 10-4mmol/kg/one minute; 1 per pmol/L) Mean difference: 0.07 x 10-4mmol/kg/one minute; 1 per mmol/L, 95% CI 0.003 x 10-4 to 0.144 x 10-4; P<0.05). *Note: Findings for cereal fiber were similar to whole grain.*	Whole grain food was defined in most studies (Fung 2002; Liu 2000; Liu 2003; Meyer 2000) according to Jacobs et al (Jacobs 1998) and Liu et al (Liu 1999) and included dark bread, popcorn, cooked oatmeal, wheat germ, brown rice, bran and other grains (e.g. bulgar, kasha, couscous). Breakfast cereals were classified as whole grain if they contained more than 25% whole grain or bran. Montonen et al, 2003, modified this classification and did not include wheat germ and bran. Koh-Banerjee et al, 2004, converted reported amounts of whole grain foods to grams of whole grain per day and also used the FDA definition for products eligible for a whole-grain health claim: Foods that contain more than 51% of whole grain (all portions of the kernel) per reference amount customarily consumed (FDA 2005). Van Dam et al, 2006, included "dark breads, such as wheat, rye, pumpernickel" and "high fibre, bran or granola cereals, shredded wheat" as whole grains.

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Research recommendations

1. Develop definitions for whole grain foods and criteria for whole grain foods that can be universally accepted.
    - Rationale: At present, there is no consistent way that whole grain foods are defined and determined. Without clear definitions for whole grain foods, it is difficult to compare research studies examining the effectiveness of various whole grains on biomarkers of interest in CVD, diabetes, and obesity. Clear definitions would also help consumers identify foods that can help them meet the Dietary Guidelines recommendations.

Search plan and results

Inclusion criteria

- Human subjects
- English language
- International
- *Sample size:* Minimum of 10 subjects per study arm; preference for larger sizes, if available
- *Dropout rate:* <20% per intervention arm; preference for smaller dropout rates
- *Ages:* Children, two to 18 years; adults, 19 years and older
- *Populations:* Healthy
- *Study design:* Systematic review, meta-analysis, clinical trial, prospective cohort. Cross-sectional studies were included for weight question.

Exclusion criteria

- Medical treatment or therapy
- Diseased subjects (already diagnosed with disease related to study purpose)
- Hospitalized patients
- Malnourished or third-world populations or disease incidence not relative to US population (e.g., malaria)
- Animal studies
- In vitro studies
- *Study design:* Cross-sectional, case control
- Articles not peer reviewed (web sites, magazine articles, Federal reports, etc.).

Search terms and electronic databases used

- PubMed

  (Whole grain* OR cereal[mh] OR amaranth OR barley OR buckwheat OR corn OR maize OR millet OR oats OR quinoa OR rice OR rye OR sorghum OR teff OR triticale OR wheat OR spelta OR emmer OR ferro OR einhorn OR kamut OR durum OR bran) AND ("CARDIOVASCULAR DISEASES"[mesh] OR "Diabetes Mellitus OR "Type 2"[Mesh]) NOT (Editorial[ptyp] OR Letter[ptyp])

  Whole grain* OR cereal[mh]) AND (("overweight"[mh] OR "Body Weights and

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Measures"[mh])

Whole grain* AND (intake or consumption) AND "published last 10 years"[Filter] AND "english and humans"[Filter]

(Whole grain* OR cereal[mh] OR amaranth OR barley OR buckwheat OR corn OR maize OR millet OR oats OR quinoa OR rice OR rye OR sorghum OR teff OR triticale OR wheat OR spelta OR emmer OR ferro OR einhorn OR kamut OR durum OR bran) AND ("CARDIOVASCULAR DISEASES"[mesh] OR "Diabetes Mellitus, Type 2"[Mesh]) AND (systematic[sb] OR Meta-Analysis[ptyp] OR"Trial"[Mesh] OR "Cohort Studies"[Mesh]) NOT (Editorial[ptyp] OR Letter[ptyp]).

Date searched: July 2009, September 2009, November 2009

Summary of articles identified to review

- Total hits from all electronic database searches: 888
- Total articles identified to review from electronic databases: 89
- Articles identified via handsearch or other means: 1
- Number of Primary Articles Identified: 11
- Number of Review Articles Identified: 7
- Total Number of Articles Identified: 18
- Number of Articles Reviewed but Excluded: 72

Included articles (References)

Cardiovascular Disease

Systematic Reviews and Meta-analyses:

1. De Moura FF, Lewis KD, Falk MC. Applying the FDA definition of whole grains to the evidence for cardiovascular disease health claims. *J Nutr.* 2009 Nov; 139 (11): 2, 220S-2, 226S. Epub 2009 Sep 23. PMID: 19776180.
2. Kelly SA, Summerbell CD, Brynes A, Whittaker V, Frost G. Wholegrain cereals for coronary heart disease. *Cochrane Database Syst Rev.* 2007 Apr 18; (2): CD005051. Review. PMID: 17443567.
3. Mellen PB, Walsh TF, Herrington DM. Whole grain intake and cardiovascular disease: A meta-analysis. *Nutr Metab Cardiovasc Dis.* 2008 May; 18 (4): 283-290. Epub 2007 Apr 20. PMID: 17449231.

Primary Citations:

1. Brownlee IA, Moore C, Chatfield M, Richardson DP, Ashby P, Kuznesof SA, Jebb SA, Seal CJ. Markers of cardiovascular risk are not changed by increased whole-grain intake: The WHOLEheart study, a randomised, controlled dietary intervention. *Br J Nutr.* 2010 Mar 23 :1-10. PMID: 20307353. (Hand Search)
2. Djoussé L, Gaziano JM. Breakfast cereals and risk of heart failure in the Physicians' Health Study I. *Arch Intern Med.* 2007 Oct 22; 167 (19): 2, 080-2, 085. PMID: 17954802.
3. Flint AJ, Hu FB, Glynn RJ, Jensen MK, Franz M, Sampson L, Rimm EB. Whole grains and incident hypertension in men. *Am J Clin Nutr.* 2009 Sep; 90 (3): 493-498. Epub 2009 Jul 1. PMID: 19571218.
4. Nettleton JA, Steffen LM, Loehr LR, Rosamond WD, Folsom AR. Incident heart failure is associated with lower whole-grain intake and greater high-fat

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dairy and egg intake in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Diet Assoc.* 2008 Nov; 108 (11): 1, 881-1, 887. PMID: 18954578; PMCID: PMC2650810.

Type 2 Diabetes

Systematic Reviews and Meta-analyses:

1. de Munter JS, Hu FB, Spiegelman D, Franz M, van Dam RM. Whole grain, bran, and germ intake and risk of type 2 diabetes: A prospective cohort study and systematic review. *PLoS Med.* 2007 Aug; 4 (8): e261. PMID: 17760498; PMCID: PMC1952203.
2. Priebe MG, van Binsbergen JJ, de Vos R, Vonk RJ. Whole grain foods for the prevention of type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2008 Jan 23; (1): CD006061. Review. PMID: 18254091.

Primary Studies:

1. Brownlee IA, Moore C, Chatfield M, Richardson DP, Ashby P, Kuznesof SA, Jebb SA, Seal CJ. Markers of cardiovascular risk are not changed by increased whole-grain intake: The WHOLEheart study, a randomised, controlled dietary intervention. *Br J Nutr.* 2010 Mar 23: 1-10. PMID: 20307353. (Hand Search)
2. Kochar J, Djoussé L, Gaziano JM. Breakfast cereals and risk of type 2 diabetes in the Physicians' Health Study I. *Obesity (Silver Spring).* 2007 Dec; 15 (12): 3, 039-3, 044. PMID:18198313.

Weight, Adiposity and Obesity

Systematic Reviews and Meta-analyses:

1. Harland JI, Garton LE. Whole-grain intake as a marker of healthy body weight and adiposity. Whole-grain intake as a marker of healthy body weight and adiposity. *Public Helath Nutrition.* 2008 Jun; 11(6): 554-563. Epub 2007 Nov 16. PMID: 18005489.
2. Williams PG, Grafenauer SJ, O'Shea JE. Cereal grains, legumes and weight management: A comprehensive review of the scientific evidence. *Nutr Rev.* 2008 Apr; 66 (4): 171-182. Review. PMID: 18366531.

Primary Studies:

1. Behall KM, Scholfield DJ, Hallfrisch J. Whole-grain diets reduce blood pressure in mildly hypercholesterolemic men and women. *J Am Diet Assoc.* 2006 Sep; 106 (9): 1, 445-1, 449. PMID: 16963350.
2. Katcher HI, Legro RS, Kunselman AR, Gillies PJ, Demers LM, Bagshaw DM, Kris-Etherton PM. The effects of a whole grain-enriched hypocaloric diet on cardiovascular disease risk factors in men and women with metabolic syndrome. *Am J Clin Nutr.* 2008 Jan; 87 (1): 79-90. PMID: 18175740.
3. Lutsey PL, Jacobs DR Jr, Kori S, Mayer-Davis E, Shea S, Steffen LM, Szklo M, Tracy R. Whole grain intake and its cross-sectional association with obesity, insulin resistance, inflammation, diabetes and subclinical CVD: The MESA Study. *Br J Nutr.* 2007 Aug; 98 (2): 397-405. Epub 2007 Mar 29. PMID: 17391554.
4. McKeown NM, Yoshida M, Shea MK, Jacques PF, Lichtenstein AH, Rogers G, Booth SL, Saltzman E. Whole-grain intake and cereal fiber are associated

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with lower abdominal adiposity in older adults. *J Nutr.* 2009 Oct; 139 (10): 1, 950-1, 955. Epub 2009 Sep 2.
5. van de Vijver LP, van den Bosch LM, van den Brandt PA, Goldbohm RA. Whole-grain consumption, dietary fibre intake and body mass index in the Netherlands cohort study. *Eur J Clin Nutr.* 2009 Jan; 63 (1): 31-38. Epub 2007 Sep 26. PMID: 17895913.

Excluded articles

Article	Reason for Exclusion
Alminger M, Eklund-Jonsson C. Whole-grain cereal products based on a high-fibre barley or oat genotype lower post-prandial glucose and insulin responses in healthy humans. *Eur J Nutr.* 2008 Sep; 47 (6): 294-300. Epub 2008 Jul 16.	Does not answer questions. Measures postprandial response.
Alonso A, Beunza JJ, Bes-Rastrollo M, Pajares RM, Martínez-González MA. Vegetable protein and fiber from cereal are inversely associated with the risk of hypertension in a Spanish cohort. *Arch Med Res.* 2006 Aug; 37 (6): 778-786. PMID: 16824939.	Does not include whole grainin analyses.
Anderson JW, Hanna TJ, Peng X, Kryscio RJ. Whole grain foods and heart disease risk. *J Am Coll Nutr.* 2000 Jun; 19 (3 Suppl): 291S-299S. PMID: 10875600.	Publication is a narrative review.
Bazzano LA, Song Y, Bubes V, Good CK, Manson JE, Liu S. Dietary intake of whole and refined grain breakfast cereals and weight gain in men. *Obes Res.* 2005 Nov; 13 (11): 1, 952-1, 960. PMID: 1633912.	Included in Harland/Garton 2007 systematic review for weight question. Does not include CVD or T2D in analyses.
Behall KM, Scholfield DJ, Hallfrisch J. Comparison of hormone and glucose responses of overweight women to barley and oats. *J Am Coll Nutr.* 2005 Jun; 24 (3): 182-188.	Does not answer questions. Measures postprandial response to whole grain intake.
Behall KM, Scholfield DJ, Hallfrisch J. Diets containing barley significantly reduce lipids in mildly hypercholesterolemic men and women. *Am J Clin* Nutr. 2004 Nov; 80 (5): 1, 185-1, 193.	Study subjects had hypercholesterolemia.

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Behall KM, Scholfield DJ, Hallfrisch J. Whole-grain diets reduce blood pressure in mildly hypercholesterolemic men and women. *J Am Diet* Assoc. 2006 Sep; 106 (9): 1, 445-1, 449.	Participants had hypercholesterolemia. However, for CVD question was included in De Moura, 2009.
Davy BM, Melby CL, Beske SD, Ho RC, Davrath LR, Davy KP. Oat consumption does not affect resting casual and ambulatory 24-hour arterial blood pressure in men with high-normal blood pressure to stage I hypertension. *J Nutr.* 2002 Mar; 132 (3): 394-398. PMID: 11880561.	For CVD question: Included in De Moura, 2009. Does not include T2D or weight in analyses.
Erkkilä AT, Herrington DM, Mozaffarian D, Lichtenstein AH. Cereal fiber and whole-grain intake are associated with reduced progression of coronary-artery atherosclerosis in postmenopausal women with coronary artery disease. *Am Heart J*. 2005 Jul; 150 (1): 94-101.	Study subjects had coronary artery disease.
Flight I, Clifton P. Cereal grains and legumes in the prevention of coronary heart disease and stroke: A review of the literature. *Eur J Clin Nutr.* 2006 Oct; 60 (10): 1, 145-1, 159. Epub 2006 May 3. Review. PMID: 16670693.	Publication is a narrative review; the literature search was systematic.
Fung TT, Hu FB, Pereira MA, Liu S, Stampfer MJ, Colditz GA, Willett WC. Whole-grain intake and the risk of type 2 diabetes: A prospective study in men. *Am J Clin Nutr.* 2002 Sep; 76 (3): 535-540. PMID: 12197996.	For T2D question: Included in systematic reviews de Munter, 2007 and Priebe, 2008. Does not include CVD or weight in analyses.
Giacco R, Brighenti F, Parillo M, Capuano M, Ciardullo AV, Rivieccio A, Rivellese AA, Riccardi G. Characteristics of some wheat-based foods of the Italian diet in relation to their influence on postprandial glucose metabolism in patients with type 2 diabetes. *Br J Nutr.* 2001 Jan; 85 (1): 33-40. PMID: 11227031.	Study subjects were type 2 diabetics.
Good CK, Holschuh N, Albertson AM, Eldridge AL. Whole grain consumption and body mass index in adult women: An analysis of NHANES 1999-2000 and the USDA pyramid servings database. *J Am Coll Nutr.* 2008 Feb; 27 (1): 80-87. PMID: 18460485.	For weight question, included in Harland/Garton 2007 systematic review. Does not include CVD or weight in analyses.

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Granfeldt Y, Nyberg L, BjörckI. Muesli with 4g oat beta-glucans lowers glucose and insulin responses after a bread meal in healthy subjects. *Eur J Clin Nutr.* 2008 May; 62 (5): 600-607. Epub 2007 Apr 4.	Does not include outcomes of interest analyses. Measures postprandial response.
Harder H, Tetens I, Let MB, Meyer AS. Rye bran bread intake elevates urinary excretion of ferulic acid in humans, but does not affect the susceptibility of LDL to oxidation ex vivo. *Eur J Nutr.* 2004 Aug; 43 (4): 230-236. Epub 2004 Jan 6.	Does not include outcomes of interest in analyses.
Hsu TF, Kise M, Wang MF, Ito Y, Yang MD, Aoto H, Yoshihara R, Yokoyama J, Kunii D, Yamamoto S. Effects of pre-germinated brown rice on blood glucose and lipid levels in free-living patients with impaired fasting glucose or type 2 diabetes. *J Nutr Sci Vitaminol* (Tokyo). 2008 Apr; 54 (2): 163-168.	Study subjects had impaired fasting glucose or T2D.
Jacobs DR Jr, Gallaher DD. Whole grain intake and cardiovascular disease: A review. *Curr Atheroscler Rep*. 2004 Nov; 6 (6): 415-423.	Publication is a narrative review.
Jacobs DR Jr, Meyer KA, Kushi LH, Folsom AR. Is whole grain intake associated with reduced total and cause-specific death rates in older women? The Iowa Women's Health Study. *Am J Public Health.* 1999 Mar; 89 (3): 322-329. PMID:10076480; PMCID: PMC1508593.	For CVD question: included in De Moura, 2009. Does not include T2D or weight in analyses.
Jacobs DR Jr, Meyer KA, Kushi LH, Folsom AR. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: The Iowa Women's Health Study. *Am J Clin Nutr.* 1998 Aug; 68 (2): 248-257. PMID: 9701180.	For CVD question: Included in De Moura, 2009. Does not include T2D or weight in analyses.
Jacobs DR Jr, Meyer HE, Solvoll K. Reduced mortality among whole grain bread eaters in men and women in the Norwegian County Study. *Eur J Clin Nutr.* 2001 Feb; 55 (2): 137-143. PMID:11305627.	Does not include outcomes of interest in analyses.
Jenkins DJ, Kendall CW, McKeown-Eyssen G, Josse RG, Silverberg J, Booth GL, Vidgen E, Josse AR, Nguyen TH, Corrigan S, Banach MS, Ares S, Mitchell S, Emam A, Augustin LS, Parker TL, Leiter LA. Effect of a low-glycemic index or a high-cereal fiber diet on type 2 diabetes: A randomized trial. *JAMA*. 2008 Dec 17; 300 (23): 2, 742-2, 753. PMID: 19088352.	Study subjects had T2D.

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Jensen MK, Koh-Banerjee P, Hu FB, Franz M, Sampson L, Grønbaek M, Rimm EB. Intakes of whole grains, bran, and germ and the risk of coronary heart disease in men. *Am J Clin Nutr.* 2004 Dec; 80(6): 1, 492-1, 499.	For CVD question: Included in De Moura, 2009. Does not include T2D or weight in analyses.
Johnsen NF, Hausner H, Olsen A, Tetens I, Christensen J, Knudsen KE, Overvad K, Tjønneland A. Intake of whole grains and vegetables determines the plasma enterolactone concentration of Danish women. J *Nutr.* 2004 Oct; 134 (10): 2, 691-2, 697.	Study design is cross-sectional.
Katcher HI, Legro RS, Kunselman AR, Gillies PJ, Demers LM, Bagshaw DM, Kris-Etherton PM. The effects of a whole grain-enriched hypocaloric diet on cardiovascular disease risk factors in men and women with metabolic syndrome. *Am J Clin Nutr.* 2008 Jan; 87(1): 79-90.	Study subjects had hyperlipidemia.
Katz DL, Evans MA, Chan W, Nawaz H, Comerford BP, Hoxley ML, Njike VY, Sarrel PM. Oats, antioxidants and endothelial function in overweight, dyslipidemic adults. *J Am Coll Nutr*. 2004 Oct; 23 (5): 397-403.	Study subjects had hyperlipidemia.
Koh-Banerjee P, Franz M, Sampson L, Liu S, Jacobs DR Jr, Spiegelman D, Willett W, Rimm E. Changes in whole-grain, bran, and cereal fiber consumption in relation to 8-year weight gain among men. *Am J Clin Nutr.* 2004 Nov; 80 (5): 1, 237-1, 245.	Does not include CHD or T2D in analyses. For weight question, included in systematic review, Williams, 2008.
Kuriyan R, Gopinath N, Vaz M, Kurpad AV. Use of rice bran oil in patients with hyperlipidaemia. *Natl Med J India*. 2005 Nov-Dec; 18 (6): 292-296.	Does not include whole grain in analyses. Study subjects had hyperlipidemia.
Lairon D, Arnault N, Bertrais S, Planells R, Clero E, Hercberg S, Boutron-Ruault MC. Dietary fiber intake and risk factors for cardiovascular disease in French adults. *Am J Clin Nutr*. 2005 Dec; 82 (6): 1, 185-1, 194.	Does not include whole grain in analyses.
Lammert A, Kratzsch J, Selhorst J, Humpert PM, Bierhaus A, Birck R, Kusterer K, Hammes HP. Clinical benefit of a short term dietary oatmeal intervention in patients with type 2 diabetes and severe insulin resistance: A pilot study. *Exp Clin Endocrinol Diabetes.* 2008 Feb; 116 (2): 132-134. Epub 2007 Dec 20. PMID: 18095234.	Study subjects had T2D.

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Landberg R, Kamal-Eldin A, Andersson A, Vessby B, Aman P. Alkylresorcinols as biomarkers of whole-grain wheat and rye intake: Plasma concentration and intake estimated from dietary records. *Am J Clin Nutr*. 2008 Apr; 87 (4): 832-838.	Does not answer questions. Examined biomarkers of whole grain wheat and rye intake.
Lee KW, Song KE, Lee HS, Kim YK, Lee SW, Kim DJ, Hwang WS, Choe SJ, Kim YS, Kim TY. The effects of Goami No. 2 rice, a natural fiber-rich rice, on body weight and lipid metabolism. *Obesity* (Silver Spring). 2006 Mar; 14(3): 423-430.	Does not include incident T2D or T2D in analyses. Examined experimental Goami rice.
Linko AM, JuntunenKS, Mykkänen HM, Adlercreutz H. Whole-grain rye bread consumption by women correlates with plasma alkylresorcinols and increases their concentration compared with low-fiber wheat bread. *J Nutr.* 2005 Mar; 135 (3): 580-583.	Does not answer questions. Examined biomarkers of whole grain wheat and rye intake.
Linko-Parvinen AM, Landberg R, Tikkanen MJ, Adlercreutz H, Peñalvo JL. Alkylresorcinols from whole-grain wheat and rye are transported in human plasma lipoproteins. *J Nutr*. 2007 May; 137 (5): 1, 137-1, 142.	Does not answer questions. Examined biomarkers of whole-grain wheat and rye intake.
Liu S, Manson JE, Stampfer MJ, Hu FB, Giovannucci E, Colditz GA, Hennekens CH, Willett WC. A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. *Am J Public Health.* 2000 Sep; 90 (9): 1, 409-1, 415. PMID: 10983198; PMCID: PMC1447620.	Included in systematic reviews: For CVD question: DeMoura, 2009. For T2D Question: de Munter, 2007 and Priebe, 2008.
Liu S, Sesso HD, Manson JE, Willett WC, Buring JE. Is intake of breakfast cereals related to total and cause-specific mortality in men? *Am J Clin Nutr.* 2003 Mar; 77 (3): 594-599. PMID: 12600848.	Does not include T2D or weight in analyses. For CVD question: Included in DeMoura, 2009 systematic review.
Liu S, Stampfer MJ, Hu FB, Giovannucci E, Rimm E, Manson JE, Hennekens CH, Willett WC. Whole-grain consumption and risk of coronary heart disease: Results from the Nurses' Health Study. *Am J Clin Nutr.* 1999 Sep; 70 (3): 412-419.	For CVD question: Included in DeMoura, 2009 systematic review. Does not include T2D or weight in analyses.

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Lu Z, Kou W, Du B, Wu Y, Zhao S, Brusco OA, Morgan JM, Capuzzi DM; Chinese Coronary Secondary Prevention Study Group, Li S. Effect of Xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction. *Am J Cardiol.* 2008 Jun 15; 101 (12): 1, 689-1, 693. Epub 2008 Apr 11.	Does not answer questions. examined the effects of an Study subjects were post myocardial infarction.
Maki KC, Davidson MH, Witchger MS, Dicklin MR, Subbaiah PV. Effects of high-fiber oat and wheat cereals on postprandial glucose and lipid responses in healthy men. *Int J Vitam Nutr Res.* 2007 Sep; 77 (5): 347-356	Does not answer questions. Measured post prandial response.
McKeown NM. Whole grain intake and insulin sensitivity: evidence from observational studies. *Nutr Rev.* 2004 Jul; 62 (7 Pt 1): 286-291. Review.	Publication is a narrative review.
Melanson KJ, Angelopoulos TJ, Nguyen VT, Martini M, Zukley L, Lowndes J, Dube TJ, Fiutem JJ, Yount BW, Rippe JM. Consumption of whole-grain cereals during weight loss: Effects on dietary quality, dietary fiber, magnesium, vitamin B-6, and obesity. *J Am Diet Assoc.* 2006 Sep; 106 (9): 1, 380-1, 388; quiz 1, 389-1, 390.	Does not examine incident T2D or CHD. Examined weight loss. Included in Harland/Garton 2007 systematic review for weight question.
Mellen PB, Liese AD, Tooze JA, Vitolins MZ, Wagenknecht LE, Herrington DM. Whole-grain intake and carotid artery atherosclerosis in a multiethnic cohort: The Insulin Resistance Atherosclerosis Study. *Am J Clin Nutr.* 2007 Jun; 85 (6): 1, 495-1, 502.	Does not examine incident T2D or weight. Study examined carotid intimal medial thickness, not CVD outcome of interest.
Merchant AT, Pitiphat W, Franz M, Joshipura KJ. Whole-grain and fiber intakes and periodontitis risk in men. *Am J Clin Nutr.* 2006 Jun; 83 (6):1395-400.	Does not examine outcomes of interest. Study examines periodontitis.
Mesci B, Oguz A, Sagun HG, Uzunlulu M, Keskin EB, Coksert D. Dietary breads: Myth or reality? *Diabetes Res Clin Pract*. 2008 Jul; 81 (1): 68-71. Epub 2008 Mar 26.	Study subjects were type 2 diabetics.
Meyer KA, Kushi LH, Jacobs DR Jr, Slavin J, Sellers TA, Folsom AR. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr.* 2000 Apr; 71 (4): 921-930. PMID:10731498.	For T2D question, included in systematic reviews, de Munter, 2007 and Priebe, 2008. Does not include CHD or weight in analyses.

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Montonen J, Knekt P, Järvinen R, Aromaa A, Reunanen A. Whole-grain and fiber intake and the incidence of type 2 diabetes. *Am J Clin Nutr.* 2003 Mar; 77 (3): 622-629. PMID: 12600852	For T2D question, included in systematic reviews, de Munter, 2007 and Priebe, 2008. Does not include CHD or weight in analyses.
Mozaffarian D, KumanyikaSK, Lemaitre RN, Olson JL, Burke GL, Siscovick DS. Cereal, fruit, and vegetable fiber intake and the risk of cardiovascular disease in elderly individuals. *JAMA*. 2003 Apr 2; 289 (13): 1, 659-1, 666. PMID: 12672734.	Did include whole grain intake in analyses.
Murtaugh MA, Jacobs DR Jr, Jacob B, Steffen LM, Marquart L. Epidemiological support for the protection of whole grains against diabetes. *Proc Nutr Soc.* 2003 Feb; 62 (1): 143-149. Review. PMID: 12740069.	Publication is a narrative review.
Newby PK, Maras J, Bakun P, Muller D, Ferrucci L, Tucker KL. Intake of whole grains, refined grains, and cereal fiber measured with seven-day diet records and associations with risk factors for chronic disease. *Am J Clin Nutr.* 2007 Dec; 86 (6): 1, 745-1, 753. PMID: 18065595; PMCID: PMC2646086.	Included in systematic reviews: For weight question, Williams, 2008; for CHD, DeMoura, 2009.
Nilsson AC, Ostman EM, Granfeldt Y, Björck IM. Effect of cereal test breakfasts differing in glycemic index and content of indigestible carbohydrates on daylong glucose tolerance in healthy subjects. *Am J Clin Nutr*. 2008 Mar; 87(3): 645-654. PMID: 18326603.	Does not examine incident T2D. Measures glucose tolerance following 24-hour intervention.
Nilsson AC, Ostman EM, Holst JJ, Björck IM. Including indigestible carbohydrates in the evening meal of healthy subjects improves glucose tolerance, lowers inflammatory markers, and increases satiety after a subsequent standardized breakfast. *J Nutr*. 2008 Apr; 138 (4): 732-739.	Does not examine incident T2D. Measures postprandial response.
Panahi S, Ezatagha A, Temelli F, Vasanthan T, Vuksan V. Beta-glucan from two sources of oat concentrates affect postprandial glycemia in relation to the level of viscosity. *J Am Coll Nutr.* 2007 Dec; 26(6): 639-644.	Does not examine incident T2D, CVD or weight. Postprandial study.
Panlasigui LN, Thompson LU. Blood glucose lowering effects of brown rice in normal and diabetic subjects. *Int J Food Sci Nutr.* 2006 May-Jun; 57(3-4): 151-158.	Does not include incident T2D, CVD or weight in analyses.

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Qi L, Hu FB. Dietary glycemic load, whole grains, and systemic inflammation in diabetes: The epidemiological evidence. *Curr Opin Lipidol.* 2007 Feb; 18 (1): 3-8.	Publication is a narrative review.
Qi L, van Dam RM, Liu S, Franz M, Mantzoros C, Hu FB. Whole-grain, bran, and cereal fiber intakes and markers of systemic inflammation in diabetic women. *Diabetes Care.* 2006 Feb; 29 (2): 207-211.	Study design is cross-sectional. Study subjects had T2D.
Rave K, Roggen K, Dellweg S, Heise T, tom Dieck H. Improvement of insulin resistance after diet with a whole-grain based dietary product: Results of a randomized, controlled cross-over study in obese subjects with elevated fasting blood glucose. *Br J Nutr*. 2007 Nov; 98 (5): 929-936. Epub 2007 Jun 12.	Study subjects had elevated fasting blood glucose.
Sadiq Butt M, Tahir-Nadeem M, Khan MK, Shabir R, Butt MS. Oat: unique among the cereals. *Eur J Nutr.* 2008 Mar; 47 (2): 68-79. Epub 2008 Feb 26.	Publication is a narrative review.
Sahyoun NR, Jacques PF, Zhang XL, Juan W, McKeown NM. Whole-grain intake is inversely associated with the metabolic syndrome and mortality in older adults. *Am J Clin Nutr.* 2006 Jan; 83 (1): 124-131.	Study design is cross-sectional.
Seal CJ, BrownleeIA, Jones AR. Grains and health: the "whole" picture. *Quintessence Int.* 2007 Jun; 38 (6): 498-503. PMID: 17625633.	Publication is a narrative review.
Seal CJ. Whole grains and CVD risk. *Proc Nutr Soc.* 2006 Feb; 65 (1): 24-34. Review. PMID: 16441941.	Publication is a narrative review.
Shimizu C, Kihara M, Aoe S, Araki S, Ito K, Hayashi K, Watari J, Sakata Y, Ikegami S. Effect of high beta-glucan barley on serum cholesterol concentrations and visceral fat area in Japanese men: A randomized, double-blinded, placebo-controlled trial. *Plant Foods Hum Nutr.* 2008 Mar; 63 (1): 21-25. Epub 2007 Dec 12.	Study subjects had hypercholesterolemia.
Smith KN, Queenan KM, Thomas W, Fulcher RG, Slavin JL. Physiological effects of concentrated barley beta-glucan in mildly hypercholesterolemic adults. *J Am Coll Nutr.* 2008 Jun; 27 (3): 434-440. PMID: 18838533.	Study subjects had hypercholesterolemia.

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

Steffen LM, Jacobs DR Jr, Stevens J, Shahar E, Carithers T, Folsom AR. Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke: The Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr*. 2003 Sep; 78 (3): 383-390.	Included in systematic reviews: For CVD question DeMoura, 2009. For Weight question Harland/Garton 2007. Does not include T2D in analyses.
Thane CW, Jones AR, Stephen AM, Seal CJ, Jebb SA. Comparative whole-grain intake of British adults in 1986-1987 and 2000-2001. *Br J Nutr.* 2007 May; 97 (5): 987-992.	Does not answer questions. Study reports dietary intake of whole grains.
Thane CW, Jones AR, Stephen AM, Seal CJ, Jebb SA. Whole-grain intake of British young people aged four-18 years. *Br J Nutr*. 2005 Nov; 94 (5): 825-831.	Study design is cross-sectional. Does not answer questions. Reports dietary intake of whole grains.
Thane CW, Stephen AM, Jebb SA. Whole grains and adiposity: Little association among British adults. *Eur J Clin Nutr*. 2009 Feb; 63 (2): 229-237. Epub 2007 Sep 19. PMID: 17882134.	Included in systematic review for weight: Harland/Garton 2007. Does not include CVD or T2D in analyses.
Theuwissen E, Plat J, Mensink RP. Consumption of oat beta-glucan with or without plant stanols did not influence inflammatory markers in hypercholesterolemic subjects. *Mol Nutr Food Res.* 2009 Mar; 53 (3): 370-376. PMID: 18979504.	Study subjects had hypercholesterolemia.
van Dam RM, Hu FB, Rosenberg L, Krishnan S, Palmer JR. Dietary calcium and magnesium, major food sources, and risk of type 2 diabetes in US black women. *Diabetes Care.* 2006 Oct; 29 (10): 2, 238-2, 243. Erratum in: *Diabetes Care.* 2008 Oct; 31(10): 2, 077. PMID: 17003299.	Included in systematic reviews for T2D: de Munter, 2007 and Priebe, 2008. Does not include CVD or weight in analyses.
Vuksan V, Whitham D, Sievenpiper JL, Jenkins AL, Rogovik AL, Bazinet RP, Vidgen E, Hanna A. Supplementation of conventional therapy with the novel grain Salba (Salvia hispanica L.) improves major and emerging cardiovascular risk factors in type 2 diabetes: Results of a randomized controlled trial. *Diabetes Care*. 2007 Nov; 30 (11): 2, 804-2, 810. Epub 2007 Aug 8.	Study subjects diagnosed with T2D.

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

Wang L, Gaziano JM, Liu S, Manson JE, Buring JE, Sesso HD. Whole- and refined-grain intakes and the risk of hypertension in women. *Am J Clin Nutr.* 2007 Aug; 86 (2): 472-479. PMID: 17684221.	Included in systematic review for CVD question: DeMoura, 2009. Does not include T2D or weight in analyses.
Weickert MO, Möhlig M, Schöfl C, Arafat AM, Otto B, Viehoff H, Koebnick C, Kohl A, Spranger J, Pfeiffer AF. Cereal fiber improves whole-body insulin sensitivity in overweight and obese women. 2006 Apr; 29 (4): 775-780.	Study examines effect of cereal fiber intake, not whole grain.
Yannakoulia M, Yiannakouris N, Melistas L, Kontogianni MD, Malagaris I, Mantzoros CS. A dietary pattern characterized by high consumption of whole-grain cereals and low-fat dairy products and low consumption of refined cereals is positively associated with plasma adiponectin levels in healthy women. *Metabolism.* 2008 Jun; 57 (6): 824-830.	Study design is cross-sectional. Outcome was adiponectin.
Zhang HW, Zhang YH, Lu MJ, Tong WJ, Cao GW. Comparison of hypertension, dyslipidaemia and hyperglycaemia between buckwheat seed-consuming and non-consuming Mongolian-Chinese populations in Inner Mongolia, China. *Clin Exp Pharmacol Physiol.* 2007 Sep; 34 (9): 838-844. PMID: 17645626.	Study design was cross-sectional.

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