Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: systematic review, meta-analysis, and dose-response of 61 controlled intervention trials[1–3]

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ABSTRACT

Background: The effects of nuts on major cardiovascular disease (CVD) risk factors, including dose-responses and potential heterogeneity by nut type or phytosterol content, are not well established.
Objectives: We examined the effects of tree nuts (walnuts, pistachios, macadamia nuts, pecans, cashews, almonds, hazelnuts, and Brazil nuts) on blood lipids [total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein, and triglycerides], lipoproteins [apolipoprotein A1, apolipoprotein B (ApoB), and apolipoprotein B100], blood pressure, and inflammation (C-reactive protein) in adults aged ≥18 y without prevalent CVD.
Design: We conducted a systematic review and meta-analysis following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Two investigators screened 1301 potentially eligible PubMed articles in duplicate. We calculated mean differences between nut intervention and control arms, dose-standardized to one 1-oz (28.4 g) serving/d, by using inverse-variance fixed-effects meta-analysis. Dose-response for nut intake was examined by using linear regression and fractional polynomial modeling. Heterogeneity by age, sex, background diet, baseline risk factors, nut type, disease condition, duration, and quality score was assessed with meta-regression. Publication bias was evaluated by using funnel plots and Egger's and Begg's tests.
Results: Sixty-one trials met eligibility criteria (*n* = 2582). Interventions ranged from 3 to 26 wk. Nut intake (per serving/d) lowered total cholesterol (−4.7 mg/dL; 95% CI: −5.3, −4.0 mg/dL), LDL cholesterol (−4.8 mg/dL; 95% CI: −5.5, −4.2 mg/dL), ApoB (−3.7 mg/dL; 95% CI: −5.2, −2.3 mg/dL), and triglycerides (−2.2 mg/dL; 95% CI: −3.8, −0.5 mg/dL) with no statistically significant effects on other outcomes. The dose-response between nut intake and total cholesterol and LDL cholesterol was nonlinear (*P*-nonlinearity < 0.001 each); stronger effects were observed for ≥60 g nuts/d. Significant heterogeneity was not observed by nut type or other factors. For ApoB, stronger effects were observed in populations with type 2 diabetes (−11.5 mg/dL; 95% CI: −16.2, −6.8 mg/dL) than in healthy populations (−2.5 mg/dL; 95% CI: −4.7, −0.3 mg/dL) (*P*-heterogeneity = 0.015). Little evidence of publication bias was found.
Conclusions: Tree nut intake lowers total cholesterol, LDL cholesterol, ApoB, and triglycerides. The major determinant of cholesterol lowering appears to be nut dose rather than nut type. Our findings also highlight the need for investigation of possible stronger effects at high nut doses and among diabetic populations. *Am J Clin Nutr* 2015;102:1347–56.

INTRODUCTION

Accumulating evidence from prospective observational studies and a large clinical trial suggests that nut intake lowers the risk of cardiovascular disease (CVD)[6] (1, 2). Tree nuts are rich in unsaturated fats, soluble fiber, antioxidants, and phytosterols (3), which separately or together may produce beneficial effects on serum lipids, blood pressure, and inflammation (4, 5). Prior meta-analyses of controlled trials have shown that tree nut intake lowers total and LDL cholesterol (6–8). However, effects of nut consumption on other key CVD risk factors, including specific lipoproteins, blood pressure, and inflammation, are not established. In addition, 2 of these prior meta-analyses evaluated only one type of nuts—almonds (6) (*n* = 5 trials) and walnuts (7) (*n* = 13 trials)—and potential effects of other tree nuts remain unclear. Furthermore, previous analyses (6–9) have not standardized pooled effects to a common dose or tested for nonlinearity of dose-responses, preventing conclusions about the magnitude of effects for a given intake of nuts or potential for nonlinear effects. Therefore, key questions remain on the major cardiovascular mechanisms influenced by tree nuts, on whether some types of nuts are preferential for improving risk, and on dose-response relations of these effects.

To address these knowledge gaps, we performed a systematic review and meta-analysis of controlled interventional trials to

examine the effects of tree nuts (walnuts, pistachios, macadamia nuts, pecans, cashews, almonds, hazelnuts, pine nuts, and Brazil nuts) on major CVD risk factors, including blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides), lipoproteins [apolipoprotein A1, apolipoprotein (ApoB), and apolipoprotein B100], blood pressure (systolic and diastolic), and inflammation (C-reactive protein, CRP) in adults aged ≥18 y without prevalent CVD. We hypothesized that tree nuts would lower concentrations of LDL cholesterol and its primary lipoprotein, ApoB. As a secondary hypothesis, we evaluated potential differences in effects by nut type.

METHODS

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (10) during all stages of implementation, analysis, and reporting of this meta-analysis. A review protocol has not been published.

Eligibility criteria

We searched for all published controlled trials that reported the effect of tree nut consumption on blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides), lipoproteins (apolipoprotein A1, ApoB, and apolipoprotein B100), blood pressure (systolic and diastolic), or inflammation (CRP). We did not include body weight or adiposity as outcomes because a meta-analysis of nut intake and body weight was recently reported (11). Trials had to be controlled but could be randomized or non-randomized (with plans to evaluate only randomized trials and all trials combined) and provided mean levels of the outcome in each group with an accompanying measure of statistical uncertainty (e.g., 95% CI, SE) or other data to calculate variance.

We excluded trials testing nonnut parts of the plant, nut oils, nuts other than tree nuts (e.g., areca, betel), or legumes (e.g., peanuts) and trials testing mixed dietary interventions for which the specific effect of nuts could not be evaluated. We also excluded trials among children (aged <18 y), participants with known CVD (myocardial infarction, angina, stroke, severe heart failure, coronary revascularization, or peripheral vascular disease), and participants receiving medication treatment of diabetes, obesity, metabolic syndrome, hypertension, or hyperlipidemia. For crossover trials without a washout period, we excluded trials with an intervention period <3 wk to minimize carryover effects (12). Trials with ≥20% dropout rates or having imbalanced dropout between intervention and control groups were also excluded. Articles presenting only observational data, editorials/commentaries, letters, and reviews were not eligible.

Search and selection of articles

Potentially eligible articles were identified by means of a systematic search in PubMed from the earliest available online indexing year to March 2013, without language restrictions. Query terms were as follows: (Apolipoproteins B[MeSH]) OR Apolipoprotein A-1[MeSH]) OR (Cholesterol, HDL [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 hazelnuts or macadamia or pine nuts or pistachios or walnuts).

Two investigators (MF, KL) screened the titles and abstracts of all potentially eligible articles in duplicate, as well as the full text of all articles identified for further review. In addition, citation lists and the first 20 "related citations" on PubMed of all final included articles were hand-searched for additional eligible trials.

Data extraction

Data were screened and extracted independently and in duplicate by 2 investigators (MF, KL) by using a standardized electronic form, including information on study randomization (yes, no), design (parallel, crossover), nut type, age (mean), sex (percent male), baseline disease condition, treatment duration, dose (g/d), and description of the placebo or control condition. Differences in data extraction between investigators were infrequent and were resolved by consensus. For each outcome, we extracted its mean value (concentration/amount), variance measure, and the number of participants in the treatment and control arms for all reported periods (e.g., baseline, end treatment).

Study quality was assessed by using the Academy of Nutrition and Dietetics (formerly American Dietetic Association) Evidence Analysis Process (13), which evaluates relevance and validity by using a 14-question quality control checklist, including questions on comparability of control and intervention groups, handling of dropouts, blinding, appropriateness of statistical methods, and potential biases (see "Assessment" on last page of **Supplemental Material**). Studies meeting criteria for ≥6 of the 10 validity questions, including questions 2, 3, 6, and 7, were given a positive quality rating; studies meeting ≥6 of the 10 validity questions, but not questions 2, 3, 6, and 7, were given a quality rating of neutral; and studies not meeting at least 6 of 10 validity questions were considered of lower quality (13).

Statistical analysis

For parallel trials, the primary effect measure was the mean difference in change from baseline to follow-up in the intervention vs. control group (14). For crossover trials, the primary effect measure was the mean difference at follow-up in the intervention vs. control periods. The SE of the difference measure was extracted (when directly reported), calculated by using a related statistical measure of uncertainty, or estimated by using the IQR of the difference measure provided in studies. To address within-individual correlation in crossover trials, the median reported correlation across all crossover trials ($r = 0.60$) was used in calculating the SE of the difference when the study-specific correlation coefficient was not otherwise provided. In trials with repeated measures, we included the estimate closest to the median duration of follow-up across trials (4 wk). For trials with more than one comparison group, we included estimates from the control diet most like the intervention diet other than the inclusion of nuts.

For each trial, the effect size and corresponding variance were standardized to one 1-oz daily serving (28.4 g) of nuts. Meta-analyses were performed by using fixed-effects inverse-variance weighting, evaluating randomized trials, nonrandomized trials,

and all trials combined. Heterogeneity was quantified by using the I^2 statistic (15), with >30% considered at least moderate heterogeneity. Heterogeneity was evaluated by prespecified sources, including randomized vs. nonrandomized trials, age, sex, background diet, baseline risk factor level, nut type, co-morbidity, intervention duration, and quality score by using meta-regression. For categorical sources of heterogeneity with ≥3 subgroups, P-heterogeneity from meta-regression was obtained for each indicator category relative to the primary reference category (16).

To test dose-response relations, we plotted the relation between absolute nut intake (g/d) and the absolute mean difference in each outcome, with nonlinearity evaluated by using the F test of linear lack of fit. Fractional polynomial models were used to evaluate nonlinear dose-response relations, with the best-fitting model considered the one with the lowest deviance.

Publication bias was evaluated by visual inspection of funnel plots and by Egger's (17) and Begg's (18) tests. All analyses were performed with STATA 12 (StataCorp LP), with 2-tailed $\alpha = 0.05$.

RESULTS

Study characteristics

Of 1301 articles, 61 trials met eligibility criteria (19–80) (**Figure 1**), totaling 2582 unique participants in 42 randomized and 18 nonrandomized trials (**Table 1**). Trials directly provided nuts to the intervention group, rather than relying only on di-etary advice to consume nuts. Compliance was most often assessed by using self-reported dietary recalls or direct supervision of nut consumption. Median participant age was 45 y, and two-thirds of trials (41/61) included both men and women (see **Supplemental Table 1** for individual study details).

Most trials examined walnuts ($n = 21$) or almonds ($n = 16$); others examined pistachios ($n = 7$), hazelnuts ($n = 6$), macadamia nuts ($n = 4$), pecans ($n = 2$), cashews ($n = 2$), mixed tree nuts ($n = 2$), and Brazil nuts ($n = 1$). The dose of nuts varied from 5 to 100 g/d (median: 56 g/d), and the duration of intervention was from 3 to 26 wk (median: 4 wk). Participants had existing disease conditions in 45% (19/42) of randomized trials and 16% (3/19) of nonrandomized trials; these were most commonly hypertension, hyperlipidemia, and metabolic syndrome (Table 1). In 14 trials, participants received detailed advice to maintain total energy constant between intervention arms; in the remaining 47 trials, participants were provided nuts on top of a common background diet. The most common background diet (i.e., recommended to both intervention and control arms) was habitual diet ($n = 30$ trials); other background diets included American Heart Association, low-fat, high-fat, and Mediterranean-type diets. Most trials obtained a positive ($n = 26$) or neutral ($n = 29$) quality score; 6 trials had a negative score.

Main outcomes

Compared with control, consumption of tree nuts significantly lowered concentrations (mg/dL) of total cholesterol (weighted mean difference per 28 g serving/d: −4.7; 95% CI: −5.3, −4.0),
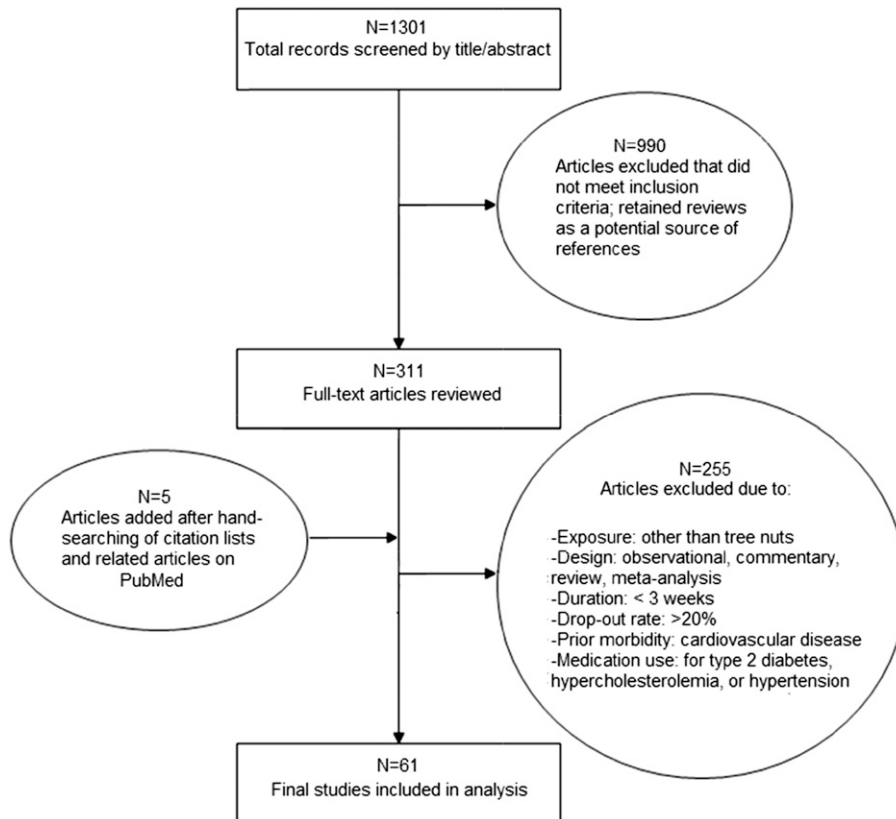
FIGURE 1 Screening and selection of randomized ($n = 42$) and nonrandomized controlled trials ($n = 19$) on tree nut intake and lipids/apolipoproteins, blood pressure, and C-reactive protein (19–80).

TABLE 1
Summary of 61 trials included in meta-analysis of the effect of tree nut intake on lipids/apolipoproteins, blood pressure, and C-reactive protein, stratified by randomization status and tree nut type[1]

Study type/ nut type	Trials, n	Participants (maximum), n	Median age, y	Male, %	Cardiovascular (CVD) comorbidities[2]	Median duration, wk	Median nut dose,[3] g/d	Quality score, n trials[4]
Randomized controlled trials								
Walnut	17	939	54	47	5 trials ($n = 1$ with diabetes)	5	49	10(+), 5(Ø), 2(−)
Pistachio	6	229	48	50	2 trials ($n = 1$ with prostate disease)	4	60	4(+), 2(Ø)
Macadamia	2	68	48	70	1 trial (overweight/obese)	4.5	59	2(Ø)
Pecan	2	65	41	45	2 trials (high cholesterol, MetS)	6	70	1(+), 1(Ø)
Cashew	2	54	64	83	2 trials ($n = 1$ with diabetes)	8	85.5	1(+), 1(Ø)
Almond	9	429	50	56	3 trials (obese, high cholesterol, diabetes)	4	60	6(+), 3(Ø)
Hazelnut	2	201	46	68	2 trials (high cholesterol)	8	36	2(Ø)
Mixed nuts	2	106	51	51	2 trials (obese, MetS)	9	30	1(+), 1(Ø)
Overall	42	2101	53	53	19/42 trials (45%) with CVD comorbidities	5.5	59.5	23(+), 17(Ø), 2(−)
Nonrandomized trials								
Walnut	4	78	60	43	0 trials	6	45	3(Ø), 1(−)
Pistachio	1	17	48	100	0 trials	3	100	1(Ø)
Macadamia	2	41	37	50	0 trials	3.5	43	2(−)
Almond	7	199	46	45	2 trials (obese, high cholesterol)	4	84	2(+), 5(Ø)
Hazelnut	4	109	45	64	1 trials (high cholesterol)	4	54	1(+), 3(Ø)
Brazil	1	37	35	0	0 trials	8	5	1(−)
Overall	19	481	45	50	3/19 trials (16%) with CVD comorbidities	4	49.5	3(+), 12(Ø), 4(−)
All trials								
Overall	61	2582	45	50	22/61 trials (36%) with CVD comorbidities	4	56	26(+), 29(Ø), 6(−)

[1]Total cholesterol and LDL cholesterol were measured as outcomes in 61 trials; HDL cholesterol in 60 trials; triglycerides in 59 trials; apolipoprotein A1 and apolipoprotein B in 23 and 20 trials, respectively; blood pressure in 21 trials; C-reactive protein in 12 trials; and apolipoprotein B100 in 5 trials (19–80). Descriptive information for individual studies is given in Supplemental Table 1. For a summary of the number of studies and effect sizes by outcome, see Table 2. Outcomes included total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, apolipoprotein A1, apolipoprotein B, apolipoprotein B100, systolic blood pressure, diastolic blood pressure, and C-reactive protein. CVD, cardiovascular disease; MetS, metabolic syndrome.

[2]CVD comorbidities refers to trials of patients with diabetes or those that enrolled at least some participants with high cholesterol, metabolic syndrome, or overweight/obesity. Other conditions are specified. Participants were either not receiving medication for CVD comorbidities, or medication use was not specified in the trial.

[3]For meta-analysis, nut dose (g/d) was standardized to 1 serving (28.4 g) of nuts/d.

[4]A quality control checklist comprising 14 questions on relevance and validity was used to award studies a positive (+), neutral (Ø), or negative score (−). Further details on the questions and scoring system are given in the **Supplemental Appendix**.

LDL cholesterol (−4.8; 95% CI: −5.5, −4.2), ApoB (−3.7; 95% CI: −5.2, −2.3), and triglycerides (−2.2; 95% CI: −3.8, −0.5) (**Table 2**). Reductions in total cholesterol were seen in both randomized trials (−3.6; 95% CI: −4.4, −2.9) and nonrandomized trials (−6.7; 95% CI: −7.8, −5.6); effects in the latter were significantly larger (*P*-interaction < 0.001) (**Supplemental Figure 1**). Similar findings were seen for LDL cholesterol: randomized trials, −4.2 (95% CI: −5.0, −3.4); nonrandomized trials, −6.0 (95% CI: −7.1, −4.9); *P*-interaction = 0.01 (**Figure 2**). For ApoB, no significant differences in effects were observed in randomized trials (−4.2; 95% CI: −5.7, −2.6) vs. nonrandomized trials (−1.1; 95% CI: −5.1, 3.0) (*P*-interaction = 0.17) (**Supplemental Figure 2**). Effects on triglycerides were also not statistically significant in nonrandomized trials (−4.6; 95% CI: −8.4, −0.8) vs. randomized trials (−1.6; 95% CI: −3.5, 0.24) (*P*-interaction = 0.16) (**Supplemental Figure 3**).

No significant effects of tree nut consumption were identified for HDL cholesterol, apolipoprotein A1, apolipoprotein B100, systolic or diastolic blood pressure, or CRP (**Supplemental Figures 4–9**). These findings were similar when randomized and nonrandomized trials were separately evaluated.

Dose-responses between nut intake and outcomes

When we evaluated dose-responses, tree nut intake lowered total cholesterol and LDL cholesterol in a nonlinear fashion (*P*-nonlinearity < 0.001); stronger effects were observed in trials providing doses of ≥60 g nuts/d (**Figure 3**). In contrast, there was little evidence for nonlinear dose-response relations between nut intake and ApoB or triglycerides (*P*-nonlinearity > 0.05 each).

Heterogeneity

Heterogeneity was at least moderate ($I^2 > 30\%$) among trials of total cholesterol and LDL cholesterol and nonrandomized trials of triglycerides and HDL cholesterol, as well as low ($I^2 < 30\%$) among trials of apolipoproteins, blood pressure, and CRP (Table 2). No significant differences in effects by nut type were observed (**Supplemental Table 2**), although relatively few trials were available for certain nut types. Heterogeneity by quality score, with greater effect sizes found in lower quality trials, was observed for total cholesterol and LDL cholesterol (*P*-heterogeneity = 0.09 and 0.005, respectively); however, these differences were no longer statistically significant in analyses

TABLE 2

WMDs in lipids/apolipoproteins, blood pressure, and CRP per 1 serving of tree nuts/d (28.4 g/d) in randomized and nonrandomized controlled trials (19–80)[1]

Outcome	Randomized controlled trials			Nonrandomized trials			All trials		
	Trials, n	WMD (95% CI)	I^2	Trials, n	WMD (95% CI)	I^2	Trials, n	WMD (95% CI)	P value[2]
Total cholesterol	38	−3.6 (−4.4, −2.9)	53.8	23	−6.7 (−7.8, −5.6)	76.8	61	−4.7 (−5.3, −4.0)	0.001
LDL cholesterol	38	−4.2 (−5.0, −3.4)	38.2	23	−6.0 (−7.1, −4.9)	62.9	61	−4.8 (−5.5, −4.2)	0.01
HDL cholesterol	38	−0.04 (−0.8, 0.7)	0	22	−0.7 (−1.7, 0.4)	35.9	60	−0.3 (−0.9, 0.4)	0.33
TG	37	−1.6 (−3.5, 0.24)	0	22	−4.6 (−8.4, −0.8)	0	59	−2.2 (−3.8, −0.5)	0.16
ApoA1	15	−0.8 (−2.1, 0.6)	12.8	8	1.0 (−2.7, 4.7)	0	23	−0.6 (−1.9, 0.7)	0.38
ApoB	13	−4.2 (−5.7, −2.6)	20.3	7	−1.1 (−5.1, 3.0)	0	20	−3.7 (−5.2, −2.3)	0.17
ApoB100	3	−1.5 (−5.8, 2.8)	0	2	−5.2 (11.0, 0.6)	0	5	−2.8 (−6.2, 0.7)	0.31
SBP	17	1.3 (−0.03, 2.6)	0	4	−3.3 (−5.7, 0.9)	0	21	0.3 (−0.8, 1.4)	0.001
DBP	17	0.6 (−0.7, 1.8)	0	3	−1.6 (−5.8, 2.5)	0	20	0.4 (−0.8, 1.6)	0.32
CRP	8	0.2 (−1.7, 2.0)	0	4	−0.4 (−5.7, 4.8)	0	12	0.1 (−1.6, 1.8)	0.84

[1]Values for lipids/apolipoproteins and CRP are presented in mg/dL; blood pressure is presented in mmHg. The WMD represents the amount by which the tree nut intervention changed the outcome on average compared with the control group or period. Estimates were pooled by using fixed-effects, inverse-variance meta-analysis. Outcomes included total cholesterol, LDL cholesterol, HDL cholesterol, TG, ApoA1, ApoB, ApoB100, SBP, DBP, and CRP. The I^2 index indicates the percentage of total variability in the effect sizes due to between-study heterogeneity, with $I^2 > 30\%$ considered at least moderate heterogeneity. ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ApoB100, apolipoprotein B100; CRP, C-reactive protein; DBP, diastolic blood pressure; SBP, systolic blood pressure; TG, triglycerides; WMD, weighted mean difference.

[2]P-heterogeneity between WMD of randomized controlled trials and nonrandomized trials is shown.

including only randomized controlled trials (**Supplemental Table 3**). Visual inspection of funnel plots suggested that non-randomized trials more frequently reported larger effect sizes for total cholesterol and LDL cholesterol (**Supplemental Figure 10**). For ApoB, significant heterogeneity by comorbidity was found, with stronger effects observed in studies including participants with type 2 diabetes (weighted mean difference: −11.5; 95% CI: −16.2, −6.8) than among healthy populations (−2.5; 95% CI: −4.7, −0.3) (P-heterogeneity = 0.015) (Supplemental Tables 2 and 3). No significant heterogeneity by other disease conditions, age, sex, background diet, baseline outcome level, or intervention duration was observed.

Evaluation of publication bias

Visual inspection of funnel plots did not suggest publication bias. Statistical evidence of publication bias was also not detected by using Egger's or Begg's tests (**Supplemental Table 4**).

DISCUSSION

In this systematic review and meta-analysis of controlled trials including 2582 participants, nut consumption lowered total cholesterol, LDL cholesterol, and its primary apolipoprotein, ApoB. Effects on total cholesterol and LDL cholesterol were generally larger in nonrandomized vs. randomized trials but statistically evident in each. For ApoB, stronger effects were also observed in populations with type 2 diabetes. These benefits were not significantly different across diverse types of tree nuts or when added to a variety of background diets. Nut consumption also lowered triglyceride concentrations, although effects were small in magnitude and only statistically significant in non-randomized trials. Significant effects of nut consumption on HDL cholesterol, ApoA, blood pressure, or CRP were not identified.

This meta-analysis provides the most comprehensive estimates to date of the effects of tree nut intake on major cardiovascular disease risk factors, including dose-response relations and presentation of effects by different nut types.

Accumulating evidence indicates that nut intake lowers risk of CVD events, including consistent findings from prospective observational studies (1, 81) and the Prevención con Dieta Mediterránea trial (2). Our findings showing that nut intake significantly improves the lipid profile, lowering LDL cholesterol, ApoB, and triglycerides, provide critical mechanistic evidence to support a causal link between nut intake and lowered CVD risk.

In dose-response analyses, the relations between tree nut intake and total cholesterol and LDL cholesterol were nonlinear, with stronger effects at consumption amounts at ≥60 g (about 2 oz, or 2 servings) per day. Trials providing 100 g nuts/d lowered concentrations of LDL cholesterol by up to 35 mg/dL, an effect size comparable to some statin regimens (82). As a point of caution, only 5 trials (4 nonrandomized, 1 randomized) provided nuts in this quantity, however, and additional trials comparing the effects of multiple nut doses on LDL cholesterol within the same study, particularly at high amounts (e.g., 100 g nuts/d) are needed. In comparison, effects of nuts on ApoB appeared more linear, which could relate to differential effects of tree nuts on LDL cholesterol particle size vs. particle number at different doses, a smaller number of studies of high-dose nut consumption and ApoB, or chance. Further randomized studies of high-dose nut consumption will help clarify whether benefits on blood lipids and apolipoproteins are nonlinear.

We did not observe significant heterogeneity in outcomes across different types of tree nuts. In addition, our meta-regression demonstrated that the major determinant of cholesterol lowering appears to be the total dose of tree nut consumption
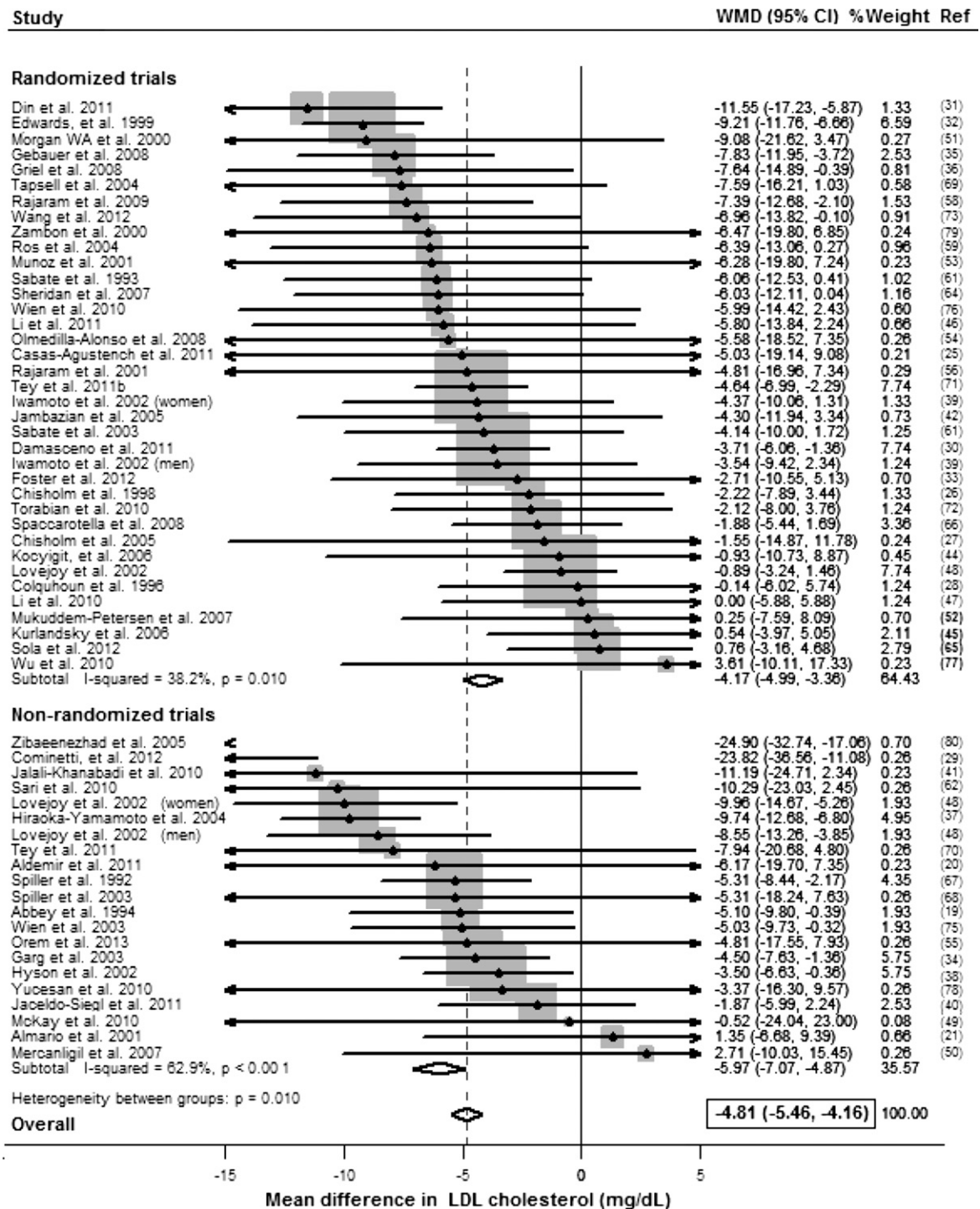
FIGURE 2 WMD in LDL cholesterol (mg/dL) per 1 serving of nuts/d (28.4 g/d) in randomized and nonrandomized controlled trials, pooled by using fixed-effects meta-analysis (19–80). To convert mg/dL to mmol/L, multiply by 0.0259. WMD, weighted mean difference.

rather than nut type. Significant heterogeneity in effects was also not observed for most other factors, including age, sex, background diet, baseline outcome level, and intervention duration; an exception was that tree nut intake lowered ApoB to a 3- to 4-fold greater degree in trials of diabetic populations in comparison to trials including only nondiabetic participants. In diabetic patients, ApoB provides more accurate information about atherogenic particles than LDL cholesterol concentrations (83). These find-

ings suggest that nut consumption may be particularly important for lowering CVD risk in patients with diabetes.

On the basis of the magnitude of effects of nut intake on lowering LDL cholesterol and ApoB observed in this meta-analysis, together with the established relation between LDL cholesterol and ApoB and CVD events (84), we calculated the predicted changes in risk of CVD events if one daily serving of nuts was incorporated into the diet. For an LDL cholesterol
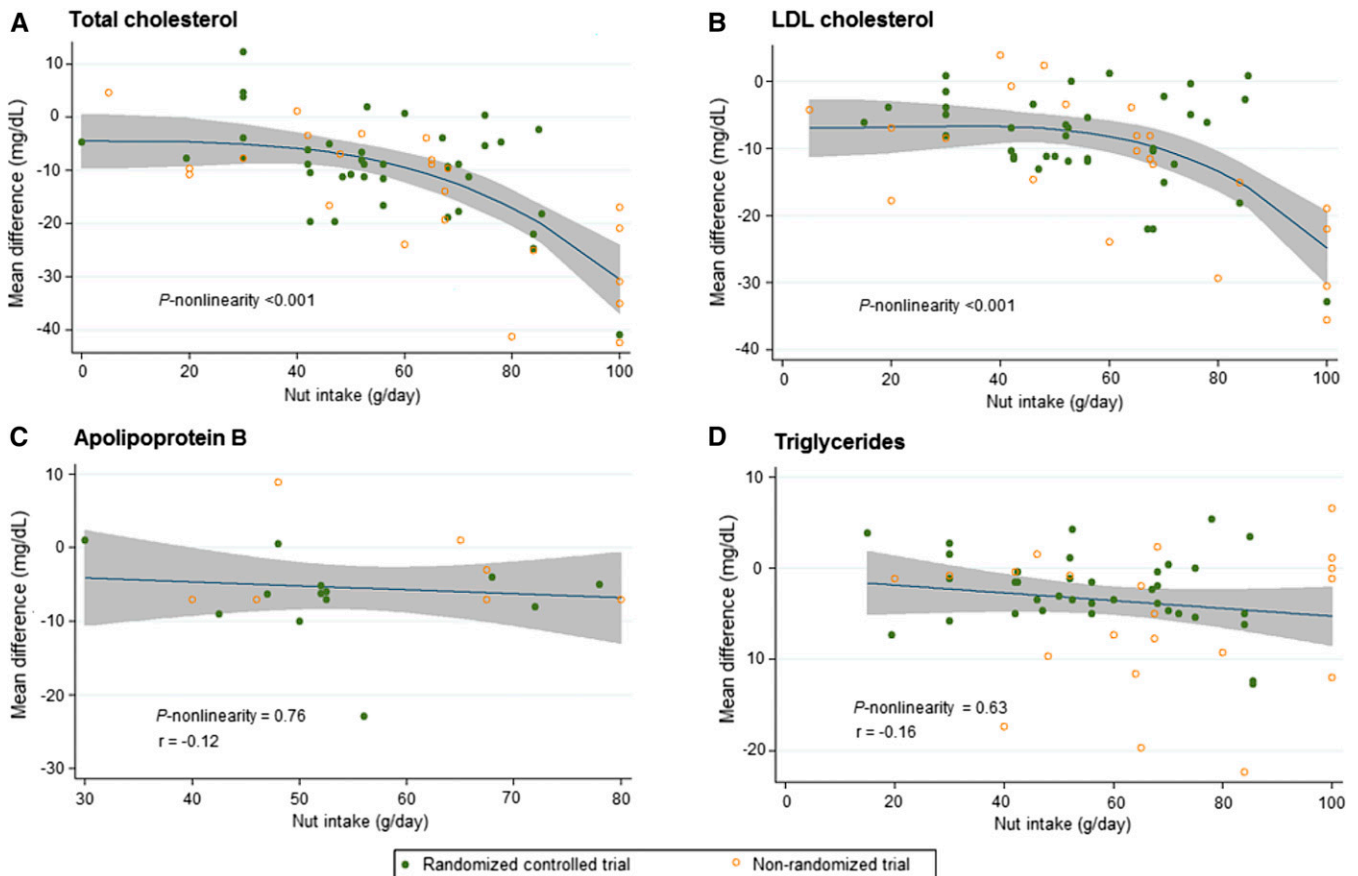
FIGURE 3 Dose-response relations between tree nut intake (g/d) and absolute (unstandardized) mean difference (mg/dL) in total cholesterol ($n = 61$ trials) (A), LDL cholesterol ($n = 61$ trials) (B), apolipoprotein B ($n = 19$ trials) (C), and triglycerides ($n = 59$ trials) (D) (19–80). Nut intake lowers total cholesterol and LDL cholesterol in a nonlinear fashion (P-nonlinearity = 0.001 for both), with stronger effects observed above a nut dose of ∼60 g nuts/d. Linear dose-response relations were observed between nut intake and apolipoprotein B ($r = -0.12$) and triglycerides ($r = -0.16$). The 95% CI is depicted in the shaded regions.

reduction of 4.2 mg/dL and an ApoB reduction of 4.1 mg/dL per daily serving of nuts observed in randomized trials of this meta-analysis, a 4% (HR: 0.96; 95% CI: 0.93, 0.99) and a 6% lower risk of coronary events are predicted, respectively. These calculated effects are smaller than associations between nut intake and CVD events observed in both prospective cohorts (81, 85) and the Prevención con Dieta Mediterránea trial (2). For instance, in prospective observational studies (85), a daily serving (28.4 g) of nuts was associated with 29% lower risk of CVD (HR: 0.71; 95% CI: 0.59, 0.85), whereas in the Prevención con Dieta Mediterránea trial, a Mediterranean diet supplemented with one daily serving (30 g) of mixed nuts reduced CVD events by 28% (HR: 0.72; 95% CI: 0.54, 0.96) over 4.8 y of follow-up (2). These consistent effect sizes in prospective studies and controlled clinical trials suggest that tree nuts have additional cardiovascular benefits beyond LDL cholesterol and ApoB lowering, for example, improving blood glucose and endothelial function (59). Similarly, specific constituents in tree nuts, such as polyunsaturated fats, are thought to influence CVD risk through both lipid and nonlipid mechanisms (86–88).

Our study has several strengths. Our systematic search makes it unlikely that large reports were missed, and error and bias were minimized by independent, duplicate decisions on study inclusion and data extraction. Effect sizes were standardized to

a common dose, avoiding combining of heterogeneous comparisons (e.g., "high vs. low" intake) and, importantly, allowing quantitative assessment of dose-response relations. The duration of trials was adequate to achieve changes and stabilization of lipid values (12). We evaluated multiple cardiovascular disease risk factors, including apolipoproteins; separately evaluated different types of tree nuts; and assessed several sources of heterogeneity. The identified trial populations were relatively diverse, including differences in age, sex, disease status, and background diet, increasing generalizability of our findings.

Potential limitations should be considered. Compliance was often assessed by self-report, and low compliance would cause underestimation of effects. Greater effect sizes were observed in lower quality, nonrandomized trials, yet significant effects on total cholesterol, LDL cholesterol, and ApoB were still seen in high-quality, randomized trials. The relatively few trials in some subgroups examined in heterogeneity analyses limited statistical power to detect potential interaction; for example, few estimates ($n \leq 2$) were available for some nut types, such as Brazil nuts, cashews, and pecans. Although larger effects on lowering LDL cholesterol were observed at higher nut doses in our study, we did not examine the effects of nuts on weight change. A recent meta-analysis of controlled trials on this topic (11) found that nut intake had nonsignificant, inverse effects on adiposity, but doses in most included trials were modest (<56 g/d, or 2

servings, of nuts). Furthermore, nut intake was associated with less weight gain over time in US cohorts of male and female health professionals (89, 90). Taken together, the inverse associations with weight gain observed in both controlled trials and free-living populations suggest that nut intake might augment satiety and displace other, less healthful foods in the diet, potentially resulting in less weight gain over time.

In conclusion, this systematic review and meta-analysis of controlled trials demonstrates that tree nut consumption lowers total cholesterol, LDL cholesterol, ApoB, and triglycerides. Our findings also highlight the need for additional investigation of potentially stronger effects at high doses of nuts and among diabetic populations.

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