AN EVIDENCE-BASED ANALYSIS OF THE RELATIONSHIP BETWEEN CONSUMPTION OF TREE NUTS AND THE RISK OF CARDIOVASCULAR DISEASE

FINAL REPORT

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1. Introduction

The International Tree Nut Council Nutrition Research & Education Foundation (INC NREF) requested that the Life Sciences Research Organization, Inc. (LSRO) conduct an evidence-based analysis of the relationship between the consumption of tree nuts and the risk of cardiovascular disease (CVD). The term “tree nuts” refers to almonds, Brazil nuts, cashews, macadamia nuts, pecans, pistachios, and walnuts, but not to betel (areca) nuts, soy nuts, or legumes such as peanuts. The current review updates a previous LSRO review that examined the relationship between dietary intake of walnuts and risk of coronary heart disease (CHD) (Feldman, 2002) and expands the previous review to include all tree nuts.

2. Methods

2.1. Overview

LSRO began the project by establishing an expert panel comprising individuals who were selected on the basis of their current work on the topic or their knowledge of the topic area to guide the review and to develop conclusions about the relationship between consumption of tree nuts and risk of CVD. Potential expert panel members were identified using scientific literature provided by the INC NREF and an expanded search of current literature by LSRO staff, as well as the recommendations of scientists identified in the initial search. LSRO implemented its standard procedures for expert panels to ensure freedom from conflict of interest and maintenance of confidentiality. The INC NREF was also provided with the list of potential expert panel members to permit comment on any potential bias or conflict of interest of candidate expert panel members. After candidate panel members indicated their willingness to serve on the project, maintain confidentiality, and demonstrate their freedom from conflicts of interest, they were provided with background information on the study and the approach being taken to the study topic by LSRO. The expert panel included scientists and physicians with expertise in nutrition, medicine, epidemiology, risk reduction, and CVD, and was approved by the LSRO Board of Directors. LSRO then conducted an evidence-based analysis of the relationship between tree nut consumption and risk of CVD.

2.2. Key Questions

The expert panel defined three key questions for the review:

(1) What is the strength of the association between nut consumption and the risk of CVD events (including CVD mortality, non-fatal CVD events, and new diagnosis of CVD) in people without known CVD (primary prevention)?

(2) Is there an effect between nut consumption and validated surrogate endpoints of CVD (total serum cholesterol (Tot-C), serum low-density lipoprotein cholesterol (LDL-C), and blood pressure?)

(3) Is there an effect between nut consumption and selected surrogate endpoints of CVD [high-density lipoprotein cholesterol (HDL-C), Tot-C:HDL-C, serum triglycerides (TG), apolipoprotein (Apo) A1, Apo B, Apo B-100, and C-reactive protein (CRP)] and
intermediate markers of cardiovascular disease (carotid artery intima-media thickness (IMT), carotid artery plaque, and coronary artery calcification)?

The panel defined CVD as myocardial infarction (MI), angina, self-reported angina, stroke, severe clinical heart failure, coronary revascularization (bypass, angioplasty), and peripheral vascular disease. Hypertension was not considered to be CVD for the purposes of this review, but high blood pressure was considered to be a validated surrogate endpoint of CVD.

2.3. Analytic Framework

2.3.1. Inclusion/Exclusion criteria

As this review may be used to support a petition to the U.S. Food and Drug Administration (FDA) of a health claim, LSRO consulted the FDA rules of evidence\(^1\), Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims – Final to develop the inclusion and exclusion criteria for the study. To be acceptable for consideration as supportive of a health claim, FDA states that studies must evaluate: (a) populations and diets representative of the U.S., (b) the risk of primary disease rather than secondary disease or disease treatment, (c) human studies rather than animal or \textit{in vitro} studies, and (d) disease endpoints or validated surrogate endpoints of disease risk\(^2\). Because the goal of LSRO expert panel was not a regulatory one, the panel decided that a more inclusive analysis of the relevant evidence could prove beneficial for making decisions about health. As a result, the panel decided to include some studies that FDA would likely eliminate in their evaluation of evidence and to summarize and weigh the evidence both using more restrictive determinants of evidence (FDA guidance) and by the panel’s more inclusive determinants.

Studies were excluded from this review if they were off topic, if there were concerns about the publication format of the study, the age or health status of the subjects or the study drop out rate, or if the study was not written in English. Specifically, studies were considered to be off topic if the intervention included consumption of leaves or other non-nut parts of the nut plant or if the study exclusively investigated nuts other than tree nuts (such as areca nuts, betel nuts, or bhallataka) or legumes, such as peanuts. Studies were also excluded if they described results of interventions with nut oils or other nut extracts. If a mixed dietary intervention was carried out and the specific effect of nuts could not be evaluated, the study was excluded. Letters to the editor (including comments, news reports, and editorials), reviews, and meta-analyses were excluded. Observational studies in which peanut consumption was not distinguished from nut consumption were included in the review. Reviews and meta-analyses were used only to identify additional relevant primary research studies. Animal studies, \textit{in vitro} studies, and human studies that included children aged 0 to 2 years or investigated populations with diets that are not representative of the US population were excluded from the review. Studies on foreign populations with basal serum concentrations of Tot-C or LDL-C that are not representative of the basal concentrations of these biomarkers in the US population were excluded from the review.


\(^2\) The FDA considers the only validated surrogate endpoints for cardiovascular disease are: serum low-density lipoprotein cholesterol concentrations (LDL-C), (2) total serum cholesterol concentration (Tot-C), and blood pressure (BP).
Studies that included subjects with heart conditions or individuals who had experienced one or more heart attacks or were being medicated for heart condition were also excluded. Data for relevant endpoints in the studies that included subjects with pre-existing diabetes, obesity, metabolic syndrome, hypertension, or hyperlipidemia were excluded if subjects were being medicated for the endpoint. Subject drop out rates of greater than 20% were grounds for study exclusion if they led to an imbalance between treatment groups or conditions.

Inclusion criteria for this review were human interventional, observational, and epidemiological studies on tree nuts that were published through March 2013 as full articles in peer-reviewed journals and included healthy study participants above 2 years of age who had not been diagnosed with CVD and who consumed diets representative of that of the US population. Included studies were of any population size, were written in English, had a participant dropout rate of 20% or lower or the participant dropout rate did not result in an imbalance between intervention and control groups or conditions, and investigated the effects of tree nuts on CVD risk. Studies conducted on subjects with pre-existing diabetes, obesity, metabolic syndrome, hypertension, or hyperlipidemia were included in the review as long as subjects had not been diagnosed with CVD and were not being medicated for the endpoints of the study. Studies in which the effects of nuts could not be differentiated from the displacement of saturated fats were included, and have been discussed as a component of the more inclusive analysis and separately.

Observational studies that evaluated the effect of tree nuts and legumes were included in the review, unless the study specified that only legumes were assessed. This is because many observational studies did not differentiate between tree nuts and legumes in their analysis (and perhaps in the food frequency questionnaires), yet useful information can be gleaned from these studies. If the effect of tree nuts was specifically analyzed in such studies, only the tree nut data was utilized.

2.4. Study Identification
2.4.1. Search strategy
LSRO conducted a systematic search of the scientific literature and employed the following search strategy to identify relevant articles:

("Apolipoprotein B"[Mesh]) OR "Apolipoprotein A-I"[Mesh] OR “Apolipoprotein”) OR (“Cholesterol” [MESH] OR "Cholesterol, HDL"[Mesh] OR “Cholesterol, Total” [MESH] OR "Cholesterol, LDL"[Mesh] )) OR "Triglycerides"[Mesh]] OR "Lipoprotein(a)[Mesh]) OR "C-Reactive Protein"[Mesh]) OR "Factor VIII"[Mesh]) OR "Fibrinogen"[Mesh]) OR "von Willebrand Factor"[Mesh]) OR "Carotid Intima-Media Thickness"[Mesh]) OR "Blood Pressure"[Mesh]) OR "Heart Rate"[Mesh] OR “diabetes” or “cardiovascular”) AND ("Nuts"[Mesh] or “Tree nuts” or “almonds” or “pecans” or “brazil nuts” or “pine nuts” or “hazelnuts” or “macadamia” or “pistachios” or “walnuts” or “cashews”.

2.4.2. Data sources
The PubMed database was searched for relevant articles published through March 2013. During the development of the report, a, article entitled paper “Frequency of nut consumption and mortality risk in the PREDIMED nutrition intervention trial” was published (Guasch-Ferre et al.,
2.4.3. Study selection – number found
One thousand, three-hundred and one studies were identified from the initial defined search. Of these, 143 were review articles. After articles were filtered for human only studies, 847 articles including 143 review articles were identified.

2.5. Abstract Screening
The titles and abstracts of studies were screened to determine the relevance of the article. Articles found to be relevant were added to the list of articles meeting the inclusion criteria.

2.6. Full Article Inclusion Criteria
It was not always possible to discern whether articles met the inclusion criteria by simply reviewing the title and abstract. As a result, full text articles were evaluated for inclusion in the review.

2.7. Additional Studies Identified During Data Abstraction
Reviews, meta-analyses, and bibliographies of studies that met the inclusion criteria were hand-searched to identify additional studies. A flow diagram for the screening process for eligible studies is shown in Figure 1.

2.8. Discussion of the FDA Guidance for Inclusion of Studies to Support Health Claims
The Nutrition Labeling and Education Act of 1990 (NLEA) authorized the FDA to permit health claims on food labels so that consumers might be informed of healthy food choices. The regulations for ruling on a petition for a health claim state that a health claim characterizing a food and the risk of a disease would be permitted only if it is determined that there is significant scientific agreement among qualified experts that the claim is supported by the totality of publicly available scientific evidence. Such evidence includes that from well-designed studies conducted in a manner that is consistent with generally recognized scientific procedures and principles. The regulations include provisions of the NLEA (PL 101-535) that state that health claims must describe (1) the relationship between a given nutrient or food component and a disease or health-related condition and (2) the significance of that nutrient or food component in affecting the disease or health-related condition. One example of this type of health claim is the claim for fruits, vegetables and grain products that contain fiber, particularly soluble fiber, and reduced risk of coronary heart disease (21 CFR 101.77).

The Food and Drug Administration Modernization Act of 1997 (FDAMA) amended the Federal Food, Drug, and Cosmetics Act by providing an alternative for establishing the scientific basis for such claims by reliance on current, published authoritative statements from certain federal scientific bodies, as well as from the National Academy of Sciences. After 120 days of filing the petition for a health claim, if the FDA has not issued a regulation prohibiting such a claim, the petitioner is permitted to use the claim on the product label.
In the case of an emerging link between a food and the risk of a disease, where currently there is insufficient evidence to achieve significant scientific agreement, FDA can utilize its enforcement discretion to permit a qualified health claim (See FDA’s 2003 Consumer Health Information for Better Nutrition Initiative). The label for this type of claim would include qualifiers of the health claim to indicate that the evidence supporting the claim is limited. One example of a qualified health claim is the claim for walnuts and reduced risk of heart disease as described below.

In 2000, at the behest of the California Walnut Commission, LSRO reviewed the evidence in support of a scientific relationship between walnuts and coronary heart disease. The LSRO report conclusions included:

1) Walnuts, as part of a heart-healthy diet, lower blood cholesterol concentrations in humans and animals...

2) Walnuts have a long dietary history and continue to be readily acceptable as part of the daily diet. The clinical dietary intervention studies show that consuming walnuts does not cause a net gain in body weight when they are eaten as a replacement food.

3) The supporting human clinical walnut intervention studies suggest reduced relative risk of coronary heart disease, yet they are inconclusive because there have been only five controlled, peer-reviewed, published trials with few subjects. There are few trials of extended duration essential for critical evaluation of the sustainability of the health-beneficial outcomes and evidence of adverse effects (e.g., body weight gain and gastrointestinal intolerance). The subjects, though, were representative of the 51% of the adult population in the United States at higher risk of coronary heart disease. The existing studies, considered in their totality, suggest that walnuts, as part of a heart-healthy diet, lower blood cholesterol concentrations. This strong trend needs to be substantiated.

4) The several large human prospective observational studies, along with their respective subpopulation cohorts, all demonstrated an inverse association of the relative risk of coronary heart disease and coronary vascular disease with the frequent daily consumption of small amounts of nuts, including walnuts. This outcome is upheld for both sexes and across racial lines for all-cause mortality, with a 30–50% decreased relative risk of coronary heart disease reported.

Subsequently, the FDA approved the following wording for a qualified health claim for nuts:

Scientific evidence suggests but does not prove that eating 1.5 ounces per day of most nuts [such as name of specific nut] as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease. [See nutrition information for fat content.] and for walnuts in particular: Supportive but not conclusive research shows that eating 1.5 ounces per day of walnuts, as part of a low saturated fat and low cholesterol diet and not resulting in increased caloric intake, may reduce the risk of coronary heart disease.4

FDA has described the criteria that a study need to fulfill in order to qualify for inclusion in the evaluation of the total scientific evidence, in the document, “Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims — Final. Below are the questions that FDA considers in order to determine whether scientific conclusions can be drawn from intervention or observational studies about the substance/disease relationship and selected descriptions of FDA’s position (US Food and Drug Administration, 2009).

**Intervention Studies**
- Were the study subjects healthy or did they have the disease that is the subject of the health claim?

*FDA considers evidence from studies with subjects who have the disease that is the subject of the claim only if it is scientifically appropriate to extrapolate to individuals

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4 [Link](http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/ucm073992.htm#walnuts)
who do not have the disease. That is, the available scientific evidence demonstrates that (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations and (2) the substance affects these mechanisms in the same way in both diseased and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions from studies that used subjects that have the disease that is the subject of the health claim to evaluate the substance/disease relationship and, therefore, the agency does not intend to use these studies to evaluate the substance/disease relationship.”

“On the other hand, if, for example, FDA was reviewing a health claim on reduction of risk of coronary heart disease, it would consider studies that include individuals who have an unrelated disease (e.g., osteoporosis) or are at risk (e.g., elevated LDL cholesterol levels) of getting the disease that is the subject of the claim.”

- Was the disease that is subject of the claim measured as a "primary" endpoint?

“Intervention studies screen for prevalent cases of the disease at the beginning of the study to minimize bias.” “Uneven distribution of important patient or disease characteristics between groups may lead to mistaken interpretation (Spilker, 1991); therefore, scientific conclusions about a disease endpoint cannot be drawn from a study unless the study evaluates that outcome as a primary endpoint.”

- Did the study include an appropriate control group?

“An appropriate control group represents study subjects who did not receive the substance.”

- Was the study designed to measure the independent role of the substance in reducing the risk of a disease?

“When the intervention study involves providing a whole food rather than a food component, the experimental and control diets should be similar enough that the relationship between the substance and disease can be evaluated.”

- Were the relevant baseline data (e.g., on the surrogate endpoint) significantly different between the control and intervention group?

“If the baseline values for the endpoint being measured are significantly different, then it is difficult to interpret the findings of the intervention.”

“Providing a "lead-in" 5 diet or a "wash-out" period 6 for studies with a cross-over design for an adequate duration prior to randomization can help reduce the likelihood of different baseline values.”

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5 Footnote 21: A diet that is provided to all groups prior to randomization.
6 Footnote 22: Time period within a cross-over design study during which subjects do not receive and intervention.
• How were the intervention and control groups results statistically analyzed?

“Furthermore, when conducting statistical analyses among more than two groups, the data should be analyzed by a test designed for multiple comparisons (e.g., Bonferroni, Duncan). Thus when statistical analyses are not performed between the control and intervention group or are conducted inappropriately, scientific conclusions cannot be drawn about the role of the substance in reducing the risk of the disease and, therefore, the agency does not intend to use such studies to evaluate the substance/disease relationship.”

• What type of biomarker of disease risk was measured?

“Scientific conclusions cannot be drawn about the relationship between the substance and risk of the disease if the risk biomarker is not a surrogate endpoint (see discussion above in Section III.C). The agency does not intend to use such studies from which scientific conclusions cannot be drawn in its evaluation of the substance/disease relationship.”

• How long was the study conducted?

“If the study is run for a short time period such that the effects of the substance cannot be evaluated, then scientific conclusions cannot be drawn about the relationship between the substance and the disease and, therefore, the agency does not intend to use such a study to evaluate the substance/disease relationship.”

“For example, FDA has considered 3 weeks to be the minimum duration for evaluating the effect of an intervention with various saturated fats on serum LDL cholesterol concentration (Kris-Etherton & Dietschy, 1997).”

• If the intervention involved dietary advice, was there proper follow-up to ascertain whether the advice resulted in altered intake of the substance?

“When the dietary intervention involves dietary advice rather than a prescribed diet administered under a controlled condition, there should be some type of assessment of the changes in intake of the substance (e.g., dietary assessment or measurement of a biomarker of intake in response to dietary advice). Without some type of assessment of whether the dietary advice resulted in a change in intake of the substance, scientific conclusions cannot be drawn about the substance/disease relationship and, therefore, the agency does not intend to use studies that lack such an assessment to evaluate the substance/disease relationship.”

• Where were the studies conducted?

“It is important that the study population is relevant to the general U.S. population or the population subgroup identified in the proposed claim. Thus, FDA evaluates each
study to determine if the study population lives in an area where malnutrition or inadequate intakes of the specific substance is common, and/or where the prevalence or etiology of the disease that is the subject of the claim is not similar to that in the United States. For certain countries, there may be risk factors of a specific disease that are not relevant to disease risk in the United States (e.g., risk factors for gastric cancer in certain Asian countries). Differences in nutrition, diet, and disease risk factors between the United States and the country where a study was done may mean that the study results cannot be extrapolated to the U.S population or population subgroup. For example, scientific conclusions about the comparatively well-nourished U.S. population cannot be drawn from studies in subjects that are malnourished. Nutrient status and metabolism can be severely altered when an individual is malnourished, and therefore the effect of the substance on a particular surrogate endpoint may be very different between a malnourished and well-nourished individual (Shils et al., 2006). Scientific conclusions cannot be drawn from studies conducted in countries or regions where inadequate intake of the substance is common since a response to the intake of the substance may be due to the correction of a nutrient deficiency for which health claims are not intended.”

Observational Studies

• What type of information was collected?

“Biological samples (e.g., blood, urine, tissue, or hair) should be used to establish intake of a substance only if a dose-response relationship has been demonstrated between intake of the substance and the level of the substance (or a metabolite of the substance) in the biological sample. There should be evidence to demonstrate a strong correlation\(^ {23}\) between the intake level of the substance and the level of the substance or a metabolite in the biological sample (e.g., selenium intake and serum selenium concentration). If the correlation is weak for a specific biological sample, then scientific conclusions cannot be drawn from studies that used that biological sample as a biomarker of intake. Biological samples in case-control studies should not be used to establish intake of the substance since the metabolism or concentration of the substance may be altered in subjects as a result of the disease”.

• Were scientifically acceptable and validated dietary assessment methods used to estimate intake of the substance?

A single 24-hour diet recall or diet record is generally regarded as an inadequate method for assessing an individual's usual intake of a substance, although it may be useful for assessing mean intake of a group. A diet history involves extensive interviews with the study subjects. However, diet histories are also usually inadequate for assessing intake of a substance since respondents are asked to make

\(^ {23}\) Footnote 23: Correlation is evaluated using correlation coefficients (r). Correlation coefficients range from -1 (negative correlation) through +1 (positive correlation). The closer to 1, the stronger the correlation; the closer to zero, the weaker the correlation.
judgments about intakes of usual foods and the amounts eaten. A food frequency questionnaire contains a limited number of food items and is inadequate for assessing intake of a substance if the major sources of the substance are not included in the questionnaire. Food frequency questionnaires also do not always account for different varieties of a particular food or different cooking methods. Because of these limitations, validation of the food frequency questionnaire method to assess food intake is essential in order to be able to draw conclusions from the scientific data, as the failure to validate may lead to false associations between dietary factors and diseases or disease-related markers.\textsuperscript{24,8}

- Did the observational study evaluate the relationship between a disease and a food or a food component?

“Because observational studies estimate intake of a whole food based on recorded dietary intake methods such as food frequency questionnaires, diet recalls, or diet records, a common weakness of observational studies is the limited ability to ascertain the actual intake of the substance for the population studied. Furthermore, if the substance is a food component rather than a whole food, there is an additional estimation of the amount of the food component that is present in the individual foods. The content of foods' components can vary based on factors such as soil composition, food processing/cooking procedures, or storage (duration, temperature). Thus, it is difficult to ascertain an accurate amount of the food component consumed based on reports of dietary intake of whole foods.”

“In addition, the whole food and products that include several food components, e.g., multi-nutrient dietary supplements, contain not only the food component that is the subject of the claim, but also other food components that may be associated with the metabolism of the food component of interest or the pathogenesis of the disease or health-related condition. Because whole foods and products such as multi-nutrient dietary supplements consist of many food components, it is difficult to study the food components in isolation (Sempos et al., 1999). For studies based on recorded dietary intake of whole foods or multiple food components, it is not possible to accurately determine whether any observed effects of the food component that is the subject of the claim on disease risk were due to: (1) that food component alone; (2) interactions with other food components; (3) other food components acting alone or together; or (4) decreased consumption of other substances contained in foods displaced from the diet by the increased intake of foods rich in the food component of interest (See (Sempos et al., 1999; Willett, 1990) and (Willett, 1998) regarding the complexity of identifying the relationship between a specific food component within a food and a disease).”

\textsuperscript{8} Footnote 24: “Validation of the food frequency questionnaire method is essential, as incorrect information may lead to false associations between dietary factors and disease or disease-related markers.”(Cade et al., 2002; Subar et al., 2001)
2.8.1. Narrow analysis
FDA considers Tot-C, LDL-C and BP to be validated surrogate endpoints for CVD (Rasnake et al., 2008); therefore, only studies that included the effects of consumption of nuts on CVD outcomes or on these endpoints and met the other FDA criteria for inclusion listed above were assessed in the narrow analysis. Studies conducted on hypercholesterolemic individuals were permitted; however, if studies included subjects who were medicated for hypercholesterolemia, lipid outcomes were not included. Similarly, for those studies in which subjects were treated with drugs for hypertension, hypertension outcomes were not included.

2.8.2. Broader analysis
The panel identified other suspected risk factors and intermediate markers for CVD. These include HDL-C, Tot-C:HDL-C, TG, lipoprotein (a) [LP(a)], Apo A1, Apo B, Apo B-100, CRP, fibrinogen, factors VII, VIII, and von Willebrand factor, platelet aggregation and risk factors for diabetes, including, hemoglobin A1c, fasting blood sugar, and fasting insulin. Of these, the panel considered HDL-C, Tot-C:HDL-C, TG, Apo A1, Apo B, Apo B-100, and CRP to be the most reliable unvalidated biomarkers of CVD.

Intermediate markers of CVD include carotid artery intima-media thickness (IMT), carotid artery plaque formation, coronary artery calcification, exercise tolerance testing, heart rate variability, flow-mediated dilation and other measures of blood flow. The panel considers carotid artery IMT, carotid artery plaque formation, and coronary artery calcification to be the most reliable intermediate markers of CVD.

In summary, the broad analysis included studies that investigated the effects of nut consumption on CVD endpoints and validated biomarkers for CVD using what the panel considered to be the most reliable unvalidated biomarkers of CVD (HDL-C, Tot-C:HDL-C, TG, Apo A1, Apo B, Apo B-100, and CRP). Searches were conducted for studies investigating the effect of tree nut consumption on the most reliable intermediate markers of CVD (carotid artery IMT, carotid artery plaque formation, coronary artery calcification).

The panel was also of the opinion that although weight gain and obesity are not surrogate endpoints for CVD risk, the evidence for an association between nut intake and obesity should also be reviewed.

2.8.3. Reasons for including the broader analysis (health status, unvalidated biomarkers and other intermediate endpoints)

There was a consensus among the panel that FDA’s evidence-based review criteria for study inclusion and for weighing the strength of the total scientific evidence could lead to the exclusion of information that might prove insightful from a clinical perspective. Consequently, the panel decided to summarize and evaluate the evidence in two ways: (1) using comparatively restrictive determinants of evidence (following FDA guidance) and (2) using the panel’s comparatively more inclusive determinants which would include some studies FDA might likely exclude in their evaluation of evidence.
As noted above, the panel decided that studies that included individuals who met the criteria for obesity, or metabolic syndrome, or were diabetic should be included in the review as long as the study participants had not been diagnosed with CVD, and were not taking CVD, antihypertensive, or antihyperlipidemic medication.

Cardiovascular disease accounted for an estimated 35% of the proportional mortality in 2008 (% of total death, all ages) (WHO-NCD Country Profiles, 2011). In 2010, the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) reported that ischemic heart disease and stroke were responsible for 1 in 4 deaths (12.9 million people worldwide) (Lozano et al., 2012). WHO identified the two leading causes of death as ischemic heart disease and stroke in 2011 (WHO Causes of Death 2000-2011). The IOM Report on Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease (2010) evaluated selected biomarkers for their criteria of (1) analytical validity, (2) qualification, (3) utilization: possible uses, and (4) utilizations: surrogate endpoint use. The report stated that the biomarker must be statistically correlated to the clinical endpoint and should account for all of the intervention’s effects (Institute of Medicine, 2010). The expert panel was of the opinion that because CVD is a cause of mortality and morbidity, both validated biomarkers and unvalidated biomarkers should be used in a broad assessment of the effect of nut consumption on CVD risk.

The panel sought to use the Bradford Hill Criteria to assess the strength of the evidence for a relationship between tree nut consumption and CVD risk (Hill, 1965). Using this framework, the data were assessed with respect to:

1. strength of the association: Is there a large change in relative risk of CVD associated with consumption of tree nuts?
2. consistency: Has the effect of tree nut consumption on risk of CVD been observed by different persons, in different places, circumstances, and times?
3. specificity of the association: Is there a unique relationship between tree nut consumption and risk of CVD?
4. temporality: Does consumption of tree nuts precede a change in risk of CVD?
5. biological gradient: Is there evidence of a dose-response relationship between consumption of tree nuts and risk of CVD?
6. biological plausibility: Is there biological knowledge that supports the relationship between tree nut consumption and risk of CVD?
7. coherence: “the cause-and effect interpretation of our data should not seriously conflict with the generally known facts”
8. experiment: Is there experimental or semi-experimental evidence that supports the relationship between tree nut consumption and risk of CVD?
9. analogy: Is there supporting evidence of the relationship between tree nuts and risk of CVD from another similar substance?

### 2.8.4. Data extraction

The approach used for evaluating the quality of the included studies was the American Dietetic Association Evidence Analysis Process (Research and Strategic Business Development, 2012). This is a bipartite process in which an evidence analysis worksheet (EAW) is used to abstract key information about the study and a quality control checklist (QCC) is used to assess the
quality of the study. Study design was categorized as follows: (1) randomized, controlled trials, cluster randomized trials, or randomized, crossover trials were categorized as “Class A”, (2) prospective and retrospective cohort studies were categorized as “Class B”, (3) non-randomized controlled trials, non-randomized crossover trials, case-control studies, time series studies, and diagnostic validity or reliability studies, were categorized as “Class C”, and (4) non-controlled trials, case studies or case series, other descriptive studies, cross-sectional studies, trend studies, and before-after studies were categorized as “Class D” (Research and Strategic Business Development, 2012).

The EAW also included information about the purpose of the research study, the inclusion and exclusion criteria, study protocol, intervention(s), regimens, risk factors, and procedure methods. Information was also provided about the timing of measurement of outcomes and how the intervening factors were managed. Study results were reported, including the variables measured and method of measurement used. The descriptions of the sample and comparison groups at baseline, the number of subjects who withdrew from the study and the dropouts were noted. Relevant results, including quantitative data and statistics were extracted and tabulated in most instances and P values, confidence intervals, relative risk, odds ratios, likelihood ratios, and the number need to treat were indicated where available. The authors’ conclusions were noted and an assessment of the strengths and limitations of the study was made. Comments were made about factors that could affect study validity and generalizability. The funding source(s) of the study was also noted to assess the potential for conflict of interest (Research and Strategic Business Development, 2012).

2.8.5. Grading the evidence

Study details were concurrently extracted and noted in the EAW and critically assessed in terms of their relevance and validity to the key questions of the review using a quality control checklist (QCC) to evaluate the research design and implementation (Research and Strategic Business Development, 2012).

The relevance of each study was assessed by answering the following questions:

1. Would implementation of the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group)?
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?
4. Is the intervention or procedure feasible?

Studies that did not provide a positive response to the above questions were not considered to be relevant and were not evaluated. The validity of relevant studies was assessed by answering the following questions:

1. Was the research question clearly stated?
2. Was the selection of study subjects/patients free from bias?
3. Were study groups comparable?
4. Was the method of handling withdrawals described?
5. Was blinding used to prevent introduction of bias?
(6) Were intervention/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?
(7) Were outcomes clearly defined and the measurements valid and reliable?
(8) Was the statistical analysis appropriate for the study design and type of outcome indicators?
(9) Are conclusions supported by results with biases and limitations taken into consideration?
(10) Is bias due to study’s funding or sponsorship unlikely?

Each validity question included multiple sub-questions. Answers to the sub-questions determine the answer for the validity question. Each validity question was awarded a grade of positive (+), neutral (Ø), negative (–), or unclear (U). Studies that received a positive rating for 6 or more validity questions, including questions 2, 3, 6, and 7 were designated as positive. Studies for which answers to the validity criteria 2, 3, 6, and 7 did not suggest that the study was unusually strong were given a quality rating of neutral (Ø). If six or more of the validity questions were “No”, the study was given a negative validity score.

3. Summarizing the Evidence

3.1. Results
3.1.1. Results of the literature search

Analyses of 94 studies meeting the inclusion criteria were identified. (See Section 8 for complete listing of included studies). We have used the term “analyses” because some articles included more than one analysis of data as they described the effect of consumption of more than one type of nut, the effect of consumption of more than one dose of one type of nut, the response of different populations to nuts, or multiple studies on the effect of nuts in different populations.

3.1.1.1. Interventional Study Analyses
Analyses of 67 interventional studies met the broad inclusion criteria for this review (See Section 8).

3.1.1.2. Observational Study Analyses
Twenty-seven observational studies met the broad inclusion criteria in this review (See Section 8 for included studies).

3.2. Primary Cardiovascular Disease Outcomes
Interventional and observational studies meeting the inclusion for primary cardiovascular disease outcomes, validated biomarkers, and other biomarkers are discussed below.

3.2.1. Interventional analyses
No interventional studies reported on primary disease outcomes.

3.2.2. Observational analyses

3.2.2.1 Total coronary heart disease (Total CHD)
Six analyses of data from two prospective cohort studies with positive quality ratings, the Adventist Health Study (AHS) and the Nurses Health Study (NHS), reported an inverse association between nut consumption and the risk of Total CHD (Bernstein et al., 2010; Fraser et al., 1992; Fraser et al., 1995; Fraser, 1999; Hu et al., 1998; Li et al., 2009). These analyses reported 5,057 incident cases (with likely duplication) and up to 26 years of exposure (Table 1; Figure 2).

3.2.2.2. Fatal coronary heart disease (Fatal CHD)

Twelve analyses of data from four prospective cohort studies: the AHS, NHS, Physician’s Health Study (PHS), and Iowa Women’s Health Study (IWHS), all with positive quality ratings, investigated the association between nut consumption and Fatal CHD. Nine analyses reported an inverse association between nut consumption and Fatal CHD (Albert et al., 2002; Blomhoff et al., 2006; Fraser et al., 1992; Fraser, 1999; Fraser & Shavlik, 1997; Hu et al., 1998; Kushi et al., 1996; Prineas et al., 1993) with Albert et al. (2002) reporting inverse associations for both total fatal CHD and sudden CHD). Only the non-sudden CHD death sub-analysis of the PHS (Albert et al., 2002), an analysis of the IWHS (Ellsworth et al., 2001), and an analysis of the NHS (Baer et al., 2011) did not attain a statistically significant result. In total, these analyses report 3,960 incident cases (with likely duplication) and up to 26 years of exposure. (Figure 2)
<table>
<thead>
<tr>
<th>Reference</th>
<th>QR</th>
<th>Trial Design</th>
<th>Dietary assessment tool used</th>
<th>Sample Size</th>
<th>Duration (year(s))</th>
<th>Gender</th>
<th>Age (y)</th>
<th>Nut(s)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albert et al. 2002</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>21454 PHS</td>
<td>17</td>
<td>M</td>
<td>53.1</td>
<td>Not specified</td>
<td>None, 1–3/mo, 1/wk, ≥2/wk</td>
</tr>
<tr>
<td>Baer et al. 2011</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>50112 NHS</td>
<td>18</td>
<td>F</td>
<td>52.5 ± 7.1</td>
<td>Not specified</td>
<td>None, ≤1/wk, ≥2/wk</td>
</tr>
<tr>
<td>Bernstein et al. 2010</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>84136 NHS</td>
<td>26</td>
<td>F</td>
<td>58</td>
<td>Not specified</td>
<td>0.00/d, 0.04/d, 0.07/d, 0.12/d, 0.40/d</td>
</tr>
<tr>
<td>Blomhoff et al. 2006</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>34411 IWHS</td>
<td>15</td>
<td>F</td>
<td>61.6 ± 9.4; 40.7–87.1</td>
<td>Nuts and peanut butter</td>
<td>0, &lt;1/wk, 1–4/wk, ≥5/wk</td>
</tr>
<tr>
<td>Djoussé et al. 2008</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>20976 PHS</td>
<td>19.6</td>
<td>M</td>
<td>54.6 ± 9.4; 40.7–87.1</td>
<td>Not specified</td>
<td>None, &lt;1, 1, or ≥2 1 oz servings/wk</td>
</tr>
<tr>
<td>Ellsworth et al. 2001</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>34411 IWHS</td>
<td>11</td>
<td>F</td>
<td>61.6 ± 69</td>
<td>Nuts and seeds</td>
<td>&lt;1/mo, 1–3/mo, 1/wk, ≥2/wk</td>
</tr>
<tr>
<td>Fraser et al. 1992</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>26473 AHS</td>
<td>6</td>
<td>M &amp; F</td>
<td>52.5 ± 16</td>
<td>Not specified</td>
<td>1/wk, 1–4/wk, and ≥5/wk</td>
</tr>
<tr>
<td>Fraser et al. 1995</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>27321 AHS</td>
<td>6</td>
<td>M &amp; F</td>
<td>52.5 ± 16</td>
<td>Not specified</td>
<td>1/wk, 1–4/wk, and ≥5/wk</td>
</tr>
<tr>
<td>Fraser et al. 1997</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>26473 AHS</td>
<td>12</td>
<td>M &amp; F</td>
<td>≥ 84</td>
<td>Not specified</td>
<td>1/wk, 1–4/wk, and ≥5/wk</td>
</tr>
<tr>
<td>Fraser et al. 1999</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>26473 AHS</td>
<td>6</td>
<td>M &amp; F</td>
<td>53.1 M; 55 F</td>
<td>Not specified</td>
<td>1/wk, 1–4/wk, and ≥5/wk</td>
</tr>
<tr>
<td>Reference</td>
<td>QR</td>
<td>Trial Design</td>
<td>Dietary assessment tool used</td>
<td>Sample Size</td>
<td>Duration year(s)</td>
<td>Gender</td>
<td>Age (y)</td>
<td>Nut(s)</td>
<td>Dose</td>
</tr>
<tr>
<td>------------------------</td>
<td>----</td>
<td>--------------</td>
<td>------------------------------</td>
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<td>------------------</td>
<td>--------</td>
<td>---------</td>
<td>--------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>He et al. 2003</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>43732 HPFS</td>
<td>14 M</td>
<td>Not specified</td>
<td>40–75</td>
<td>&lt;1/wk, 1 wk, 2–4/wk, 5–6/wk, and ≥ 1/d</td>
<td></td>
</tr>
<tr>
<td>Kushi et al. 1996</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>34486 IWHS</td>
<td>7 F</td>
<td>61.6 55–69</td>
<td>Nut + seeds</td>
<td>0, 1–2, 3–4, &gt;4 svgs/mo</td>
<td></td>
</tr>
<tr>
<td>Li et al. 2009</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>6309 NHS</td>
<td>22 F</td>
<td>57.1 ± 9</td>
<td>Tree nuts + peanuts</td>
<td>Almost/never, 1–3 svgs/mo to 1 svgs/wk, 2–4 svgs/wk, &gt;5 svgs/wk</td>
<td></td>
</tr>
<tr>
<td>Nettleton et al. 2008</td>
<td>Ø</td>
<td>PC</td>
<td>FFQ</td>
<td>14153</td>
<td>24 M &amp; F</td>
<td>54.1</td>
<td>Not specified</td>
<td>1 svg/d</td>
<td></td>
</tr>
<tr>
<td>Panagiotakos et al. 2009</td>
<td>+</td>
<td>XS</td>
<td>FFQ</td>
<td>3042 N/A</td>
<td>5 M &amp; F</td>
<td>45.3</td>
<td>Nuts with salt or Nuts without salt</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Panagiotakos et al. 2009</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>3042</td>
<td>5 M &amp; F</td>
<td>45.3</td>
<td>Nuts with salt or Nuts without salt</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Prineas et al. 1993</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>34484 IWHS</td>
<td>5 F</td>
<td>61.6 55–69</td>
<td>Not specified</td>
<td>No Nuts; 1–3/wk; 1/wk; 2–4/wk</td>
<td></td>
</tr>
</tbody>
</table>

CARDIA: Coronary Artery Risk Development in Young Adults; F: Female; FFQ: Food frequency questionnaire; HPFS: Health Professionals Follow-up Study; IWHS: Iowa Women's Health Study; IHD: ischemic heart disease; M: Male; MESA: Multi-Ethnic Study of Atherosclerosis; MI: Myocardial infarction; N: No effect; N/A: Not applicable; NHANES: National Health and Nutrition Examination Survey; NHS: Nurses Health Study; PC: Placebo-controlled; PHS: Physicians Health Study; SBP: Systolic blood pressure; AHS: Adventist Health Study; SU.VI.MAX: Supplementation en Vitamines et Minéraux Antioxydants study; QR: Quality rating; Wt: Weight; XS: Cross-sectional
Figure 2: Observational studies reporting the relative risk of CHD, stroke, heart failure and all cause mortality
3.2.2.3. Total cardiovascular disease (Total CVD)
Four analyses addressed the effect of nut consumption on Tot CVD. Two analyses, both of which were prospective cohort studies with positive quality ratings, reported an inverse association between nut consumption and the risk of Tot CVD (Figure 2). One analysis reported on the IWHS cohort (Blomhoff et al., 2006) and the other reported on the NHS cohort (Li et al., 2009) (Figure 2). Two analyses of a prospective cohort study (Panagiotakos et al., 2009) reported on the association of baseline dietary characteristics of the ATTICA cohort and Tot CVD. Because it was not possible to depict these data in Figure 2 they are described only in the text. (Panagiotakos et al., 2009) reported that individuals with incident CVD over the 5-yr follow up consumed 1.7 ± 1.8 servings of nuts with salt compared with 1.0 ± 1.1 servings for those without CVD events (p=0.05). This result differs from those of other observational studies in which higher nut consumption was associated with a decreased risk of CVD. In contrast, Panagiotakos et al. (2009), reported those with incident CVD over the 5-yr follow up consumed 0.4 ± 1.3 servings of nuts without salt compared with 0.5 ± 1.2 servings for those without CVD events (p=0.34).

3.2.2.4. Nonfatal myocardial infarction
Two analyses addressed the effect of nut consumption on nonfatal myocardial infarction. Both were prospective cohort studies with positive quality ratings (Figure 2). One analysis reported on the PHS cohort and found a positive, non-significant association (Albert et al., 2002) and the other reported on the IWHS cohort and found a significant inverse association (Hu et al, 1998).

3.2.2.5. Stroke
One analysis of the Health Professionals Follow-up Study (HPFS) reported no association between nut consumption and the risk of stroke. This was a prospective cohort study of positive quality rating (He et al., 2003) (Figure 2).

3.2.2.6. Heart failure
Two prospective cohort studies reported no association between nut consumption and the risk of heart failure. One study with a positive quality rating reported on the PHS cohort (Djoussé et al., 2008) and the other study, which had a neutral quality rating, reported on the ARIC cohort (Nettleton et al., 2008) (Figure 2).

3.2.2.7. All cause mortality
Four analyses reported an inverse association between nut consumption and all cause mortality. All were prospective cohort studies with a positive quality rating and represent three cohorts, the AHS (Fraser & Shavlik, 1997), the NHS (Baer et al., 2011), and the IWHS (Blomhoff et al., 2006; Ellsworth et al., 2001) (Figure 2).

3.2.2.8. Hypertension
The association between nut consumption and the risk of hypertension was examined in 5 analyses, all of which received a positive quality rating. Four analyses found an inverse association: two examined data from prospective cohort studies (PHS and the CARDIA study) (Djoussé et al., 2009; Steffen et al., 2005) and two examined data from cross-sectional studies (SU.VI.MAX study and the NHANES population) (Lairon et al., 2005; O'Neil et al., 2012). One prospective cohort study that analyzed data from the SUN population did not find an association between nut consumption and risk of hypertension (Martinez-Lapiscina et al., 2010) (Figure 3).
### Hypertension

<table>
<thead>
<tr>
<th>Reference</th>
<th>Quality Rating</th>
<th>Study Design</th>
<th>Dietary assessment tool</th>
<th>Sample Size</th>
<th>Dose Comparison</th>
<th>Incident Cases</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Djoussé et al. 2009 (PHS)</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>15,966</td>
<td>≥ 2, 1 oz svg/wk vs None</td>
<td>8423*</td>
<td>0.014</td>
</tr>
<tr>
<td>Lairon et al. 2005 (SU.VI.MAX)</td>
<td>+</td>
<td>XS</td>
<td>Multiple 24-h dietary recalls</td>
<td>5,961</td>
<td>&gt; 0.56 g fiber vs &lt; 0.05 g</td>
<td>NR</td>
<td>0.014</td>
</tr>
<tr>
<td>Martínez-Lapiscina et al. 2010 (SUN)</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>9919</td>
<td>&gt; 2 svg/wk vs Never</td>
<td>542</td>
<td>0.746</td>
</tr>
<tr>
<td>O’Neil et al. 2012 (NHANES)</td>
<td>+</td>
<td>XS</td>
<td>NHANES surveys</td>
<td>24,385</td>
<td>≥ ¼ oz vs &lt; ¼ oz</td>
<td>875*</td>
<td>NR</td>
</tr>
<tr>
<td>Steffen et al. 2005 (CARDIA)</td>
<td>+</td>
<td>PC</td>
<td>Diet history interviewer-administered</td>
<td>4,304</td>
<td>&gt; 0.3 times/d vs &lt; 0.1 times/d</td>
<td>591</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Number of cases in highest category

Hypertension is defined as: Djoussé et al. 2009, ≥ 140 mm Hg or ≥ 90 mm Hg or hypertensive medication; Lairon et al. 2005, ≥ 140 mm Hg or ≥ 90 mm Hg or hypertensive medication; Martínez-Lapiscina et al. 2010, ≥ 140 mm Hg or ≥ 90 mm Hg or hypertensive medication; O’Neill et al. 2012, ≥ 140 mm Hg or ≥ 90 mmHg; Steffen et al. 2005, ≥ 130 mm Hg or ≥ 85 mm Hg or hypertensive medication.
3.3. Validated Biomarkers

Seventy-six analyses of interventional studies meeting the criteria for inclusion in this review measured the effect of nut consumption on Tot-C. In this review, the numbers in parentheses denote the percentage of number of analyses measuring that biomarker. Forty-three (57%) reported a significant negative difference compared with control and 33 (43%) reported a non-significant difference compared with control. No analyses reported a significant positive difference compared with control.

Seventy-four analyses of interventional studies meeting the criteria for inclusion in this review reported on the effect of tree nut consumption on LDL-C. Forty analyses (54%) reported a significant negative difference compared with control, one (1%) reported a significant positive difference, and (33 %) reported a non-significant difference.

Twenty-six analyses of interventional studies meeting the criteria for inclusion in the review investigated the effect of nut consumption on systolic blood pressure. Two (8%) reported a significant negative difference compared with control, one (4%) reported a significant positive difference, and twenty-three (88%) reported a non-significant difference.

Twenty-four interventional study analyses meeting the criteria for inclusion reported on the effect of nut consumption on diastolic blood pressure (DBP). One analysis reported a significant negative difference (4%) compared with control, one reported a significant positive difference (4%) and 22 analyses (92%) reported no significant difference between nut intervention and DBP.

3.3.1. Intervventional study analyses

3.3.1.1. Narrow: Intervritional study analyses meeting the FDA criteria

Analyses that met the expert panel’s criteria for inclusion in the review were evaluated to determine whether they met FDA’s criteria. For all studies that met the FDA criteria, nut intervention values were compared with control intervention values for Tot-C, LDL-C, SBP, or DBP.

**Tot-C**

Fifty-three interventional study analyses meeting the FDA criteria investigated the effect of nut consumption on Tot-C concentration. Twenty-nine analyses (55% of analyses meeting the FDA criteria) of which 19 received a positive quality rating, 10 received a neutral quality rating, and none received a negative quality rating, reported a significant negative difference between the nut intervention and control (Figure 4, Appendix A). No analyses meeting the FDA criteria for inclusion reported a significant positive difference between the nut intervention and control. Of the 24 analyses (45% of analyses meeting the FDA criteria) that reported no significant difference between the intervention group and the control group, 12 had a positive quality rating, 12 had a neutral quality rating, and none had a negative quality rating (Table 2).
Table 2. Interventional Study Analyses Meeting the Criteria for Inclusion in the Review that Measured Total-C, LDL-C, SBP, and DBP

<table>
<thead>
<tr>
<th>Reference</th>
<th>Quality Rating</th>
<th>Study Design</th>
<th>Nut(s)</th>
<th>Placebo or Comparator</th>
<th>Intervention Duration (wk)</th>
<th>Final N</th>
<th>Tot-C Diff</th>
<th>p</th>
<th>LDL-C Diff</th>
<th>p</th>
<th>Systolic BP Diff</th>
<th>p</th>
<th>Diastolic BP Diff</th>
<th>p</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbey, et al. 1994 (nut)</td>
<td>Ø</td>
<td>NCT</td>
<td>Almonds</td>
<td>Habitual (Australian) w/peanuts and coconut</td>
<td>3</td>
<td>16</td>
<td>-0.36</td>
<td>0.01</td>
<td>-0.37</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Abbey, et al. 1994 (nut)</td>
<td>Ø</td>
<td>NCT</td>
<td>Walnuts</td>
<td>Habitual (Australian) w/peanuts and coconut</td>
<td>3</td>
<td>16</td>
<td>-0.25</td>
<td>0.01</td>
<td>-0.32</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Aldemir et al. 2011</td>
<td>Ø</td>
<td>NCT</td>
<td>Pistachios</td>
<td>Habitual diet</td>
<td>3</td>
<td>17</td>
<td>-0.81</td>
<td>0.01</td>
<td>-0.55</td>
<td>0.007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Almaro et al. 2001 (diet)</td>
<td>Ø</td>
<td>NRCOT</td>
<td>Walnuts</td>
<td>Habitual diet</td>
<td>6</td>
<td>18</td>
<td>-0.18</td>
<td>NS</td>
<td>0.06</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Almaro et al. 2001 (diet)</td>
<td>Ø</td>
<td>NRCOT</td>
<td>Walnuts</td>
<td>Low fat diet</td>
<td>6</td>
<td>18</td>
<td>-0.45</td>
<td>0.01</td>
<td>-0.45</td>
<td>0.0125</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Casas-Agustench et al. 2011</td>
<td>+</td>
<td>RCOT</td>
<td>Walnuts, Almonds, &amp; Hazelnuts</td>
<td>Healthy diet</td>
<td>12</td>
<td>50</td>
<td>-0.12</td>
<td>NS</td>
<td>-0.11</td>
<td>NS</td>
<td>12</td>
<td>NS</td>
<td>5</td>
<td>NS</td>
<td>Y</td>
</tr>
<tr>
<td>Chisholm et al. 1999</td>
<td>–</td>
<td>RCOT</td>
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## DRAFT FINAL REPORT
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<td>Ø</td>
<td>RCT</td>
<td>Cashews</td>
<td>63–108 g/d (20% of energy)</td>
<td>Isoenergetic controlled diet</td>
<td>8</td>
<td>64</td>
<td>-0.88</td>
<td>NS</td>
<td>-0.52</td>
<td>NS</td>
<td>-5</td>
<td>NS</td>
<td>-3.6</td>
<td>NS</td>
<td>Y</td>
</tr>
<tr>
<td>Munoz et al. 2001</td>
<td>+</td>
<td>RCOT</td>
<td>Walnut</td>
<td>50 g/d (38% total energy from OO/MUF A)</td>
<td>Isoenergetic controlled (Mediterranean) diet</td>
<td>6</td>
<td>10</td>
<td>-0.28</td>
<td>NS</td>
<td>-0.29</td>
<td>NS</td>
<td>Y</td>
<td></td>
<td></td>
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<tr>
<td>Olmedilla-Alonso et al. 2008</td>
<td>Ø</td>
<td>RCOT</td>
<td>Walnuts</td>
<td>19.4 g/d</td>
<td>Habitual diet + red meat w/o walnuts</td>
<td>5</td>
<td>25</td>
<td>-0.18</td>
<td>0.027</td>
<td>-0.12</td>
<td>NS</td>
<td>-5</td>
<td>NS</td>
<td>-1.3</td>
<td>NS</td>
<td>Y</td>
</tr>
<tr>
<td>Orem et al. 2013</td>
<td>+</td>
<td>NRCOT</td>
<td>Hazelnuts</td>
<td>49–86 g/d (18%–20% of energy)</td>
<td>Isoenergetic NCEP step 2 diet</td>
<td>4</td>
<td>21</td>
<td>-0.47</td>
<td>&lt;0.05</td>
<td>-0.26</td>
<td>&lt;0.05</td>
<td>Y</td>
<td></td>
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<td>Perez-Martinez et al. 2011</td>
<td>Ø</td>
<td>RCOT</td>
<td>Walnuts</td>
<td>High CHO enriched w/ALNA diet</td>
<td>Controlled (Western) diet</td>
<td>4</td>
<td>20</td>
<td>-0.34</td>
<td>0.05</td>
<td>-0.23</td>
<td>0.05</td>
<td>Y</td>
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<td></td>
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<tr>
<td>Rajaram et al. 2001</td>
<td>+</td>
<td>RCOT</td>
<td>Pecans</td>
<td>72 g/d (20% of energy)</td>
<td>Controlled, isoenergetic, Ste p I diet</td>
<td>4</td>
<td>23</td>
<td>-0.57</td>
<td>≤0.001</td>
<td>-0.54</td>
<td>≤0.001</td>
<td>Y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rajaram et al. 2009</td>
<td>Ø</td>
<td>RCOT</td>
<td>Walnuts</td>
<td>42.5 g/d</td>
<td>Controlled (American) diet w/o nuts</td>
<td>4</td>
<td>25</td>
<td>-0.27</td>
<td>&lt;0.0001</td>
<td>-0.29</td>
<td>&lt;0.001</td>
<td>Y</td>
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<tr>
<td>Ros et al. 2004</td>
<td>+</td>
<td>RCT</td>
<td>Walnuts</td>
<td>40 to 65 g/d (18% of the energy)</td>
<td>Controlled (Mediterranean) diet</td>
<td>4</td>
<td>20</td>
<td>-0.29</td>
<td>0.02</td>
<td>-0.31</td>
<td>0.010</td>
<td>0</td>
<td>NS</td>
<td>2</td>
<td>NS</td>
<td>Y</td>
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<td>Quality Rating</td>
<td>Study Design</td>
<td>Nut(s)</td>
<td>Dose</td>
<td>Placebo or Comparator</td>
<td>Intervention Duration (wk)</td>
<td>Final N</td>
<td>Diff</td>
<td>p</td>
<td>Diff</td>
<td>p</td>
<td>Diff</td>
<td>p</td>
<td>Diff</td>
<td>p</td>
<td>Diff</td>
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<tr>
<td>Sabaté et al. 1993</td>
<td>+</td>
<td>RCT</td>
<td>Walnuts</td>
<td>84 g/d</td>
<td>Isoenergetic controlled (NCEP Step 1) diet</td>
<td>4</td>
<td>18</td>
<td>-0.57</td>
<td>&lt;0.001</td>
<td>-0.47</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Sabaté et al. 2003 (dose)</td>
<td>+</td>
<td>RCOT</td>
<td>Almonds</td>
<td>34g (10% energy of diet)</td>
<td>Isoenergetic controlled diet</td>
<td>4</td>
<td>25</td>
<td>-0.05</td>
<td>NS</td>
<td>-0.04</td>
<td>NS</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sabaté et al. 2003 (dose)</td>
<td>+</td>
<td>RCOT</td>
<td>Almonds</td>
<td>68g (20% energy of diet)</td>
<td>Isoenergetic controlled diet</td>
<td>4</td>
<td>25</td>
<td>-0.24</td>
<td>&lt;0.001</td>
<td>-0.26</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
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<tr>
<td>Sari et al. 2010</td>
<td>Ø</td>
<td>NRCOT</td>
<td>Pistachios</td>
<td>60–100 g/d (20% of energy)</td>
<td>Control (Mediterranean) diet</td>
<td>4</td>
<td>32</td>
<td>-1.07</td>
<td>&lt;0.001</td>
<td>-0.76</td>
<td>&lt;0.001</td>
<td>-2</td>
<td>NS</td>
<td>-8</td>
<td>&lt;0.001</td>
<td>Y</td>
</tr>
<tr>
<td>Schutte et al. 2006 (nut)</td>
<td>–</td>
<td>RCT</td>
<td>Walnuts</td>
<td>63–108 g/d (20% of energy)</td>
<td>Isoenergetic controlled (habitual) diet w/o nuts</td>
<td>8</td>
<td>62</td>
<td>-3</td>
<td>NS</td>
<td>0.1</td>
<td>NS</td>
<td></td>
<td>Y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schutte et al. 2006 (nut)</td>
<td>–</td>
<td>RCT</td>
<td>Cashews</td>
<td>63–108 g/d (20% of energy)</td>
<td>Isoenergetic controlled (habitual) diet w/o nuts</td>
<td>8</td>
<td>62</td>
<td>-4</td>
<td>NS</td>
<td>-3.0</td>
<td>NS</td>
<td></td>
<td>Y</td>
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<tr>
<td>Sheridan et al. 2007</td>
<td>+</td>
<td>RCOT</td>
<td>Pistachios</td>
<td>56–84 g/d</td>
<td>Habitual diet w/o nuts</td>
<td>4</td>
<td>15</td>
<td>-0.23</td>
<td>NS</td>
<td>-0.39</td>
<td>NS</td>
<td>3.0</td>
<td>NS</td>
<td>3.0</td>
<td>NS</td>
<td>Y</td>
</tr>
<tr>
<td>Solá et al. 2012</td>
<td>+</td>
<td>RCT</td>
<td>Hazelnuts</td>
<td>30 g/d + cocoa</td>
<td>Isoenergetic controlled (Spanish) diet + cocoa</td>
<td>4</td>
<td>102</td>
<td>0.05</td>
<td>NS</td>
<td>0.02</td>
<td>NS</td>
<td>7.6</td>
<td>NS+</td>
<td>1.9</td>
<td>0.04</td>
<td>Y</td>
</tr>
<tr>
<td>Spaccarotella et al. 2008</td>
<td>Ø</td>
<td>RCOT</td>
<td>Walnuts</td>
<td>75 g/d</td>
<td>Habitual (American) diet</td>
<td>8</td>
<td>20</td>
<td>-0.16</td>
<td>NS</td>
<td>0.00</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Spiller et al 1998</td>
<td>+</td>
<td>RCT</td>
<td>Almonds</td>
<td>100 g/d</td>
<td>OO enriched habitual (American) diet</td>
<td>4</td>
<td>45</td>
<td>-1.06</td>
<td>&lt;0.001</td>
<td>-0.85</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Spiller et al. 1992</td>
<td>Ø</td>
<td>NCT</td>
<td>Almonds</td>
<td>100 g/d</td>
<td>Habitual (American) diet</td>
<td>9</td>
<td>26</td>
<td>-0.54</td>
<td>&lt;0.05</td>
<td>-0.49</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Spiller et al. 2003 (nut)</td>
<td>Ø</td>
<td>NCT</td>
<td>Almonds (raw)</td>
<td>100 g/d</td>
<td>Habitual (American) diet</td>
<td>4</td>
<td>38</td>
<td>-0.44</td>
<td>&lt;0.01</td>
<td>-0.49</td>
<td>&lt;0.002</td>
<td>-1</td>
<td>NS</td>
<td>-1</td>
<td>NS</td>
<td>N</td>
</tr>
<tr>
<td>Spiller et al. 2003 (nut)</td>
<td>Ø</td>
<td>NCT</td>
<td>Almonds (roasted)</td>
<td>100 g/d</td>
<td>Habitual (American) diet</td>
<td>4</td>
<td>38</td>
<td>-0.31</td>
<td>&lt;0.034</td>
<td>-0.28</td>
<td>&lt;0.012</td>
<td>1</td>
<td>NS</td>
<td>1</td>
<td>NS</td>
<td>N</td>
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<td>Reference</td>
<td>Quality Rating</td>
<td>Study Design</td>
<td>Nut(s)</td>
<td>Dose</td>
<td>Placebo or Comparator</td>
<td>Intervention Duration (wk)</td>
<td>Final N</td>
<td>Diff</td>
<td>p</td>
<td>Diff</td>
<td>p</td>
<td>Diff</td>
<td>p</td>
<td>Diff</td>
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</tr>
<tr>
<td>Tapsell et al. 2004</td>
<td>+</td>
<td>RCT</td>
<td>Walnuts</td>
<td>30 g/d</td>
<td>Advised low fat diet</td>
<td>26</td>
<td>55</td>
<td>-0.81</td>
<td>0.02</td>
<td>-0.78</td>
<td>0.032</td>
<td>-0.81</td>
<td>0.02</td>
<td>-0.78</td>
<td>0.032</td>
<td>Y</td>
</tr>
<tr>
<td>Tey et al. 2011a</td>
<td>+</td>
<td>RCT</td>
<td>Hazelnuts</td>
<td>30 g/d</td>
<td>Ground, sliced or whole hazelnuts on habitual diet</td>
<td>4</td>
<td>46</td>
<td>-0.20</td>
<td>&lt;0.001</td>
<td>-0.22</td>
<td>&lt;0.001</td>
<td>-0.20</td>
<td>&lt;0.001</td>
<td>-0.22</td>
<td>&lt;0.001</td>
<td>N</td>
</tr>
<tr>
<td>Tey et al. 2011b</td>
<td>Ø</td>
<td>NCT</td>
<td>Hazelnuts</td>
<td>42 g/d</td>
<td>Habitual (New Zealand) diet + chocolate or potato chips</td>
<td>12</td>
<td>100</td>
<td>-0.16</td>
<td>NS</td>
<td>-0.18</td>
<td>NS</td>
<td>-0.16</td>
<td>NS</td>
<td>-0.18</td>
<td>NS</td>
<td>Y</td>
</tr>
<tr>
<td>Torabian et al. 2010</td>
<td>+</td>
<td>RCOT</td>
<td>Walnuts</td>
<td>28–64 g/d (12% of energy)</td>
<td>Habitual (American) diet</td>
<td>26</td>
<td>87</td>
<td>-0.13</td>
<td>0.01</td>
<td>-0.09</td>
<td>NS</td>
<td>-0.13</td>
<td>0.01</td>
<td>-0.09</td>
<td>NS</td>
<td>Y</td>
</tr>
<tr>
<td>Wang et al. 2012 (dose)</td>
<td>Ø</td>
<td>RCT</td>
<td>Pistachios</td>
<td>42 g/d</td>
<td>Advised AHA Step 1 diet</td>
<td>12</td>
<td>86</td>
<td>0.05</td>
<td>NS</td>
<td>0.11</td>
<td>NS</td>
<td>0.05</td>
<td>NS</td>
<td>0.11</td>
<td>NS</td>
<td>Y</td>
</tr>
<tr>
<td>Wang et al. 2012 (dose)</td>
<td>Ø</td>
<td>RCT</td>
<td>Pistachios</td>
<td>70 g/d</td>
<td>Advised AHA Step 1 diet</td>
<td>12</td>
<td>86</td>
<td>0.25</td>
<td>NS</td>
<td>0.31</td>
<td>&lt;0.01</td>
<td>0.25</td>
<td>NS</td>
<td>0.31</td>
<td>&lt;0.01</td>
<td>Y</td>
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<tr>
<td>West et al. 2012 (dose)</td>
<td>+</td>
<td>RCOT</td>
<td>Pistachios</td>
<td>32–63 g/d (10% of energy)</td>
<td>AHA Step 1 diet</td>
<td>4</td>
<td>28</td>
<td>-3.0</td>
<td>0</td>
<td>-0.7</td>
<td>NS</td>
<td>-3.0</td>
<td>0</td>
<td>-0.7</td>
<td>NS</td>
<td>Y</td>
</tr>
<tr>
<td>West et al. 2012 (dose)</td>
<td>+</td>
<td>RCOT</td>
<td>Pistachios</td>
<td>63–126 g/d (20% of energy)</td>
<td>AHA Step 1 diet</td>
<td>4</td>
<td>28</td>
<td>-0.6</td>
<td>0</td>
<td>-0.7</td>
<td>NS</td>
<td>-0.6</td>
<td>0</td>
<td>-0.7</td>
<td>NS</td>
<td>Y</td>
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<td>Wien et al. 2003</td>
<td>+</td>
<td>NCT</td>
<td>Almonds</td>
<td>84 g/d</td>
<td>Isoenergetic self-selected complex CHO</td>
<td>24</td>
<td>52</td>
<td>-0.65</td>
<td>NS</td>
<td>-0.39</td>
<td>NS</td>
<td>-0.65</td>
<td>NS</td>
<td>-0.39</td>
<td>NS</td>
<td>N</td>
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<td>Wien et al. 2010</td>
<td>+</td>
<td>RCT</td>
<td>Almonds</td>
<td>56 g/d (20% of energy)</td>
<td>Isoenergetic ADA diet</td>
<td>16</td>
<td>54</td>
<td>-1</td>
<td>NS</td>
<td>1</td>
<td>NS</td>
<td>-1</td>
<td>NS</td>
<td>1</td>
<td>NS</td>
<td>Y</td>
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<tr>
<td>Wu et al. 2010</td>
<td>+</td>
<td>RCT</td>
<td>Walnuts</td>
<td>30 g/d</td>
<td>AHA diet + flaxseed</td>
<td>12</td>
<td>277</td>
<td>-0.18</td>
<td>NS</td>
<td>-0.10</td>
<td>NS</td>
<td>-0.18</td>
<td>NS</td>
<td>-0.10</td>
<td>NS</td>
<td>Y</td>
</tr>
<tr>
<td>Yucesan et al. 2010</td>
<td>Ø</td>
<td>NCT</td>
<td>Hazelnuts</td>
<td>49–86 g/d</td>
<td>Habitual (Turkish) diet</td>
<td>4</td>
<td>21</td>
<td>-0.36</td>
<td>0.0001</td>
<td>-0.21</td>
<td>0.008</td>
<td>-0.36</td>
<td>0.0001</td>
<td>-0.21</td>
<td>0.008</td>
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<tr>
<td>Zambrón et al. 2000</td>
<td>+</td>
<td>RCOT</td>
<td>Walnuts</td>
<td>41–56 g/d</td>
<td>Advised Mediterranean-type diet</td>
<td>6</td>
<td>49</td>
<td>-0.29</td>
<td>&lt;0.001</td>
<td>-0.29</td>
<td>&lt;0.001</td>
<td>-0.29</td>
<td>&lt;0.001</td>
<td>-0.29</td>
<td>&lt;0.001</td>
<td>Y</td>
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<tr>
<td>Zibaeeezhad et al. 2005</td>
<td>–</td>
<td>NCT</td>
<td>Walnuts</td>
<td>20 g/d</td>
<td>Habitual (Turkish) diet w/o nuts</td>
<td>8</td>
<td>20</td>
<td>-0.03</td>
<td>NS</td>
<td>-0.05</td>
<td>NS</td>
<td>-0.03</td>
<td>NS</td>
<td>-0.05</td>
<td>NS</td>
<td>N</td>
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</table>
ADA: American Dietetic Association; AHA: American Heart Association; CHO: Cholesterol; MUFA: Mono-unsaturated fatty acids; OO: Olive oil, Diff: Test Mean – Control Mean or Test Mean – Test Baseline; RCT, Randomized Clinical Trial; RCOT, Randomized Cross-over Trial; NCT, Nonrandomized Clinical Trial; NCOT, Nonrandomized Cross-over Trial;
Figure 4. Frequency distribution of the difference between control or baseline and test values for Tot-C.
Data were first sorted according to whether they met the FDA criteria and were then sorted by order of magnitude of change. Analyses to the left of the hatched line met the FDA criteria and analyses to the right of the hatched line did not meet the FDA criteria. One analysis in which there was no difference between test and control or baseline values shows a value of y=0. The diamond denotes a statistically significant difference between control and test values or between test and baseline values. The references for this figure may be found in Appendix A.
**LDL-C**

Fifty-one interventional study analyses meeting the FDA criteria investigated the effect of nut consumption on LDL-C concentration (Figure 5, Appendix B). Twenty-four analyses (47%), 15 with a positive quality rating, and 9 with a neutral quality rating, reported a significant negative difference compared with control. One (2%) analysis with a neutral quality rating reported a significant positive difference between test and control values (Figure 5, Appendix B). Twenty-six analyses (51%) reported no significant difference; 16 had a positive quality rating and 10 had a neutral quality rating (Table 2).

**Systolic Blood Pressure**

Twenty-one analyses meeting the FDA criteria for review investigated the effect of nut consumption on systolic BP (Figure 6, Appendix C). One analysis (5%) with a positive quality rating reported a significant negative difference compared with control. Of the 20 analyses (95%) that reported no significant difference between test and control values, 13 had a positive quality rating, 5 had a neutral quality rating, and 2 had a negative quality rating (Table 2).

**Diastolic Blood Pressure**

Twenty analyses meeting the FDA criteria for review investigated the effect of nut consumption on diastolic blood pressure (Figure 6, Appendix C). One analysis (5%) with a positive quality rating reported a significant positive difference between nut intervention and the control intervention. One analysis (5%) with a neutral quality rating reported a significant negative difference between nut intervention and the control intervention. Of the 18 analyses (90%) that reported no significant difference, 12 had a positive quality rating, 4 had a neutral quality rating, and 2 had a negative quality rating (Table 2).

### 3.3.1.2. Broad: Interventional study analyses that failed to meet FDA criteria

For studies that measured FDA validated biomarkers for CVD, but failed to meet other FDA criteria for inclusion, comparisons were made between test and control or baseline values when these data were available. If control values were not available, comparisons were made between test and baseline values.

**Tot-C**

Twenty-four interventional study analyses that failed to meet the FDA criteria investigated the effect of nut consumption on Tot-C concentration. Of the 15 analyses (63%) that reported a significant negative difference between the nut intervention and control on Tot-C, one had a positive quality rating, 13 had a neutral quality rating, and one had a negative quality rating. No analyses reported a significant positive difference compared with control. Of the 9 analyses (37%) that reported a non-significant difference between test and control or baseline values on Tot-C, two had positive quality ratings, three had a neutral quality rating, and four had a negative quality rating (Figure 4).
Figure 5. Frequency distribution of the difference between control and test values for LDL-C.
Data were first sorted according to whether they met the FDA criteria and were then sorted by order of magnitude of change. Analyses to the left of the hatched line met the FDA criteria and analyses to the right of the hatched line did not meet the FDA criteria. Analyses in which there was no difference between control and test values show values of y=0 (2 analyses). A diamond denotes a statistically significant difference between control and test values or baseline and test values. The references for this figure may be found in Appendix B.
Figure 6. Frequency distribution of the difference between control and test values for systolic blood pressure (SBP) (shaded bars) and diastolic blood pressure (DBP) (unshaded bars).
Analyses to the left of the hatched line met the FDA criteria and analyses to the right of the hatched line did not meet the FDA criteria. Analyses where there was no change from baseline (1 for SBP and 1 for DBP) show values of y=0. A diamond denotes a significant difference between control or baseline and test values. The references for this figure may be found in Appendix C.
**LDL-C**

Twenty-four interventional study analyses that failed to meet the FDA criteria investigated the effect of nut consumption on LDL-C concentration. Of the 16 analyses (67%) that reported a significant negative difference on LDL-C, one had a positive quality rating, 14 had a neutral quality rating, and one had a negative quality rating. No analyses reported a significant positive difference compared with control or baseline groups. Of the 8 analyses (33%) that reported a non-significant effect on LDL-C, two had positive quality ratings, two had a neutral quality rating, and 4 had a negative quality rating (Figure 5, Appendix B, Table 2).

**Systolic Blood Pressure**

Five interventional study analyses that failed to meet the FDA criteria investigated the effect of nut consumption on systolic blood pressure. One of the analyses with a positive quality rating reported a significant negative difference compared with control. Four analyses, including two that had a neutral quality rating and two with a negative quality rating reported no significant difference between nut intervention and control or baseline SBP (Figure 6, Appendix C, Table 2).

**Diastolic Blood Pressure**

Four analyses that failed to meet the FDA criteria investigated the effect of nut consumption on diastolic blood pressure. None of the analyses reported a significant negative or positive difference compared with control. All analyses including one with a positive quality rating, two that had a neutral quality rating, and one with a negative quality rating reported no significant difference between nut intervention and control or baseline DBP values (Figure 6, Appendix C, Table 2).

### 3.3.2. Observational study analyses

Four observational study analyses reported data on the relationship between nut consumption and validated biomarkers of CVD.

#### 3.3.2.1. Narrow: Observational study analyses meeting the FDA Criteria for Biomarkers

Three observational study analyses addressed the association of nut consumption and Tot-C. Three analyses addressed the association between nut consumption and FDA-validated biomarkers of CVD reported as continuous variables (Li et al., 2009; O'Neil et al., 2011; O'Neil et al., 2012) (Table 3). One cross-sectional study analysis with a positive quality rating reported no association between fiber intake from nut consumption and the risk of Tot-C concentrations greater than 6.2 nmol/L (Lairon et al., 2005). Because this analysis reported only consumption of fiber intake from nuts and seeds, it was not possible to determine the nut consumption levels (Figure 10).

In a cross-sectional analysis of a prospective cohort study, Li et al. (2009) reported decreased concentrations of Tot-C comparing the highest to the lowest categories of nut consumption, while two cross-sectional study analyses (O'Neil et al., 2011; O'Neil et al., 2012) did not find significant differences. The same three analyses addressed the association of nut consumption and decreased concentrations of LDL-C. Li et al (2009) reported lower LDL-C levels comparing the highest to the lowest nut consumption categories while two analyses (O'Neil et al., 2011; O'Neil et al., 2012) reported no significant differences. Two analyses found significant decreases between 1–2 mmHg in SBP, but no changes in DBP (O'Neil et al., 2011; O'Neil et al., 2012) (Table 3).
3.4. Other Biomarkers

For biomarkers that FDA does not consider to be validated biomarkers for CVD, comparisons were made between nut intervention and control whenever data for a control group was reported. When there was no control intervention group, the comparison was between nut intervention and baseline values. The unvalidated biomarkers measured in this study were HDL-C, Tot-C:HDL-triglyceride, Apo A1, Apo B, Apo B 100, and CRP.

3.4.1. HDL-C

Seventy-five interventional study analyses that met the criteria for inclusion in this review measured the effect of nut consumption on HDL-C concentration. Twelve (16%) reported that there was a significant negative difference compared with control or baseline values, 12 (16%) reported a significant positive difference, and 51 (68%) reported a non-significant difference.

3.4.1.1 Narrow: Intervventional study analyses measuring HDL-C, a non-FDA validated biomarker for CVD, that otherwise met the FDA criteria

Fifty interventional study analyses that otherwise met the FDA criteria investigated the effect of nut consumption on HDL-C concentration (Figure 7, Appendix D). Ten (20%) analyses, 5 with a positive quality rating, and 5 with a neutral rating reported a significant negative difference between the nut intervention and control. Six analyses (12%), four with a positive quality rating and two with a neutral quality rating reported a significant positive difference between the test and control values. Of the 34 analyses (68%) reporting a non-significant difference between the test group and control group values, 21 had a positive quality rating, 11 had a neutral quality rating and two had a negative quality rating.

3.4.1.2 Broad: Intervential study analyses measuring HDL-C, a non-FDA validated biomarker for CVD, that did not meet other FDA criteria

Twenty-five interventional study analyses that failed to meet the FDA criteria investigated the effect of nut consumption on HDL-C concentration (Figure 7, Appendix D). Two analyses (8%), both of which 2 received a neutral quality rating, reported a significant negative difference between the test and control or baseline values. Six analyses (24%) of which 3 received a neutral quality rating and 3 received a negative quality rating reported a significant positive difference between the test and control or baseline values. Of the 17 (68%) analyses that reported no significant difference between the test group and the control group or baseline value, 2 had a positive quality rating, 12 had a neutral quality rating, and 3 had a negative quality rating.
Table 3. Observational Studies Reporting the Effect of Nut Consumption on Studies Meeting the FDA Criteria for Biomarkers (Narrow Analysis)

<table>
<thead>
<tr>
<th>QR</th>
<th>Trial Design</th>
<th>Dietary Assessment Tool</th>
<th>Sample Size</th>
<th>Duration</th>
<th>Highest Dose</th>
<th>Tot-C (mg/dL)</th>
<th>LDL-C (mg/dL)</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>PC*** FFQ</td>
<td>6309 22 y</td>
<td>≥ 5 servgs/wk</td>
<td></td>
<td></td>
<td>1171 236.3</td>
<td>1171 141.5</td>
<td>0.007</td>
<td>0.008</td>
</tr>
<tr>
<td>O'Neil et al. 2011 (NHANES)</td>
<td>+ XS NHANES surveys</td>
<td>24385 N/A</td>
<td>≥ ¼ oz</td>
<td></td>
<td></td>
<td>725 202.6</td>
<td>5243 121.1</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>O'Neil et al. 2012 (NHANES)</td>
<td>+ XS NHANES surveys</td>
<td>24385 N/A</td>
<td>≥ ¼ oz</td>
<td></td>
<td></td>
<td>876 202.4</td>
<td>5175 120.9</td>
<td>NS</td>
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</tr>
</tbody>
</table>

*Mean = value of highest consumption category
**Diff = the difference between highest and lowest consumption categories
***Cross-sectional analysis of a prospective cohort study
Figure 7: Frequency distribution of the difference between control and test values for HDL-C. Data were first sorted according to whether they met the FDA criteria and were then sorted by order of magnitude of change. Analyses to the left of the hatched line met the FDA criteria.
and analyses to the right of the hatched line did not meet the FDA criteria. Analyses in which there was no change from baseline show values on
the y=0 (14 analyses). The diamond denotes a significant difference between control or baseline and test values. The references for this figure
may be found in Appendix D.
3.4.1.3. Observational study analyses reporting the effect of nut consumption on HDL-C

Five observational study analyses addressed the relationship between nut consumption and HDL-C concentration. In a cross-sectional analysis of a prospective cohort study, Li et al. (2009) reported no difference in HDL-C concentrations comparing the highest to the lowest nut consumption categories. Two cross-sectional analyses, O’Neil et al. (2011) and O’Neil et al. (2012), reported significantly increased concentrations. A cross-sectional analysis of a prospective cohort study with a positive quality rating reported significant negative partial correlation coefficient for the association of dietary nuts and seeds and TG concentrations and positive partial correlation coefficient for HDL-C concentrations as part of a reduced rank regression analysis (Li et al., 2009). Álvarez León et al. (2006), in a cross-sectional study with a negative quality rating, reported no association between nut consumption and the risk of abnormally low HDL-C concentrations (less than 1.04 mmol/L for males or 1.3 mmol/L for females) Table 4, Figure 10.

3.4.2. Tot-C:HDL-C

Twenty-four interventional study analyses meeting the criteria for inclusion in this review investigated the effect of nut consumption on Tot-C:HDL-C. Fourteen analyses (58.3%) reported a significant negative difference, two (8.3%) reported a significant positive difference, and 8 (33.3%) reported a non-significant difference compared with control (Figure 8, Appendix E). Ten of the analyses had a positive quality rating, 11 had a neutral quality rating, and three had a negative quality rating.

3.4.2.1 Narrow: Interventional study analyses measuring Tot-C:HDL-C, a non-FDA validated biomarker for CVD, that otherwise met the FDA criteria

Sixteen interventional study analyses that otherwise met the FDA criteria investigated the effect of nut consumption on Tot-C:HDL-C (Figure 8, Appendix E). Eight (50%) analyses, of which 3 received a positive quality rating and 5 (31.3%) received a neutral rating reported a significant negative difference between the nut intervention and comparison group. One analysis (6%) that received a positive quality rating reported a significant positive difference between the nut intervention and control. Seven analyses (44%) reported no significant difference between intervention and control.

3.4.2.2. Broad: Interventional study analyses measuring Tot-C:HDL-C, a non-FDA validated biomarker for CVD, that did not meet other FDA criteria

Eight analyses that failed to meet the FDA criteria investigated the effect of nut consumption on Tot-C:HDL-C (Figure 8, Appendix E). Six analyses (75%), 4 of which received a neutral quality rating and 2 of which received a negative quality rating reported a significant negative difference between the nut intervention and control or baseline values. No analyses reported a significant positive difference between the nut intervention and control or baseline values. Of the 2 analyses (25%) that reported no significant difference between the intervention and the control or baseline values, 1 was a neutral quality study, and 1 was a negative quality study.
Figure 8: Frequency distribution of the difference between control and test values for Tot-C:HDL-C. Data were first sorted according to whether they met the FDA criteria and were then sorted by order of magnitude of change. Analyses to the left of the
hatched line met the FDA criteria and analyses to the right of the hatched line did not meet the FDA criteria. One analysis that reported no change from baseline show values on the x-axis. The diamond denotes a significant difference between control and test or baseline values. The references for this figure may be found in Appendix E.
3.4.2.3. Observational Study Analyses
No observational studies included in the review reported on the relationship between tree nut consumption and Total-C: HDL-C.

3.4.3. Triglycerides
Seventy-seven interventional study analyses that met the criteria for inclusion in this review reported on the effect of tree nut consumption on TG. Fourteen analyses (18%) reported a significant negative difference, 2 (3%) reported a significant positive difference, and 61 (79%) reported a non-significant difference.

3.4.3.1 Narrow: Intervventional study analyses measuring TG, a non-FDA validated biomarker for CVD, that otherwise met the FDA criteria
Fifty-five interventional study analyses that otherwise met the FDA criteria investigated the effect of nut consumption on TG (Figure 9, Appendix F). No studies reported a significant positive difference between intervention and control groups. Eleven (20%) analyses, 5 with a positive quality rating and 6 with a neutral quality rating reported a significant negative difference between the nut intervention and control. Of the 44 analyses (80%) that reported a non-significant difference between the intervention group and the control group, 26 were positive quality analyses, 16 were neutral quality analyses, and 2 were negative quality studies.

3.4.3.2. Broad: Intervventional study analyses measuring TG, a non-FDA validated biomarker for CVD that did not meet other FDA criteria
Twenty-two analyses that failed to meet the FDA criteria investigated the effect of nut consumption on TG concentration (Figure 9, Appendix F). Three analyses (14%), two of which received a neutral quality rating and one that received a negative quality rating reported a significant negative difference between the nut intervention and control. Two studies (9%), one with a positive quality rating and one with a negative quality rating reported a significant positive difference between the nut intervention and control. Of the 17 analyses (77%) that reported a non-significant difference between the intervention group and the control group, 1 was a positive quality analysis, 14 were neutral quality analyses, and 4 were negative quality analyses.

3.4.3.3. Observational study analyses measuring TG, a non-FDA validated biomarker for CVD that did not meet other FDA criteria
Álvarez León et al. (2006), in a cross-sectional study with a negative quality rating, reported no association between nut consumption and the risk of TG concentrations greater than 1.65 mmol/L. O’Neil et al. (2011) in a cross-sectional study with positive quality rating reported no association between nut consumption and the risk of TG levels greater than 1.65 mmol/L (Figure 10). In a cross-sectional study with a positive quality rating, Lairon et al. (2005) reported no association between nut consumption and the risk of TG concentrations greater than 1.69 mmol/L (Figure 10). O’Neil et al. (2012) reported no differences in TG concentrations between the high and low intake groups (Table 4).

3.4.4. Apolipoproteins
3.4.4.1. Apolipoprotein A1
Twenty-nine interventional study analyses meeting the criteria for inclusion in this review investigated the effect of nut consumption on Apo A1. Two analyses (7%) reported a significant negative difference, three (10%) reported a significant positive difference, and twenty-four (83%) reported a non-significant difference compared with control or baseline values.
3.4.4.1.1. Narrow: Interventional study analyses measuring Apo A1, a non-FDA validated biomarker for CVD, that otherwise met the FDA criteria
Twenty-two interventional study analyses that otherwise met the FDA criteria investigated the effect of nut consumption on Apo A1 concentration (Figure 11, Appendix G). Two analyses (14%), one that received a positive quality rating and one that received a neutral quality rating, reported a significant negative difference between the nut intervention and control. One analysis reported a significant positive difference between the nut intervention and control group values. Of the 19 analyses (86%) that reported a non-significant negative difference between the intervention group and the control group, 11 were positive quality analyses and 8 were neutral quality analyses.

3.4.4.1.2. Broad: Interventional study analyses measuring Apo A1, a non-FDA validated biomarker for CVD, that did not meet other FDA criteria
Seven analyses that failed to meet the FDA criteria investigated the effect of nut consumption on Apo A1 concentration (Figure 11, Appendix G). No analyses reported a significant negative difference between the nut intervention and control or baseline values. Two analyses (29%), both of which received a neutral quality rating reported a significant positive difference. Of the 5 analyses (71%) that reported a non-significant negative difference, 4 were neutral quality analyses, and 1 was a negative quality study.

3.4.4.1.3. Observational study analyses
One observational study analysis examined the effect of nut consumption on Apo A1. Lairon et al. (2005) was a positive quality, cross-sectional study that found no significant difference in the odds ratio of the fifth versus the first quintile for intake of fiber from nuts and seeds the relative risk of Apo A1. Data is not shown because the dependent variable is expressed as fiber intake rather than nut intake.
Figure 9: Frequency distribution of the difference between control and test values for TG. Data were first sorted according to whether they met the FDA criteria and were then sorted by order of magnitude of change. Analyses to the left of the hatched line met the FDA criteria and analyses to the right...
of the hatched line did not meet the FDA criteria. Two analyses where there was no change from baseline show values of $y=0$. The diamond denotes a significant difference between control or baseline and test values. The references for this figure may be found in Appendix F.

Figure 10. Observational study analyses showing the relative risk of Total-C, HDL-C, triglycerides (TG), Apo A1, and Apo B. Abnormal defined as: Total-C > 6.2 nmol/L; HDL-C < 1.04 mmol/L (M) or < 1.3 mmol/L (F), TG > 1.65 mmol/L.
Table 4. Observational Studies Reporting the Effect of Nut Consumption on Studies Meeting the FDA Criteria for Biomarkers (Broad Analysis)

<table>
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<tr>
<th>QR</th>
<th>Trial Design</th>
<th>Dietary Assessment Tool</th>
<th>Sample Size</th>
<th>Duration</th>
<th>Highest Dose</th>
<th>HDL-C (mmol/L)</th>
<th>TG (mmol/L)</th>
<th>Apo B (mg/dL)</th>
<th>CRP (mg/dL)</th>
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<tbody>
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<td>+</td>
<td>PC***</td>
<td>FFQ</td>
<td>1171</td>
<td>22 y</td>
<td>≥ 5 svgs/wk</td>
<td>N</td>
<td>N</td>
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<td></td>
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<td></td>
<td></td>
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</tr>
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<td>+</td>
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<td>NHANES surveys</td>
<td>24385</td>
<td>N/A</td>
<td>≥ ¼ oz</td>
<td>11826</td>
<td>1.39</td>
<td>0.05</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>vs. &lt; ¼ oz</td>
<td>539</td>
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<td>- 0.05</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>3</td>
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<td>0</td>
<td>S</td>
<td>9</td>
</tr>
<tr>
<td>+</td>
<td>XS</td>
<td>NHANES surveys</td>
<td>24385</td>
<td>N/A</td>
<td>≥ ¼ oz</td>
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<td>1.34</td>
<td>0.05</td>
<td>0.0</td>
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<td></td>
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<td></td>
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<td>vs. &lt; ¼ oz</td>
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<td>7</td>
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<td>9</td>
</tr>
<tr>
<td>Ø</td>
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<td>FFQ</td>
<td>6080</td>
<td>N/A</td>
<td>≥ 5 times/wk</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

*Mean = value of highest consumption category
**Diff = the difference between highest and lowest consumption categories
***Cross-sectional analysis of a prospective cohort study.
Figure 11: Frequency distribution of the difference between control and test values for Apo A1.
Data were first sorted according to whether they met the FDA criteria and were then sorted by order of magnitude of change. Analyses to the left of the hatched line met the FDA criteria and analyses to the right of the hatched line did not meet the FDA criteria. Analyses where there was no change from baseline or control show values of $y=0$ (2 analyses). The diamond denotes a significant difference between control or baseline and test values. The references for this figure may be found in Appendix F.
3.4.4.2. Apolipoprotein B
Twenty-seven interventional analyses meeting the criteria for inclusion in this review reported on the effect of nut consumption on Apo B. Fifteen analyses reported a significant negative difference between test and control or baseline values (56%), none reported a significant positive difference, and 12 analyses (44%) reported no significant difference between nut intervention and Apo B compared with control.

3.4.4.2.1. Narrow: Interventional study analyses measuring Apo B, a non-FDA validated biomarker for CVD, that otherwise met the FDA criteria
Twenty-one interventional analyses meeting the FDA criteria investigated the effect of nut consumption on Apo B concentration (Figure 12, Appendix H). Thirteen (62%) analyses, 6 with a positive quality rating, and 7 with a neutral quality rating reported a significant negative difference between the nut intervention and control. No analyses reported a significant positive difference between the nut intervention and control. Of the 8 (38%) analyses that reported no significant negative difference between the intervention group and the control group, 6 had positive quality ratings and 2 were rated as neutral quality analyses.

3.4.4.2.2. Broad: Interventional study analyses measuring Apo B, a non-FDA validated biomarker for CVD, that did not meet other FDA criteria
Six analyses that failed to meet the FDA criteria investigated the effect of nut consumption on Apo B concentration (Figure 12, Appendix H). Two (33%) analyses, both of which received a neutral quality rating reported a significant negative difference between the nut intervention and control or baseline values. No analyses reported a significant positive difference between the nut intervention and control or baseline values. Of the 4 (67%) analyses that reported no significant negative difference, 3 were neutral quality analyses, and one was a negative quality analyses.

3.4.4.2.3. Observational study analyses
Two observational studies assessed the effect of nuts on Apo B. In a cross-sectional analysis of a prospective cohort study, Li et al. (2009) reported decreased concentrations of Apo B comparing the highest to the lowest nut consumption categories. Lairon et al. (2005) found a significant difference in the odds ratio of the fifth versus the first quintile for intake of fiber from nuts and seeds the relative risk of Apo B (Table 4) Data from Lairon et al. (2005) is not shown because the dependent variable is expressed as fiber intake rather than nut intake.

3.4.4.3. Apo B-100
Four interventional study analyses reported on the effect of nut consumption on Apo B-100. Two positive quality analyses that met the FDA criteria reported no effect (Sheridan et al., 2007; Solá et al., 2012) and two neutral quality analyses that did not meet the FDA criteria reported a significant negative effect (Jalali-Khanabadi et al., 2010; Tey et al., 2011b) (Figure 13, Appendix I).
Figure 12: Frequency distribution of the difference between control and test values for Apo B. Data were first sorted according to whether they met the FDA criteria and were then sorted by order of magnitude of change. Analyses to the left of the hatched line met the FDA criteria and analyses to the right of the hatched line did not meet the FDA criteria. The diamond denotes a significant difference between control or baseline and test values. The references for this figure may be found in Appendix H.
Figure 13: Frequency distribution of the difference between control and test values for Apo B-100.
Data were first sorted according to whether they met the FDA criteria and were then sorted by order of magnitude of change. Analyses to the left of the hatched line met the FDA criteria and analyses to the right of the hatched line did not meet the FDA criteria. The diamond denotes a significant difference between control or baseline and test values. The references for this figure may be found in Appendix I.
3.4.5. CRP
Eighteen interventional study analyses meeting the criteria for inclusion in this review investigated the effect of nut consumption on CRP. Two (11%) reported a significant negative difference, none reported a significant positive difference, and 16 (89%) reported a non-significant difference compared with control (Figure 14, Appendix J).

3.4.5.1. Narrow: Interventional study analyses measuring CRP, a non-FDA validated biomarker for CVD, that otherwise met the FDA criteria
Fourteen interventional study analyses that otherwise met the FDA criteria investigated the effect of nut consumption on CRP concentration. Two (14%) analyses, both of which were of neutral quality rating reported a significant negative effect. Of the 12 (86%) analyses that reported no significant negative difference between the test and the control or baseline values, 6 had a positive quality rating, 4 had a neutral quality rating, and 2 had a negative quality rating.

3.4.5.2. Broad: Interventional study analyses measuring CRP, a non-FDA validated biomarker for CVD that did not meet other FDA criteria
Four analyses that failed to meet the FDA criteria investigated the effect of nut consumption on CRP concentration. These analyses, all of which had a neutral quality rating, reported no significant difference between intervention and control or baseline values.

3.4.5.3. Observational study analyses
Five observational study analyses investigated the effects on nut consumption on CRP (Table 4). Three cross-sectional study analyses reported decreased CRP concentrations comparing the highest to the lowest nut consumption categories (Jiang et al., 2006; O'Neil et al., 2011; O'Neil et al., 2012). One prospective cohort study of neutral quality rating reported a significant negative Spearman correlation coefficient for the dietary correlation of nuts and CRP concentrations as part of a reduced rank regression analysis (data not shown) (Meyer et al., 2011) (Table 5). Li et al. (2009) in a positive quality prospective cohort study, when data were analyzed for women with type 2 diabetes reported that there was no effect of consuming 5 or more serving of nuts and peanut butter/week compared almost never consumption of nuts or peanut butter on CRP concentrations (data not reported).

3.5. Ancillary Issues
3.5.1. Displacement of other dietary factors
The panel investigated whether substitution of saturated fat with nuts was responsible for any observed change in Tot-C. All of the twenty-nine analyses in which nuts were substituted for SFA showed reductions in Tot-C compared with control. The reductions were significant for 22 of the 29 analyses (76%). Forty-seven analyses did not substitute nuts for saturated fat, 21 (45%) of which reported a significant negative effect. The remaining 26 analyses reported no significant effect (Figure 15, Appendix K).
Figure 14: Frequency distribution of the difference between control and test values for CRP.
Data were first sorted according to whether they met the FDA criteria and were then sorted by order of magnitude of change. Analyses to the left of the hatched line met the FDA criteria and analyses to the right of the hatched line did not meet the FDA criteria. One analysis in which there was no difference from control and test values, showed values showed a difference of 0 (y=0). The diamond denotes a significant difference between control or baseline and test values. The references for this figure may be found in Appendix J.
Twenty-five of the analyses substituted nuts for SFA in studies that investigated the effect of nut consumption on LDL-C (Figure 16, Appendix L). Sixteen of the 25 analyses that substitute saturated fat (64%) reported decreased LDL-C concentrations compared with control. The remaining 9 analyses reported no significant effect. Forty-nine analyses did not substitute nuts for SFA. Twenty-four of the 49 analyses (49%) reported non-significant effects of nut consumption compared with control. Twenty-five analyses (51%) reported significant differences compared with control, 24 of the 25 analyses reported a significant negative effect and one reported a significant positive effect.

### 3.5.2. Weight gain or loss

The high energy density and high fat content of nuts have led to a widespread perception that their consumption may lead to increase in body weight and increased risk of developing overweight or obesity.

Flores-Mateo et al., (2013) conducted a systematic review and meta-analysis of 33 published, randomized clinical trials evaluating the association between tree nut consumption and measures of adiposity (body weight, waist circumference, and BMI) (Figure 17). Most, but not all of the clinical trials included in the meta-analysis were also included in the current systematic review. They reported a non-significant effect on body weight WMD: -0.47 kg; 95% CI -1.17, 0.22 kg; I² = 7%; BMI WMD: -0.40 kg/m²; 95% CI -0.97, 0.17 kg/m²; I² = 49%, or waist circumference WMD: -1.25 cm; 95% CI; -2.82, 0.31 cm; I² = 28% comparing diets including nuts with control diets. Length of follow-up (<24 wk vs ≥24 wk), study focus (energy restriction vs no energy restriction), study design (parallel vs crossover), quality, or intervention diet (supplementation vs replacement) did not influence pooled estimates. The type of nut did not influence the pooled estimate. These results were consistent with those reported in a previous meta-analysis (Banel & Hu, 2009).

Seven of the observational study analyses that met the inclusion criteria for this report also reported on measures of weight (Álvarez León et al., 2006; Djoussé et al., 2008; Jiang et al., 2006; Lairon et al., 2005; Liu et al., 2009; O'Neil et al., 2011; O'Neil et al., 2012). Four of the seven reported small but significant inverse association of weight and nut consumption (Jiang et al., 2006; Lairon et al., 2005; Liu et al., 2009; O'Neil et al., 2011). Two of the seven reported no association between weight and nut consumption (Álvarez León et al., 2006; Djoussé et al., 2008). One cross-sectional study reported results that varied among age groups (O'Neil et al., 2012). For all three age groups, 2 – 11 yr olds, 12 – 18 yr olds, and 19+ yr olds waist circumference, and BMI were unchanged comparing consumers to non-consumers. The prevalence of obesity was increased for 2 – 11 yr olds, decreased for 12 – 18 yr olds, and unchanged for individuals age 19 years or older (O'Neil et al., 2012).

One observational study that did not meet the inclusion criteria for this report found no association between nut consumption and the risk of weight gain (Martínez-González & Bes-Rastrollo, 2011). Three clinical trials not included in the Flores-Mateo et al. (2013), meta-analysis reported no effect of tree nut consumption on weight gain (Li et al., 2010; Tey et al., 2011a; Zaveri & Drummond, 2009). There is no evidence that nut consumption increases measures of adiposity or the risk of developing overweight or obesity.
### Table 5. Observational Studies Reporting the Effect of Nut Consumption on Selected Surrogate CVD Endpoints, HDL-C, TG, Apo A1, Apo B, Apo B-100, CRP and Weight (Broad Analysis)

<table>
<thead>
<tr>
<th>Reference</th>
<th>QR</th>
<th>Trial Design</th>
<th>Dietary assessment tool used</th>
<th>Sample Size</th>
<th>Duration</th>
<th>Gender</th>
<th>Age (y)</th>
<th>Nut(s)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Álvarez León et al. 2006</td>
<td>–</td>
<td>XS</td>
<td>FFQ</td>
<td>578</td>
<td>N/A</td>
<td>M &amp; F</td>
<td>≥ 18</td>
<td>Not specified</td>
<td>?</td>
</tr>
<tr>
<td>Djoussé et al. 2008</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>20976 PHS</td>
<td>19.6 y</td>
<td>M</td>
<td>54.6 ± 9.4; 40.7–87.1</td>
<td>Not specified</td>
<td>None &lt;1, 1, or ≥2 1 oz servings/wk</td>
</tr>
<tr>
<td>Djoussé et al. 2009</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>15966 PHS</td>
<td>28 y</td>
<td>M</td>
<td>52.3 ± 8.9</td>
<td>Does not include peanut butter</td>
<td>None, &lt;1, 1, or ≥2 1 oz servings/wk</td>
</tr>
<tr>
<td>Jiang et al. 2006</td>
<td>Ø</td>
<td>XS</td>
<td>FFQ</td>
<td>6080</td>
<td>N/A</td>
<td>F</td>
<td>62.2 ± 10.1</td>
<td>Nut + seeds</td>
<td>Never/rare &lt; 1/wk</td>
</tr>
<tr>
<td>Lairon et al. 2005</td>
<td>+</td>
<td>XS</td>
<td>multiple 24-h dietary recalls</td>
<td>5961 SU.VI.MAX</td>
<td>N/A</td>
<td>M &amp; F</td>
<td>52.1 ± 4.7</td>
<td>Nut + seeds</td>
<td>Fiber from nuts/seeds &gt;0.05 vs &gt;0.56 M &lt;0.05 vs &gt;0.48 F</td>
</tr>
<tr>
<td>Lavedrine et al. 1999</td>
<td>+</td>
<td>XS</td>
<td>FFQ plus specific questions for walnut</td>
<td>793</td>
<td>N/A</td>
<td>M &amp; F</td>
<td>50.73 ± 11.25F and 48.57 ± 12.55M</td>
<td>Walnut kernel and oil</td>
<td>Never, &gt; 2/wk and &gt; 6mo plus walnut oil daily, and all others</td>
</tr>
<tr>
<td>Li et al. 2009</td>
<td>+</td>
<td>PC</td>
<td>FFQ</td>
<td>6309 NHS</td>
<td>22 y</td>
<td>F</td>
<td>57.1 ± 9</td>
<td>Tree nuts + peanuts</td>
<td>Almost/never 1–3 svg/mo to 1 svg/wk 2–4 svgs/wk ≥ 5 svgs/wk</td>
</tr>
<tr>
<td>Liu et al. 2009</td>
<td>Ø</td>
<td>XS</td>
<td>FFQ</td>
<td>5004 MESA</td>
<td>?</td>
<td>M &amp; F</td>
<td>62.2 ± 10.1</td>
<td>Nut + seeds</td>
<td>?</td>
</tr>
<tr>
<td>Meyer et al. 2011</td>
<td>Ø</td>
<td>PC</td>
<td>Seven day dietary surveys</td>
<td>981</td>
<td>23 y</td>
<td>M</td>
<td>54.9</td>
<td>Not specified</td>
<td>Not reported</td>
</tr>
<tr>
<td>O’Neil et al. 2011</td>
<td>+</td>
<td>XS</td>
<td>NHANES surveys</td>
<td>24385</td>
<td>N/A</td>
<td>M &amp; F</td>
<td>19+</td>
<td>Out-of-hand-nut consumption Analyzed all nuts and nut butter and tree nuts and tree nut butter</td>
<td>≥¼ oz &lt;¼ oz</td>
</tr>
<tr>
<td>Reference</td>
<td>QR</td>
<td>Trial Design</td>
<td>Dietary assessment tool used</td>
<td>Sample Size</td>
<td>Duration</td>
<td>Gender</td>
<td>Age (y)</td>
<td>Nut(s)</td>
<td>Dose</td>
</tr>
<tr>
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<td>-----------------------------------------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>O'Neil et al. 2012</td>
<td>+</td>
<td>XS</td>
<td>NHANES surveys</td>
<td>24385</td>
<td>N/A</td>
<td>M &amp; F</td>
<td>2–11 or 12–18 or 19+</td>
<td>Out-of-hand-nut consumption</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Analyzed all nuts and nut butter and tree nuts and tree nut butter</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥¼ oz &lt;¼ oz</td>
<td></td>
</tr>
</tbody>
</table>

Apo A1: Apolipoprotein A1; Apo B: Apolipoprotein B; B: Beneficial; BP: Blood pressure; C: Cholesterol; CARDIA: Coronary Artery Risk Development in Young Adults; CRP: C-reactive protein; DBP: Diastolic blood pressure; F: Female; FFQ: Food frequency questionnaire; HDL: High-density lipoprotein; M: Male; MESA: Multi-Ethnic Study of Atherosclerosis; N: No effect; N/A: Not applicable; NHANES: National Health and Nutrition Examination Survey; NHS: Nurses Health Study; PC: Placebo-controlled; PHS: Physicians Health Study; SBP: Systolic blood pressure; SU.VI.MAX: Supplementation en Vitamines et Mineraux Antioxydants study; QR: Quality rating; TG: Triglycerides; Wt: Weight; XS: Cross-sectional
Figure 15. Frequency distribution of the difference between control and test values for Total-C. Analyses on the left of the vertical line indicate substitution for fatty acids and analyses to the right indicate no substitution for fatty acids. One study in which there was no difference between control and test values or baseline and test values is found at y=0. The references for this figure may be found in Appendix K.
Figure 16. Frequency distribution of the difference between control and test values for LDL-C. Analyses on the left of the vertical line, indicate substitution for fatty acids and analyses to the right, indicate no substitution for fatty acids. Analyses in which there was no difference have y axis values of 0.
<table>
<thead>
<tr>
<th>Number of trials</th>
<th>N</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>1836</td>
<td>Body weight (kg)</td>
</tr>
<tr>
<td>14</td>
<td>1057</td>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>5</td>
<td>681</td>
<td>Waist circumference (cm)</td>
</tr>
</tbody>
</table>

Figure 17. Net changes in body weight, BMI and waist circumference from a nut-enriched diet compared with a control diet from a meta-analysis of Flores-Mateo et al. (2013)
3.6. PREDIMED Trial Results on the Frequency of Nut Consumption and the Risk of Total Mortality and Cardiovascular Disease

The Prevención con Dieta Mediterránea (PREDIMED) was a 4-year, parallel group, multicenter, randomized, controlled, clinical trial conducted in Spain that compared the effectiveness of an energy-unrestricted, Mediterranean diet supplemented with olive oil or mixed nuts with the effectiveness of a low-fat diet in reducing CVD risk. The study was funded by the Spanish Ministry of Health–Instituto de Salud Carlos III, Centros de Investigación Biomédica En Red, and other groups. Olive oil (OO) was provided by Patrimonio Comunal Olivarero and nuts were provided by The California Walnut Commission, Borges, La Morell Nuts, and Hojiblanca. The PREDIMED studies were not included in this review because some PREDIMED study subjects were taking blood pressure, lipid-lowering, and other CVD medications. However, the PREDIMED studies are an extensive and important body of work. For this reason, the panel considered a separate discussion of these studies to be appropriate.

In the PREDIMED trial, individuals at high risk for CVD (n=7,447) were assigned to one of three dietary intervention groups: the Mediterranean diet with OO (1 L/wk), the Mediterranean diet with 30 g/d mixed nuts (15 g/d walnuts, 7.5 g/d hazelnuts, and 7.5 g/d almonds), or a low-fat diet. The primary outcomes for the PREDIMED trial were cardiovascular events, including cardiovascular death, nonfatal MI, and nonfatal stroke. Secondary outcomes were death from any cause, incidence of heart failure, diabetes mellitus, dementia, and cancer; and intermediate outcomes, such as blood pressure (BP), fasting blood glucose, lipid profile, markers of inflammation, and other intermediate markers of cardiovascular risk.

Study participants were community-dwelling men, aged 55 to 80 y, and women, aged 60 to 80 y, who met one of the two criteria: type 2 diabetes or 3 or more CHD risk factors: (current smoking (>1 cigarette/d for the last month); hypertension (systolic BP ≥ 140/90 mmHg or diastolic BP ≥ 90 mmHg or treatment with antihypertensive drugs); elevated LDL-C (≥4.14 mmol/L or ≥ 160 mg/dL or treatment with hypolipidemic drugs), HDL-C ≤1.04 mmol/L or ≤40 mg/dL in men and ≤50 mg/dL in women, BMI ≥25 kg/m², and a family history of premature CHD (≤ 55 y in men and ≤60 y in women). Exclusion criteria were a history of CVD, severe chronic illness, illegal drug or alcohol addiction, history of allergy or intolerance to OO or nuts, or low predicted likelihood of changing dietary habits according the Prochaska and DiClemente stages-of-change model (Nigg et al., 1999). Primary care physicians determined subject eligibility based on a review of clinical records and a screening visit. All subjects were recruited between October 2003 and January 2009. The median follow-up period for the study was 4.78 years.

Guasch-Ferré et al. (2013) investigated the relationship between the frequency of nut consumption and the risk of cardiovascular events including MI, stroke, and cardiovascular death. Subjects were randomly assigned to one of three groups: low fat (control) diet, a Mediterranean diet supplemented with extra-virgin olive oil (EVOO), or a Mediterranean diet supplemented with nuts. Subjects completed a 137-item FFQ that included one item inquiring about the frequency of consumption of a subset of “nuts”, as described in the article: almonds, peanuts, hazelnuts, pistachios and pine nuts and another item specifically inquiring about consumption of walnuts. The questionnaire limited assessment of nut consumption to these nuts because macadamias, cashews, and Brazil nuts are not frequently consumed in Spain. Study
participants were also asked about their degree of adherence to the Mediterranean diet. Participants were separated into three categories with regard to their nut consumption: never, or almost never; 1–3 servings/wk; and greater than 3 servings/wk, with a serving of nuts equaling 28g. Individuals in the Mediterranean diet/nuts group had a mean ± SD change in total nut consumption of +15.95 ± 21.10 g/d, those in the Mediterranean diet/EVOO group had a mean ± SD change in total nut consumption of -0.80 ± 16.31 g/d, and those in the control group had a mean ± SD change in total nut consumption of -3.12 ± 13.85 g/d. Data for 7,216 individuals (3,071 men and 4,145 women; mean age 67 years) were analyzed after data for individuals with extremes of total energy intake and incomplete dietary data were excluded. The median follow-up duration was 4.8 y, during which there were 323 total deaths, 81 cardiovascular deaths and 130 cancer deaths.

A crude model and three Cox regression models were used to determine the risk of total and cardiovascular mortality with respect to nut consumption. Multivariate model 3, the most rigorous analysis, was adjusted for age (years), sex, intervention groups, BMI, smoking status, educational level, kg/m², smoking status (never, former, current smoker), educational level (illiterate/primary education, secondary education, academic/graduate), leisure time physical activity in MET-min/d, history of diabetes (yes/no), history of hypercholesterolemia (yes/no), use of oral anti-diabetic medication (yes/no), use of antihypertensive medication (yes/no), use of statins (yes/no), total energy intake (kcal/d), dietary variables in quintiles (vegetables, fruits, red meat, eggs, and fish), alcohol intake (continuous, adding a quadratic term) and Mediterranean diet adherence (13-point score). All models were stratified by recruitment centre.

Multivariate model 3 showed significant effects of frequency of total nut consumption on risk of total mortality: Hazard ratio (HR) (95% CI) = 0.61 (0.45 to 0.83), \( P \) for trend = 0.012], frequency of consumption of nuts other than walnuts \( HR = 0.55 \) (0.40 to 0.76), \( P \) for trend = <0.001] and frequency of walnut consumption \( HR = 0.66 \) (0.46 to 0.93) \( P \) for trend = 0.047], and for consumers of more than 3 servings nuts/wk (Figure 18). These data provide strong support for the effect of nut consumption on reducing the risk of death from all causes (Guasch-Ferre et al., 2013).

Multivariate model 3 showed no significant effect of frequency of total nut consumption on risk of cardiovascular disease, but showed significant differences for frequency of consumption of nuts other than walnuts \( HR = 0.42 \) (0.20 to 0.89), \( P \) for trend = 0.031] and frequency of walnut consumption \( HR = 0.53 \) (0.29 to 0.98) \( P \) for trend = 0.047], and for consumers of more than 3 servings per week. These data provide strong support for the effect of nut consumption on reducing the risk of CVD (Guasch-Ferre et al., 2013).
### Figure 18. The effect of consumption of >3 servings of nuts/day on risk of CVD mortality and all-cause mortality (Guasch-Ferre et al., 2013).

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVD Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Nut</td>
<td>2295</td>
<td>0.091</td>
</tr>
<tr>
<td>Walnut</td>
<td>1753</td>
<td>0.047</td>
</tr>
<tr>
<td>Other Nuts (Excluding Walnuts)</td>
<td>1265</td>
<td>0.031</td>
</tr>
<tr>
<td><strong>All-Cause Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Nut</td>
<td>2295</td>
<td>0.012</td>
</tr>
<tr>
<td>Walnut</td>
<td>1753</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other Nuts (Excluding Walnuts)</td>
<td>1265</td>
<td>0.031</td>
</tr>
</tbody>
</table>
Appel and Van Horn (2013) reported that the control group of the PREDIMED study did not, in fact, follow a low-fat diet, but seemed to follow a variant of the Mediterranean Diet. This control group diet contained 37% total fat as a percentage of energy intake, while for the groups following the Mediterranean diet, the value was 41%. Saturated fat intake was similar for the three diet group (9%). The most significant difference between groups was considered to be in terms of supplemented foods.

4. Discussion
The expert panel analyzed the strength of the evidence for the relationship between tree nut consumption and risk of CVD.

4.1. Observational Study Analyses
Based on the data from observational study analyses, Tot CHD, Fatal CHD, Tot CVD, and all cause mortality had a consistent inverse association with tree nut consumption. Although multiple analyses were reported these analyses represent a limited number of populations. There was no significant association with nut consumption for stroke, nonfatal MI or heart failure. Observational studies in which peanut consumption was not distinguished from nut consumption were included in the review.

Very few cross-sectional study analyses have evaluated blood pressure or cholesterol and those analyses that did so did not find consistent significant inverse associations. Three analyses reported continuous outcomes for FDA approved biomarkers, but the data from these studies could not be shown in a Forest plot. Two analyses reported no significant effects on Tot-C, LDL-C, or diastolic BP, but reported a significant effect on systolic BP. The third study reported significant reductions in Tot-C and LDL-C.

Four analyses reported continuous outcomes for non-FDA approved biomarkers that could not be shown in a Forest plot. Two of three analyses measuring HDL-C reported a significant reduction in HDL-C, while the other reported no effect compared with base concentrations. Neither of two analyses that measured the effects on TG reported a significant effect compared with base concentrations. The only study that measured Apo B reported a significant reduction compared with base concentrations. All three analyses that measured CRP reported a reduction in CRP compared with base.

Although relatively few cohorts were studied, the observational evidence consistently reports inverse associations between nut consumption and the risk of total CHD, fatal CHD, total CVD, all cause mortality, or hypertension. No associations were reported for heart failure or stroke. Analyses of the association of nut consumption with biomarkers yielded variable results for Tot-C, LDL-C, BP, HDL-C or TG. A few analyses reported decreased concentrations of CRP or Apo B.

4.2. Interventional Study Analyses
Analyses that only reported within group comparisons are listed as NCT (non-controlled trials) even if they described themselves otherwise and did not meet the FDA criteria for inclusion. Of the 81 analyses that met our broad inclusion criteria and addressed biomarkers for CVD, 53...
analyses also met FDA inclusion criteria. Considering only analyses that reported on validated biomarkers and otherwise met FDA criteria, 28 out of 53 (53%) reported that nuts significantly lowered Tot-C, and 23 out of 51 (45%) reported that nuts significantly lowered LDL-C compared with control. No analyses reported a significant increase in Tot-C, and only one analysis with a neutral quality rating reported a significant increase in LDL-C. Of those analyses that failed to meet FDA criteria, 15 out of 23 (65%) reported that nuts significantly lowered Tot-C and 16 out of 23 (70%) reported that nuts significantly lowered LDL-C. The vast majority of analyses were of positive or neutral quality rating. Approximately 56% of analyses showed benefit of nut consumption on Tot-C or LDL-C, 44% showed no effect, and none showed harm. Although most analyses reported lower Tot-C and LDL-C concentrations after consumption of tree nuts, the number of non-significant findings limits the strength of this association.

The vast majority of analyses reporting on either systolic BP or diastolic BP did not attain statistical significance. Of those that did attain statistical significance, 3 reported a decrease and 2 reported an increase compared with control. In contrast to the consistent significant inverse association between tree nut consumption and the risk of hypertension in the observational analyses, the interventional analyses reported no consistent effect on either SBP or DBP. Many analyses reported on comparisons to baseline (within group comparisons) as well as between group comparisons.

As a part of the panel’s broader evaluation of the effect of tree nuts on CVD, they considered analyses that reported on CVD biomarkers that are not validated, but were selected by the panel as providing supportive evidence. Of those analyses that otherwise met FDA criteria with respect to study design, 34 out of 50 (68%) did not attain statistical significance for HDL-C, 10 (20%) reported values significantly less than control and 6 (12%) reported values significantly greater than control. Of those analyses that failed to meet FDA criteria, 17 out of 25 (68%) did not attain statistical significance for HDL-C, 2 (8%) reported values significantly less than control, and 6 (24%) reported values greater than control. Considering narrow and broad studies together, 50 out of 76 analyses (68%) did not attain statistical significance, and 12 analyses each reported increased or decreased values. There is no effect on HDL-C.

In examining the effect of nut consumption on Tot-C:HDL-C, an unvalidated biomarker, analyses that otherwise met the FDA criteria showed that 8 out of 16 (50%) of studies reported a significant negative difference, 1 out of 16 (6%) reported a significant positive difference, and 7 out of 16 (44%) reported no significant difference. Of those analyses that failed to meet FDA criteria, 6 out of 8 analyses (75%) reported a significant negative difference and 2 out of 8 (25%) reported no significant difference, and none reported a significant positive difference. Considering narrow and broad studies together, 8 out of 24 analyses (33.3%) did not attain significance, 14 out of 24 analyses (58.3%) reported values less than control and 2 out of 24 (8.3%) reported values greater than control. These data, in particular for studies that failed to meet the FDA criteria, suggest that nut consumption has a significant positive effect on Tot-C:HDL-C.

Of those analyses that otherwise met FDA criteria, 44 (80%) out of 55 did not attain statistical significance for TG, another non-FDA-validated biomarker for CVD, 11 (20%) reported values less than control and 1 (2%) reported a value greater than control. Of those analyses that failed to
meet FDA criteria, 17 out of 22 (77%) did not attain statistical significance; 3 (14%) reported values less than control, and 2 (9%) reported a value greater than control. Considering narrow and broad studies together, 61 out of 77 (79%) analyses did not attain significance, 14 (18%) reported values less than control and 3 (4%) reported values greater than control. These data suggest that there is no effect on TG.

The effect of tree nut consumption on apolipoproteins was also assessed. Combining all analyses reporting values on Apo A1, 24 out of 29 analyses (83%) did not attain significance, 3 (10%) reported values less than control and 2 (7%) reported values greater than control. It can be inferred that there is no effect on Apo A1. Of those analyses that otherwise met FDA criteria, 13 out of 21 (62%) analyses reported values for Apo B less than control and the remaining 8 analyses (38%) did not attain significance. Of those analyses that failed to meet FDA criteria, 2 analyses (33%) reported values less than control and the remaining 5 (67%) analyses did not attain significance. Combining all analyses reporting values on Apo B, 15 out of 27 (44%) did not attain significance, 12 (56%) reported values less than control, and none reported values greater than control. There appears to be an effect on Apo B. Four analyses examined the effect of nut consumption on Apo B-100. Two analyses showed a significant negative effect and two analyses showed no effect. Based on this information, there appears to be no effect of tree nut consumption on Apo B-100.

Of those analyses that otherwise met FDA criteria, 12 out of 14 (86%) did not attain significance for CRP; the remaining two analyses (14%) reported a significant decrease from control. None of the four analyses that failed to meet FDA criteria attained significance for CRP. These data suggest that there is no effect on CRP.

The results of this review are consistent with previous meta-analyses of the effects of nuts on biomarkers of CVD. Banel and Hu (2009) evaluated 13 randomized controlled clinical trials (representing 365 participants) to estimate the effect of walnuts on blood lipids. The trials ranged from 4 to 24 weeks in length and walnuts provided 10-24% of total calories. Compared to control diets, diets supplemented with walnuts resulted in decreased Tot-C and LDL-C, WMD = -10.3 mg/dL, P < 0.001; LDL cholesterol: WMD = -9.2 mg/dL, P < 0.001), respectively. There were no significant differences in HDL-C or TG.

Sabaté et al. (2010) pooled data from 25 randomized controlled nut consumption trials (representing 583 participants) and evaluated the effects of nut consumption on blood lipids. The mean consumption of nuts was 67 g/day and the analyses ranged from 3 to 43 wk. Analyses on almonds, hazelnuts, macadamia nuts, peanuts, pecans, pistachios, and walnuts were included. Compared to control diets, diets supplemented with nuts resulted in lower Tot-C (-0.28 mmol/L), LDL-C (-0.26 mmol/L), LDL-C:HDL-C ratio (-0.22) and Tot-C:HDL-C ratio (-0.24) (P < 0.001 for all). TG concentrations were reduced in subjects with TG concentrations ≥ 150 mg/dL (P < 0.05), but not in those with lower concentrations.

Phung et al. (2009) combined data from 5 randomized controlled clinical trials (representing 142 participants) evaluating the effect of almond consumption on blood lipid parameters. The mean consumption of almonds ranged from 25 – 168 g/d. Compared to control diets, diets supplemented with almonds resulted in lowered Tot-C (-0.18 mmol/L) [95% CI -0.34 to -0.02)],
showed a “strong trend” to lowered LDL-C (-0.15 mmol/L) [95% CI -0.29 to 0.00]) but resulted in no change in HDL-C or LDL-C:HDL-C ratio.

5. Limitations

- In some cases, these were multiple analyses of the same cohort which lead to the inference that there were more observational studies of clinical endpoints than there actually were.
- There is a concern about publication bias for observational studies of clinical endpoints.
- These limitations would be much less likely to influence the summary of findings from controlled intervention studies evaluating blood lipid levels, given the much larger numbers of such published studies.
- Use of multiple survey instruments with various serving sizes made dose comparisons difficult.
- Use of multiple comparatives and/or different placebo controls may have added additional confounding.

6. Conclusions

- Combining the results of the observational study analyses with the interventional study analyses meeting the FDA criteria, there is strong evidence that consumption of tree nuts has a beneficial effect on cardiovascular health and a real and practical effect in reducing the risk of CVD.
- This beneficial health effect is also supported by the results of the analyses that did not meet the FDA criteria and by the results on unvalidated biomarkers in observational and interventional studies.
- This beneficial health effect is consistent with published meta-analyses studying the effect of nuts.
- This beneficial health effect is consistent with the results of several analyses of the PREDIMED cohort.
- The beneficial effects of nut consumption on blood total cholesterol may be mediated in part by the replacement of saturated fat with nuts but replacement of saturated fat does not account for all the beneficial effects.
- The consumption of nuts under the experimental conditions of the analyses reviewed in this report is not obesogenic.
7. References


8. Included Studies
Interventional Studies Included in Review


Observational Studies Included in Review


9. Acronyms and Abbreviations

Acronyms and abbreviations

AHS Adventist Health Study
Apo A1 Apolipoprotein A1
Apo B Apolipoprotein B
Apo B-100 Apolipoprotein B-100
BP Blood pressure
CVD Cardiovascular disease
CARDIA Coronary Artery Risk Development in Young Adults study
CHD Coronary Heart Disease
CRP C-reactive protein
XS Cross-sectional
DBP Diastolic blood pressure
EAW Evidence analysis worksheet
EVOO Extra virgin olive oil
FDA Food and Drug Administration
FDAMA Food and Drug Administration Modernization Act
FFQ Food frequency questionnaire
HPFS Health Professionals Follow-up Study
HDL-C High-density lipoprotein-Cholesterol
IOM Institute of Medicine
INC NREF International Tree Nut Council Nutrition Research & Education Foundation
IMT Intima-media thickness
IWHS Iowa Women’s Health Study
LSRO Life Sciences Research Organization
LP(a) Lipoprotein (a)
LDL-C Low-density lipoprotein-cholesterol
MESA Multi-Ethnic Study of Atherosclerosis
MI Myocardial infarction
MUFA Monounsaturated fatty acids
NHANES National Health and Nutrition Examination Survey
N/A Not applicable
NCT Non-controlled trial
NHS Nurses Health Study
NLEA Nutrition Labeling and Education Act
NRCOT Non-randomized Controlled Trial
NRCT Non-randomized Crossover Trial
NS Not significant
PHS Physicians Health Study
OO Olive oil
PC Placebo-controlled
QCC Quality control checklist
QR Quality rating
RCT Randomized Controlled Trial
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>RCOT</td>
<td>Randomized Crossover Trial</td>
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<tr>
<td>SU.VI.MAX</td>
<td>Supplementation en Vitamines et Mineraux Antioxydants study</td>
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<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
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<tr>
<td>Total-C</td>
<td>Total serum cholesterol</td>
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<td>TG</td>
<td>Triglycerides</td>
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10. Expert Panel and LSRO Staff

**Rebecca Bortz Costello, Ph.D.**, received her B.S. and M.S. degrees in biology from the American University, Washington, D.C., and her Ph.D. in clinical nutrition from the University of Maryland at College Park in 1994. Her research interests include mineral nutrition and dietary interventions to reduce cardiovascular disease.

Dr. Costello currently serves as a part-time scientific consultant to the NIH Office of Dietary Supplements (ODS). Prior to retiring in September 2011, Dr. Costello held the position of Director of Grants and Extramural Activities for the ODS from May 2006 to September 2011. From January 1999 to April 2006 she served as Deputy Director and from January 1999 to October 1999 as Acting Director. During her tenure, Dr. Costello took part in the development of the ODS Strategic Plan and through organizing workshops and conferences helped to implement the plan's goals and objectives.

Prior to her NIH appointment, Dr. Costello served as the Project Director for the Committee on Military Nutrition Research with the Food and Nutrition Board of the National Academy of Sciences. At the NAS her research focused the use of nutritional supplements by military personnel for enhancing and sustaining performance. Prior to her work at the NAS, she served as a Research Associate and Program Director for the Risk Factor Reduction Center at the Washington Adventist Hospital and as a Research Biologist at the Veterans Administration Medical Center in Washington, D.C.

Dr. Costello is an active member of the American Society for Nutrition, American Heart Association, and the Southern Society for Clinical Investigation. She is a liaison member to the Nutrition Committee of the American Heart Association and serves as an adjunct assistant professor in the Department of Military and Emergency Medicine of the Uniformed Services University of the Health Sciences in Bethesda, MD. She has authored many journals and textbooks and has been invited to speak at numerous professional meetings.

**Richard J. Deckelbaum, M.D., C.M., F.R.C.P.**, currently serves as the Robert R. Williams Professor of Nutrition, Professor of Pediatrics and as Professor of Epidemiology; Director, Institute of Human Nutrition at Columbia University, New York, NY. He received his B.Sc. and M.D., C.M. at McGill University in Montreal, Canada. The major focus of Dr. Deckelbaum's research is to determine regulatory mechanisms for cell-lipid particle interaction, lipid-related gene expression, and cell cholesterol and triglyceride metabolism. He has also been active in interpreting his basic research findings to practical applications in various populations.

Dr. Deckelbaum has chaired many task forces including those for the American Heart Association, the European Atherosclerosis Society, the Institute of Medicine, and the March of Dimes. He has also served on and/or chaired advisory committees at the NIH, RAND Corporation, the U.S. National Academy of Sciences, and is a Senior Fellow of the Synergos Institute.
Prior to his tenure at Columbia University, Dr. Deckelbaum served as a physician in Zambia, helped to establish the first children’s hospital in the West Bank of the Jordan and organized research and health programs among the Egyptian, Palestinian, and Israeli populations. He helped to initiate and presently directs, in collaboration with the Columbia University Medical Center, the Medical School for International Health, a medical school at Ben-Gurion University of the Negev, Israel.

Among his many honors he was the 2011 recipient of the Global Health Education Consortium’s Lifetime Achievement Award. Along with his research and teaching responsibilities, Dr. Deckelbaum continues his projects related to health and science as a bridge between different populations in the Mideast, Africa, and Asia.

Dr. Deckelbaum has published over 350 research publications, as well as being co-editor of a number of books, such as Preventive Nutrition, now in its 4th edition.

**Michael Lefevre, Ph.D.,** is the Scientific Director of the Applied Nutrition Research team at Utah State University (USU), Logan, UT. He is also the Utah Science Technology and Research (USTAR) Professor, in the Center for Advanced Nutrition at USU. Prior to coming to USU, Dr. Lefevre served as the Chief of the Division of Functional Foods Research and professor in the Division of Nutrition and Chronic Diseases at the Pennington Biomedical Research Center in Louisiana as well as an adjunct professor at Louisiana State University’s School of Human Ecology.

Dr. Lefevre received his B.S. and Ph.D. degrees in Nutrition from the University of California, Davis, CA, and did post-doctoral work in nutrition and physiology at UC Davis and at the Louisiana State University Medical Center, New Orleans, LA, respectively. His main research interests include the role of phytochemical dietary components on overall health, the role of dietary constituents as risk factors of CVD, and the role of identified genetic factors that contribute to coronary disease risk.

Dr. Lefevre, a member of the American Association for the Advancement of Science, the American Society for Nutrition, and the Institute of Food Technology, is also a Fellow of the American Heart Association, Council on Arteriosclerosis; Council on Nutrition, Metabolism and Physical Activity; Council on Epidemiology and Prevention. Moreover, he has served as a member of Kraft’s Worldwide Health and Wellness Advisory Council, as a scientific advisor to ILSI North America’s Technical Committee on Fatty Acids, and as Scientific Advisor to the Soy Nutrition Institute.

Dr. Lefevre has authored or co-authored nearly 90 scientific publications and has served as a peer-reviewer on nearly 20 scientific journals notably, American Journal of Clinical Nutrition, Circulation, Journal of Lipid Research, Metabolism, and Obesity Reviews.

**Dariush Mozaffarian, M.D., Dr.PH,** earned his B.S. in Biological Sciences from Stanford University, Palo Alto, CA his M.D. from Columbia College of Physicians and Surgeons, New York, NY, his M.P.H. in epidemiology from The University of
Washington School of Public Health, Seattle, WA and his Dr.PH. in epidemiology from the Harvard School of Public Health (HSPH) Boston, MA.

Dr. Mozaffarian is Co-Founder and Co-Director of the Harvard Program in Cardiovascular Epidemiology; Associate Professor in the Division of Cardiovascular Medicine, Brigham and Women’s Hospital and Harvard Medical School; and Associate Professor in the Department of Epidemiology, Harvard School of Public Health. He is a clinically active cardiologist with a doctorate in Epidemiology whose research focuses on lifestyle and cardiometabolic health in the US and globally. He is a recognized expert in the field of diet and cardiometabolic risk, having authored or co-authored nearly 200 scientific publications on lifestyle and cardiovascular health, obesity, diabetes, and related national and global policies. He has extensive experience in leading and directing development, implementation, and evaluation of programs and projects in epidemiology, global demography, and translational research. He teaches three courses at Harvard, including two that he founded, on cardiovascular disease epidemiology and global policies. Dr. Mozaffarian has served in leadership and advisory roles for numerous national and international advisory and working groups, including for the World Health Organization, United Nations Food and Agriculture Organization, American Heart Association, Canadian government, and Chicago Council on Global Affairs. Dr. Mozaffarian has also managed several large interdisciplinary, multi-site, multi-country initiatives, including serving as Co-PI and Co-Chair of the Steering Committee for the large international OPERA trial, Co-Chair of the International CHARGE Consortium Fatty Acid Working Group, Chair of the Global Burden of Diseases Nutrition and Chronic Diseases Expert Group, US Director of the Fogarty International Research Training Program in South America, and PI of several large multicenter NIH grants.
Amy M. Brownawell, PhD, ELS, is a Senior Consultant at the Life Sciences Research Organization (LSRO). She holds both a BS and MS in Chemistry from Georgetown University and received a PhD in Cellular and Molecular Pharmacology from the University of Virginia where she also completed a postdoctoral fellowship in the Center for Cell Signaling. She is a certified Editor in the Life Sciences. Since joining LSRO in 2003, Dr. Brownawell has served as editor for two LSRO reports, Review and Analysis of the Literature on the Health Effects of Dental Amalgam and Biological Effects Assessment in the Evaluation of Potential Reduced-Risk Tobacco Products, and as a staff writer for Differentiating the Health Risks of Categories of Tobacco Products. In addition, she organized a workshop on Assessing the Environment for Regulatory Change for EPA and DHA Nutrition Labeling sponsored by the Global Organization for EPA and DHA Omega-3 (GOED) and a conference, Cholesterol: Where Science and Public Health Policy Intersect, sponsored by the Egg Nutrition Center and cosponsored by the USDA Agricultural Research Service and the American Society for Nutrition. Dr. Brownawell has served as project manager for two ILSI North America projects: a Literature Review on the Relationship between Dietary Factors and Mental Energy for the Technical Committee on Energy and a Review of the Evidence on the Relationship between Hyperactivity and Artificial Food Colorings for the Technical Committee on Food and Chemical Safety. In addition, she managed and edited Prebiotics and the Health Benefits of Fiber: Current Regulatory Status, Future Research, and Goals for the Kellogg Company. Dr. Brownawell is a member of American Medical Writers Association, Sigma Xi, and the Society of Toxicology.

Michael C. Falk, Ph.D., is Executive Director of LSRO and Secretary/Board member for the LSRO Board of Directors. Dr. Falk received a B.S. in Chemistry from Bates College, and graduated from Cornell University in 1976 with a Ph.D. in Biochemistry and a Minor in Organic Chemistry. He was awarded an NIH Postdoctoral Fellowship and attended Harvard University Medical School (1975–1978). Dr. Falk’s awards include graduating with Honors in Chemistry, NIH Postdoctoral Fellowship, Outstanding Performance Awards 1982–1996, and NMRI Most Significant Scientific Publication (1986).

Dr. Falk held various positions from 1978–1997 at the Naval Medical Research Institute, Bethesda, MD: Principal Investigator (1978–1985); Division Head and Principal Investigator (1985-1990); Director, Wound Repair Program (1988–1992); Director Biochemistry and Cell Biology (1991–1993); Director, Septic Shock Research Program (1992–1996); Acting Director, Resuscitative Medicine Program (1996); founding and key member Institute Scientific Advisory Board; Acting Scientific Director; key member Institute Organizational Transition Team; consultant to Diving Medicine Program; Adjunct Assistant Professor of Biochemistry, Uniformed Services University of the Health Sciences; and Principal, MCF Science Consultants (1997–1998). He joined the Life Sciences Research Office in 1998.

Dr. Falk has published over 80 publications, presentations, and technical articles and has served as a reviewer for various scientific journals in the fields of biochemistry, shock, and clinical research.
As the Executive Director of LSRO, Dr. Falk manages the evaluation of biomedical information and scientific opinion for regulatory and policy makers in both the public and private sectors. At LSRO, he has written papers on infant nutrition, food labeling, food safety, and military dental research. He organized several international conferences and managed studies on health claims, GRAS reviews, new dietary ingredient reviews, and various regulatory and policy issues related to food and nutrition.

Dr. Falk is a member of the American Society for Biochemistry and Molecular Biology, the American Association for the Advancement of Sciences, the American Society for Nutrition, and the Institute of Food Technologists.

Robin S. Feldman, B.S., M.B.A., is the LSRO Literature Specialist. She is a seasoned information specialist with experience in the electronic acquisition, analysis, and management of scientific, business, and regulatory information. Ms. Feldman obtained her B.S. from the George Washington University in Washington, DC, with a major in zoology, and her M.B.A. from the University of Maryland at College Park, with a concentration in science and technology. She previously worked as a Biomedical Research Assistant at Consultants in Toxicology, Risk Assessment and Product Safety, where she obtained and researched scientific literature for private and governmental clients. At the National Alliance for the Mentally Ill, she designed and implemented a document management and retrieval system for the Biological Psychiatry Branch of the National Institute of Mental Health and served as Managing Editor of Bipolar Network News, a newsletter for the Stanley Foundation Bipolar Network. At Howard Hughes Medical Institute (HHMI), she oversaw implementation of the HHMI Predoctoral Fellowship in Biological Sciences program. While serving as Science Information Specialist at the Distilled Spirits Council of the United States, she managed the installation of a local area network and participated in development and maintenance of an electronic research database for the beverage alcohol industry. She also coordinated the biomedical literature for the ILSI Europe book entitled: *Health Issues Related to Alcohol Consumption*. As a Report Coordinator at Microbiological Associates, Inc., she conducted statistical analyses and prepared technical reports about toxicology studies using animal models. She also served as data management administrator for the National Toxicology Program’s sponsored studies. Ms. Feldman manages LSRO’s publication process and manuscript submissions, maintains LSRO’s library, responds to requests for reports, and assists LSRO’s scientists and expert panels in discovering, obtaining, compiling, and documenting the scientific literature required to prepare reports for governmental, and public and private corporate clients. She is a co-editor of the LSRO Report *Phase Two: Scientific Criteria for the Evaluation of Ingredients Added to Cigarettes*, and has co-authored several abstracts and poster presentations.

Kara D. Lewis, Ph.D., is a Senior Staff Scientist at the Life Sciences Research Office (LSRO). She graduated *summa cum laude* with a B.S. in biology from Spelman College and earned a Ph.D. in biology with a concentration in neuroscience from Clark University. Dr. Lewis conducted postdoctoral research in the Department of Molecular Cellular and Developmental Biology at Yale University. She has investigated olfaction and gustation in the fruit fly, *Drosophila melanogaster*, and the molecular mechanisms of
sweet taste transduction in the blowfly, *Phormia regina*. While at LSRO, Dr. Lewis has served as editor of two LSRO reports: *Differentiating the Health Risks of Categories of Tobacco Products* and *Exposure Assessment of Potential Reduced-Risk Tobacco Products* and as co-editor of the LSRO Report, *Phase Two: Scientific Criteria for the Evaluation of Ingredients Added to Cigarettes*. Dr. Lewis helped organize the Equol, Soy, and Menopause Research Leadership Conference and was the coordinator of Journal of Nutrition supplement that was based on the conference presentations. She also has coordinated self-affirmed GRAS reviews for LSRO corporate clients and GRAS notifications to the U.S. Food and Drug Administration. Dr. Lewis has coauthored seven peer-reviewed articles and has contributed to numerous LSRO reports for government, public and private corporate clients.
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12.1 Appendix A: Figure 4. Frequency distribution of the difference between control or baseline and test values for Tot-C

References are in the order they appear from left to right.


12.2 Appendix B: Figure 5. Frequency distribution of the difference between control or baseline and test values for LDL-C

References are in the order they appear from left to right.


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References are in the order they appear from left to right.


12.4 Appendix: D: Figure 7: Frequency distribution of the difference between control and test values for HDL-C

References are in the order they appear from left to right.


References are in the order they appear from left to right.


12.6 Appendix F: Figure 9: Frequency distribution of the difference between control and test values for TG

References are in the order they appear from left to right.


12.7 Appendix G: Figure 11: Frequency distribution of the difference between control and test values for Apo A1

References are in the order they appear from left to right.


12.8 Appendix H: Figure 12: Frequency distribution of the difference between control and test values for Apo B

References are in the order they appear from left to right.


12.9 Appendix I: Figure 13: Frequency distribution of the difference between control and test values for Apo B-100

References are in the order they appear from left to right.


12.10 Appendix J: Figure 14: Frequency distribution of the difference between control and test values for CRP

References are in the order they appear from left to right.


12.11 Appendix K: Figure 15. Frequency distribution of the difference between control and test values for Total-C (Substituted Fatty Acids vs. Non-Substituted Fatty Acids)

References are in the order they appear from left to right.


12.12 Appendix L: Figure 16. Frequency distribution of the difference between control and test values for LDL-C (Substituted Fatty Acids vs. Non-Substituted Fatty Acids)

References are in the order they appear from left to right.


12.12 Appendix M: Intervention study analyses reporting surrogate endpoints that do not meet the FDA criteria
## Appendix M: Intervention Study Analyses Reporting Surrogate Endpoints That Do Not Meet FDA Criteria

<table>
<thead>
<tr>
<th>Reference</th>
<th>Quality Rating</th>
<th>Clinical Design</th>
<th>Nut(s)</th>
<th>Dose (g/d)</th>
<th>Placebo or Comparator</th>
<th>Intervention Duration (wk)</th>
<th>Final N</th>
<th>Apo A1 (mg/dL)</th>
<th>Apo B (mg/dL)</th>
<th>Apo B-100 (mg/dL)</th>
<th>CRP</th>
<th>CVD Endpoints</th>
<th>FDA</th>
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<tr>
<td>Abbey, et al. 1994 (nut)</td>
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<td>Almonds</td>
<td>84</td>
<td>Habitual (Australian) with peanuts and coconut</td>
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<td>16</td>
<td>0.00 NS</td>
<td>0.02 NS</td>
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<td>7.0 0.009 Y</td>
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<td>Habitual (Australian) with peanuts and coconut</td>
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<td>Aldemir et al. 2011</td>
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<td>Pistachios</td>
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<td>18</td>
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<td>1.96 NS</td>
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<td>Almario et al. 2001 (diet)</td>
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<td>Walnuts</td>
<td>48</td>
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<td>18</td>
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<td>0.00 NS</td>
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<td>-15.97 NS</td>
<td>0.00 NS</td>
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<td>Aminis, et al. 2012</td>
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<td>Isoenergetic-linoleic diet</td>
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<td>Canales et al. 2007</td>
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<td>Walnuts</td>
<td>19.4</td>
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<td>22</td>
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<td>0.00 NS</td>
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<td>Canales et al. 2011</td>
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<td>-15.97 NS</td>
<td>0.00 NS</td>
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<td>Chisholm et al. 1998</td>
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<td>Low fat (30%) diet</td>
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<td>Colquhoun et al. 1996</td>
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<td>75</td>
<td>High CHO diet</td>
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<td>Y</td>
<td></td>
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<td>Coccaci et al. 2012</td>
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<td>30</td>
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<td>-6 NS</td>
<td>0.2 NS</td>
<td>Y</td>
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<td>Damasceno et al. 2011 (nut)</td>
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<td>52.5</td>
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<td>18</td>
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<td>-0.09 NS</td>
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<td>-6 NS</td>
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<td>-0.09 NS</td>
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<td>Habitual diet</td>
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<td>Low calorie diet w/o nuts</td>
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<td>56</td>
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<td>72</td>
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<td>65</td>
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<td>Morgan JM et al. 2002</td>
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<td>Walnuts</td>
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<td>RCT</td>
<td>Walnuts</td>
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<td>Wang et al. 2012 (closed)</td>
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<td>RCT</td>
<td>Pistachios</td>
<td>42</td>
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<td>12</td>
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<td>Wang et al. 2012 (closed)</td>
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<td>Wein et al. 2003</td>
<td>+</td>
<td>NCT</td>
<td>Almonds</td>
<td>84</td>
<td>Isoenergetic self-selected complex CHO</td>
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<td>&lt;0.05</td>
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<td>Almonds</td>
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<td>Yucesan et al. 2010</td>
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