Nut Consumption and Blood Lipid Levels

A Pooled Analysis of 25 Intervention Trials

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Background: Epidemiological studies have consistently associated nut consumption with reduced risk for coronary heart disease. Subsequently, many dietary intervention trials investigated the effects of nut consumption on blood lipid levels. The objectives of this study were to estimate the effects of nut consumption on blood lipid levels and to examine whether different factors modify the effects.

Methods: We pooled individual primary data from 25 nut consumption trials conducted in 7 countries among 583 men and women with normolipidemia and hypercholesterolemia who were not taking lipid-lowering medications. In a pooled analysis, we used mixed linear models to assess the effects of nut consumption and the potential interactions.

Results: With a mean daily consumption of 67 g of nuts, the following estimated mean reductions were achieved: total cholesterol concentration (10.9 mg/dL [5.1% change]), low-density lipoprotein cholesterol concentration (LDL-C) (10.2 mg/dL [7.4% change]), ratio of LDL-C to high-density lipoprotein cholesterol concentration (HDL-C) (0.22 [8.3% change]), and ratio of total cholesterol concentration to HDL-C (0.24 [5.6% change]) ($P < .001$ for all) (to convert all cholesterol concentrations to millimoles per liter, multiply by 0.0259). Triglyceride levels were reduced by 20.6 mg/dL (10.2%) in subjects with blood triglyceride levels of at least 150 mg/dL ($P < .05$) but not in those with lower levels (to convert triglyceride level to millimoles per liter, multiply by 0.0113). The effects of nut consumption were dose related, and different types of nuts had similar effects on blood lipid levels. The effects of nut consumption were significantly modified by LDL-C, body mass index, and diet type: the lipid-lowering effects of nut consumption were greatest among subjects with high baseline LDL-C and with low body mass index and among those consuming Western diets.

Conclusion: Nut consumption improves blood lipid levels in a dose-related manner, particularly among subjects with higher LDL-C or with lower BMI.

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DIETARY INTERVENTIONS TO lower blood cholesterol concentrations and to modify blood lipoprotein levels are the cornerstone of prevention and treatment plans for coronary heart disease (CHD).[1] Recently, consumption of nuts has been the focus of intense research because of their potential to reduce CHD risk and to lower blood lipid levels based on their unique nutritional attributes.[2,3] Nuts are a nutrient-dense food rich in plant protein (10%-25%) and fat (50%-75%), mostly unsaturated fatty acids.[2-4] They are a rich source of additional nutrients, dietary fiber, minerals (eg, copper, magnesium, and potassium), vitamins (eg, folic acid, niacin, vitamin E, and vitamin B_6), and other bioactive constituents such as phenolic antioxidants and phytosterols.[2-4]

Epidemiological investigations have consistently shown that frequent nut consumption reduces CHD risk.[5] In a summary estimate of 4 major epidemiological studies,[6-9] the mean CHD risk was 37% lower among subjects who consumed 4 or more servings of nuts a week compared with those who seldom or never ate nuts, with a mean reduction of 8.3% for each incremental serving per week of nuts consumed.[5] Based on scientific data documenting the benefits of nut consumption, the US Food and Drug Administration[10] issued a qualified health claim in 2003 stating that eating 43 g/d (1.5 oz/d) of specific nuts (almonds, hazelnuts, pecans, pistachios, walnuts, and peanuts) may reduce CHD risk. While many mechanisms by which nuts exert this CHD protective effect have been postulated,[11,12] their lipid-lowering properties have been studied extensively.

More than 25 human dietary intervention studies have been conducted investigating the effects of nut consumption on blood lipid levels. These studies differ in the type and amount of nuts consumed, study design, subject selection criteria, and duration. Because analyses have also varied, factors that may be responsible for inconsistencies among studies and for dose-response relationships have remained elusive.

We examined the effects of nut consumption on blood lipid levels and further examined whether these effects were consistent when stratified by different population groups and variables, including sex, age, type of nut, type of control diet, and body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]) by pooling and analyzing raw data from 25 nut consumption trials conducted in 7 countries. Results have been published for 23 studies (1 study reported results from 2 different studies),[13-34] and 2 studies remain unpublished (M. Most, PhD, unpublished data, 2004; and E.R., unpublished data, 2004).

METHODS

STUDY DESIGN

A comprehensive MEDLINE search was conducted for English-language human studies between January 1, 1992, and December 31, 2004, that assessed the effects of nut consumption on blood lipid levels. The cutoff (2004) was selected because of the changes in standards of care that occurred on release of the "Third Report of the National Cholesterol Education Program" Adult Treatment Panel guidelines[35] and the potential problems with confounding in patients who may be taking statin drugs. Search terms included *human*, *cholesterol*, *nuts*, *almond*, *cashew*, *peanut*, *pecan*, *pine nut*, *pistachio nut*, *macadamia nut*, *hazelnut*, and *walnut*. Although peanuts are members of the legume family, we included them in the analysis given their comparable nutrient profile to nuts and their common identification as part of the nut food group. The literature search yielded 25 articles, one of which reported results from 2 different studies.[26] We identified 2 unpublished studies, for a total of 28 studies, and contacted the authors of the published and unpublished research to obtain disaggregated data for inclusion in a pooled analysis.

Articles were selected for the pooled analysis based on the following a priori inclusion criteria: (1) the study involved human subjects; (2) a control group existed, or stable baseline lipid measurements were present before nut consumption; (3) the dietary intervention was exclusively nuts; (4) the nut consumption period was at least 3 weeks; (5) the subjects had no recent exposure to lipid-lowering medications; and (6) there were no body weight changes between diets at the end of the intervention. Based on these inclusion criteria, 2 published studies[36,37] were excluded because the intervention included other sources of monounsaturated fat in addition to nuts. Another published study[38] was excluded because of differential weight loss at the end of the intervention. In total, 25 studies (23 published and 2 unpublished) were selected for inclusion.

STATISTICAL ANALYSIS

Each research team provided their original data sets electronically. On receipt, we conducted preliminary statistical analyses to confirm appropriate transfer of data. In all cases, we were able to reproduce the results presented in the original articles. Data were then combined into a single data set and were analyzed using statistical software (SAS version 9.1; SAS Institute, Cary, North Carolina).

Each subject contributed 1 data point for each dietary treatment received. Therefore, subjects of crossover studies contributed 2 or more data points to the data set. The final data set contained 1284 observations contributed by 583 unique subjects. Analyses were conducted using mixed linear models that included a fixed-effects term for diet and random-effects terms for study, diet nested in study, and subject nested in study. To test for study heterogeneity, fixed-effects terms for study and diet × study interaction were included in the model.

We investigated whether sex, age, BMI, controlled vs uncontrolled study design, degree of investigator control over subjects' diets, type of funding source, type of nut, and type of control diet modified the effects of nut consumption by adding appropriate fixed-effects terms for main effect × diet interaction to the model. For some analyses, subjects were stratified into the following 3 low-density lipoprotein cholesterol concentration (LDL-C) categories according to "Third Report of the National Cholesterol Education Program" Adult Treatment Panel criteria[35]: less than 130 mg/dL (n=262), 130 to 160 mg/dL (n=125), or greater than 160 mg/dL (n=195) (to convert cholesterol concentration to millimoles per liter, multiply by 0.0259). Subjects were also stratified into 2 triglyceride level categories (<150 mg/dL [n=410] or ≥150 mg/dL [n=145]) (to convert triglyceride level to millimoles per liter, multiply by 0.0113), and BMIs were classified as normal weight (<25 [n=244]), overweight (25-30 [n=181]), or obese (>30 [n=82]). One value for LDL-C, 28 values for triglyceride levels, and 76 height measurements were missing from the original data sets. Almonds (n=210) and walnuts (n=178) were the 2 nuts most commonly used, and all other nut types were grouped into a single category (n=195).

Each study was categorized according to its design. Crossover and parallel design studies were classified as controlled (n=18), and consecutive design (preintervention and postintervention) studies were classified as uncontrolled (n=7). Types of control diets were represented by the following 3 categories: Western (total fat ≥30% and saturated fat ≥10%), Mediterranean (monounsaturated fat ≥20% and saturated fat <7%), and low total and saturated fat (total fat ≤30% and saturated fat <7%). To estimate a possible dose-response effect of nut consumption, individual nut consumption was recomputed and expressed as percentage of total calories in the diet.

To assess the possible influence of the degree of dietary control on the results, each study was classified as having low, medium, or high dietary control. The low dietary control category included studies in which subjects consumed nuts without dietary advice and there was no biologic measure of dietary compliance. The medium dietary control studies gave dietary advice and used a biologic measure of dietary compliance. The high dietary control category comprised studies and metabolic trials in which nuts and all meals were provided. Last, each study was classified as industry sponsored or as non–industry sponsored based on the type of funding source.

RESULTS

Of 25 studies in the pooled analysis, 16 used a crossover design, 7 used a consecutive design, and 2 used a parallel design (**Table 1**). Sample size ranged from 10 to 49 subjects (median, 20 subjects), and age ranged from 19 to 86 years (mean age, 46 years). All but 4 studies included both sexes, and there were 307 men and 276 women. Subjects in 9 studies had hypercholesterolemia (mean range, 236-259 mg/dL for total cholesterol concentration [TC] and 154-178 mg/dL for LDL-C), and subjects in 16 studies had nor-

Table 1. Characteristics of 25 Intervention Trials Included in the Pooled Analysis

Source	No. of Subjects/ Sex/Mean Age, y	Subject Characteristic	Daily Amount of Type of Nut, g	Duration of Dietary Intervention, wk	Study Design	Control Diet	Industry Sponsored
Sabaté et al,[13] 1993, USA	18/18M/30	Normocholesterolemia	79 Walnut	4	Crossover	Low saturated fat	Yes
Abbey et al,[14] 1994, Australia	16/16M/41	Normocholesterolemia	84 Almond, 68 walnut	3	Consecutive	Western	No
Colquhoun et al,[15] 1996, Australia	14/7M, 7F/46	Normocholesterolemia	54 Macadamia	4	Crossover	Low fat	Yes
Spiller et al,[16] 1998, Canada	45/12M, 33F/53	Hypercholesterolemia	100 Almond	4	Parallel	Western, Mediterranean	Yes
Chisholm et al,[17] 1998, New Zealand	16/16M/45	Hypercholesterolemia	78 Walnut	4	Crossover	Low saturated fat	No
Kris-Etherton et al,[18] 1999, USA	22/9M, 13F/unknown	Normocholesterolemia	Unknown peanut	3.4	Crossover	Western	Yes
Edwards et al,[19] 1999, USA	10/4M, 6F/46	Hypercholesterolemia	60 Pistachio	3	Crossover	Western	No
Durak et al,[20] 1999, Turkey	30/18M, 12F/unknown	Normocholesterolemia	69 Hazelnut	4.3	Consecutive	Unknown	No
Zambón et al,[21] 2000, Spain	49/26M, 23F/56	Hypercholesterolemia	46 Walnut	6	Crossover	Mediterranean	Yes
Morgan and Clayshulte,[22] 2000, USA	19/4M, 15F/41	Normocholesterolemia	68 Pecan	8	Parallel	Western	Yes
Curb et al,[23] 2000, USA	30/15M, 15F/unknown	Normocholesterolemia	Unknown macadamia	4.3	Crossover	Western	Yes
Rajaram et al,[24] 2001, USA	23/14M, 9F/38	Normocholesterolemia	85 Pecan	4	Crossover	Low saturated fat	Yes
Almario et al,[25] 2001, USA	18/5M, 13F/unknown	Normocholesterolemia	52 Walnut	6	Consecutive	Western, low saturated fat	Yes
Lovejoy et al,[26] 2002, USA	30/13M, 17F/25	Normocholesterolemia	100 Almond	4	Crossover	Low saturated fat, Mediterranean	No
Lovejoy et al,[26] 2002, USA	20/10M, 10F/54	Normocholesterolemia	100 Almond	4	Consecutive	Western	No
Jenkins et al,[27] 2002, Canada	27/15M, 12F/64	Hypercholesterolemia	73 Almond (high dose), 37 almond (low dose)	6	Crossover	Low saturated fat	Yes
Iwamoto et al,[28] 2002, Japan	40/20M, 20F/24	Normocholesterolemia	51 Walnut	4	Crossover	Low fat	Yes
Hyson et al,[29] 2002, USA	22/10M, 12F/44	Normocholesterolemia	66 Almond	6	Consecutive	Low saturated fat	Yes
Sabaté et al,[30] 2003, USA	25/14M, 11F/41	Normocholesterolemia	68 Almond (high dose), 34 almond (low dose)	4	Crossover	Low saturated fat	Yes
Garg et al,[31] 2003, Australia	17/17M/54	Hypercholesterolemia	48 Macadamia	4	Consecutive	Western	No
Alper and Mattes,[32] 2003, USA	15/8M, 7F/33	Normocholesterolemia	89 Peanut	8	Consecutive	Western	No
Ros et al,[33] 2004, Spain	20/8M, 12F/55	Hypercholesterolemia	55 Walnut	4	Crossover	Mediterranean	Yes
Sheridan et al,[34] 2007, USA	15/11M, 4F/60	Hypercholesterolemia	95 Pistachio	4	Crossover	Western	Yes
Most, 2004, USA[a]	24/8M, 16F/46	Normocholesterolemia	87 Almond	Unknown	Crossover	Western	Unknown
Ros, 2004, Spain[a]	18/9M, 9F/55	Hypercholesterolemia	58 Almond, 48 walnut	4	Crossover	Mediterranean	No

Abbreviation: USA, United States.
[a] Unpublished.

mocholesterolemia (125-222 mg/dL for TC and 67-142 mg/dL for LDL-C). Across studies, individual BMIs ranged from 17 to 49 (mean, 27). Daily nut consumption ranged from 23 to 132 g (mean, 67 g), which is approximately 0.8 to 4.8 oz/d (mean, 2.4 oz/d).

Compared with control diets, nut diets reduced TC, LDL-C, ratio of LDL-C to high-density lipoprotein cholesterol concentration (HDL-C), and ratio of TC to HDL-C ($P<.001$ for all) (**Table 2**). Nut consumption had no significant effect on the mean HDL-C, nor was there an effect on triglyceride level except in subjects with hypertriglyceridemia. For all blood lipid levels and ratios evaluated, study and diet × study interaction were significant ($P<.001$ for all), suggesting heterogeneity among the studies.

The effects of nut consumption on blood lipid levels were similar in men and women ($P>.2$ for all nut diet × sex interactions) and across all age groups ($P>.2$ for all nut diet × age interactions). They were independent of the specific type of nut consumed ($P>.45$ for all nut diet × nut type interactions).

The estimated cholesterol-lowering effects of nut consumption were greater for subjects with higher baseline LDL-C (**Table 3** and **Figure 1**). Responses differed between subjects with baseline LDL-C of less than 130 mg/dL vs greater than 160 mg/dL (mean decrease, 12.5 mg/dL for TC and 14.9 mg/dL for LDL-C). There was also a differential cholesterol-lowering effect of nut consumption depending on baseline BMI, with greater response among subjects having lower BMI. A significant nut diet × BMI interaction was found for ratio of LDL-C to HDL-C and for ratio of TC to HDL-C ($P=.02$ for both). Similar trends existed for TC, LDL-C, and triglyceride

Table 2. Estimated Changes in Blood Lipid and Lipoprotein Levels Among Subjects Consuming Nut Diets vs Control Diets

Variable	Mean Change (95% Confidence Interval)[a]	% Change	*P* Value[b]
Concentration, mg/dL			
TC	−10.9 (−14.1 to −7.8)	−5.1	<.001
LDL-C	−10.2 (−13.1 to −7.4)	−7.4	<.001
HDL-C	0.09 (−1.00 to 1.19)	0.2	.88
Ratio			
LDL-C/HDL-C	−0.2 (−0.3 to −0.1)	−8.3	<.001
TC/HDL-C	−0.2 (−0.3 to −0.1)	−5.6	<.001
Triglyceride level, mg/dL	−3.1 (−7.2 to 1.2)	−2.8	.15
<150	0.7 (−3.2 to 4.7)	0.7	.74
≥150	−20.6 (−30.7 to −9.9)	−10.2	<.05

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.
SI conversion factors: To convert cholesterol concentration to millimoles per liter, multiply by 0.0259; to convert triglyceride level to millimoles per liter, multiply by 0.0113.
[a] Nut diet values minus control diet values.
[b] Difference between nut diet and control diet.

Table 3. Estimated Changes in Blood Lipid and Lipoprotein Levels by Baseline LDL-C Concentration and by Baseline BMI Among Subjects Consuming Nut Diets vs Control Diets

		Mean Change (95% Confidence Interval)				
Variable	No.	TC Concentration, mg/dL	LDL-C Concentration, mg/dL	LDL-C/HDL-C	TC/HDL-C	Triglyceride Level, mg/dL[a]
LDL-C concentration, mg/dL						
<130	262	−5.0 (−9.2 to −0.9)[b]	−3.5 (−7.5 to 0.5)	−0.11 (−0.19 to −0.02)[b]	−0.14 (−0.24 to −0.04)[b]	−2.0 (−6.5 to 2.8)
130-160	125	−11.0 (−15.5 to −6.6)[c]	−9.9 (−14.2 to −5.6)[c]	−0.26 (−0.38 to −0.13)[b]	−0.28 (−0.41 to −0.15)[c]	−8.5 (−14.7 to −1.3)[b]
>160	195	−17.5 (−22.0 to −13.0)[c]	−18.4 (−22.7 to −14.1)[c]	−0.38 (−0.52 to −0.24)[c]	−0.35 (−0.48 to −0.20)[c]	−0.6 (−7.1 to 6.3)
BMI						
<25	244	−12.0 (−15.9 to −8.1)[c]	−11.9 (−15.4 to −8.4)[c]	−0.24 (−0.32 to −0.16)[c]	−0.24 (−0.33 to −0.15)[c]	−5.8 (−9.8 to −1.6)[b]
25-30	181	−10.5 (−14.4 to −6.6)[c]	−9.2 (−12.8 to −5.7)[c]	−0.14 (−0.23 to −0.04)[b]	−0.15 (−0.25 to −0.04)[b]	−0.6 (−6.0 to 5.0)
>30	82	−8.9 (−13.7 to −4.1)[b]	−6.8 (−11.2 to −2.4)[b]	−0.10 (−0.21 to 0.02)	−0.12 (−0.25 to 0.01)	−1.6 (−9.2 to 6.4)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.
SI conversion factors: To convert cholesterol concentrations to millimoles per liter, multiply by 0.0259; to convert triglyceride level to millimoles per liter, multiply by 0.0113.
[a] Median triglyceride levels for LDL-C cutoffs of less than 130, 130 to 160, and greater than 160 mg/dL were 95, 118, and 123 mg/dL, respectively. Median triglyceride levels for BMI cutoffs less than 25, 25 to 30, and greater than 30 were 98, 129, and 146 mg/dL, respectively.
[b] $P<.05$ for difference between nut diet and control diet.
[c] $P<.001$ for difference between nut diet and control diet.

level, but results of formal interaction tests did not reach statistical significance.

Nut consumption had greater relative effects in reducing TC and LDL-C (−7.4% and −9.6%, respectively) when assessed against a Western control diet vs against Mediterranean (−4.3% and −6.7%, respectively) or low-fat (−4.1% and −6.0%, respectively) control diets (**Figure 2**). The type of study design (controlled vs uncontrolled) did not modify the effects on blood lipid levels; however, estimated differences were nonsignificantly greater for TC ($P=.23$) and for ratio of TC to HDL-C ($P=.28$) in uncontrolled studies. No significant difference was noted in the effects of nut consumption by degree of dietary control. For all blood lipid level fractions given in Table 2, the type of funding (industry sponsored vs non–industry sponsored) did not have an effect, except for triglyceride level, which showed a decrease among industry-sponsored studies compared with no change among non–industry-sponsored studies ($P=.01$ for nut diet–funding source interaction) (data not shown).

The estimated effects of nut consumption on blood lipid levels were dose related (**Figure 3**). At 20% of dietary energy from nuts (equivalent to 71 g [2.5 oz] for a 2000-kcal diet), blood lipid levels were reduced by 9.9 mg/dL (4.5% change) for TC and by 9.5 mg/dL (6.5% change) for LDL-C. At 12.2% of dietary energy from nuts (equivalent to 43 g [1.5 oz]), the amount of nut consumption recommended by the US Food and Drug Administration,[10] blood lipid levels were reduced by 7.1 mg/dL (3.2% change) for TC and by 7.2 mg/dL (4.9% change) for LDL-C. At 10% of dietary energy from nuts (equivalent to 35 g [1.2 oz]), blood lipid levels were reduced by 6.1 mg/dL (2.8% change) for TC and by 6.2 mg/dL (4.2% change) for LDL-C. Similar dose responses were estimated for ratio of LDL-C to HDL-C and for triglyceride level in subjects with baseline triglyceride levels of at least 150 mg/dL.

COMMENT

In this pooled analysis of 583 unique subjects in 25 clinical trials, incorporating nuts into the diet lowered TC, LDL-C, ratio of LDL-C to HDL-C, and ratio of TC to HDL-C.

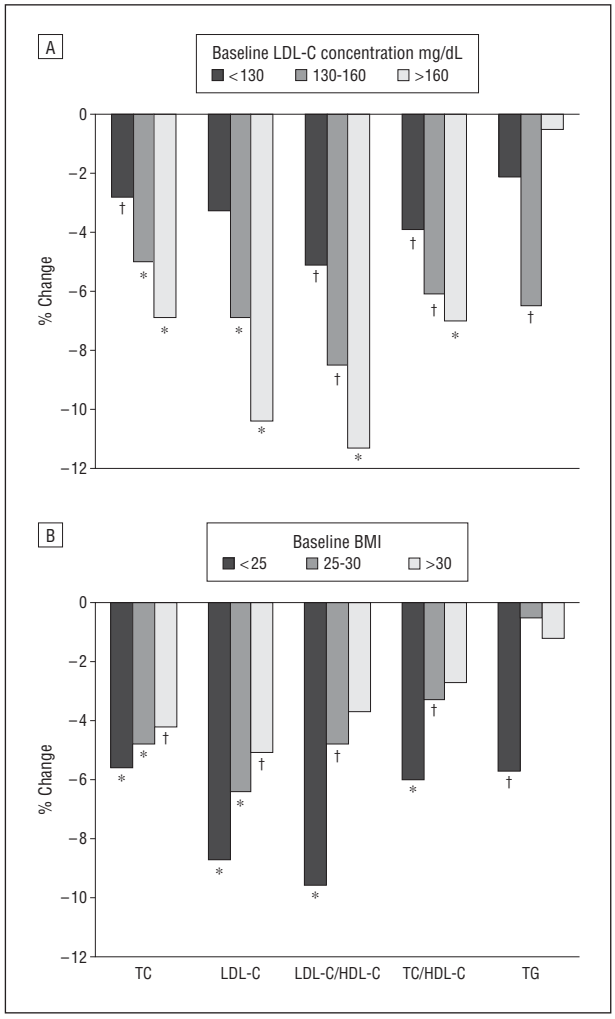

Figure 1. Estimated effects of nut consumption on blood lipid and lipoprotein levels by baseline LDL-C concentration (A) and by baseline BMI (B). *$P<.001$ and †$P<.05$ for difference between nut diet and control diet. To convert cholesterol concentrations to millimoles per liter, multiply by 0.0259. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; and TG, triglycerides.

Most important is the finding that the cholesterol-lowering effects of nut consumption are dose related and are more pronounced in subjects with higher baseline LDL-C or lower BMI. Nut consumption also lowered triglyceride levels in subjects with hypertriglyceridemia. Study design, type of funding source, and degree of dietary control did not significantly affect these outcomes. This study provides the best estimate of the effects of nut consumption on blood lipid levels. Specifically, a mean daily consumption of 67 g (2.4 oz) of nuts resulted in estimated mean reductions of 10.9 mg/dL (5.1% change) in TC, 10.2 mg/dL (7.4% change) in LDL-C, 0.22 (8.3% change) in ratio of LDL-C to HDL-C, and 0.24 (5.6% change) in ratio of TC to HDL-C. The estimated reductions in this pooled analysis are almost identical to those obtained in a recent meta-analysis[39] of walnut consumption studies (–10.3 mg/dL for TC and –9.2 mg/dL for LDL-C). The similarity of the results obtained by different methodologic approaches confirms the validity of our findings.

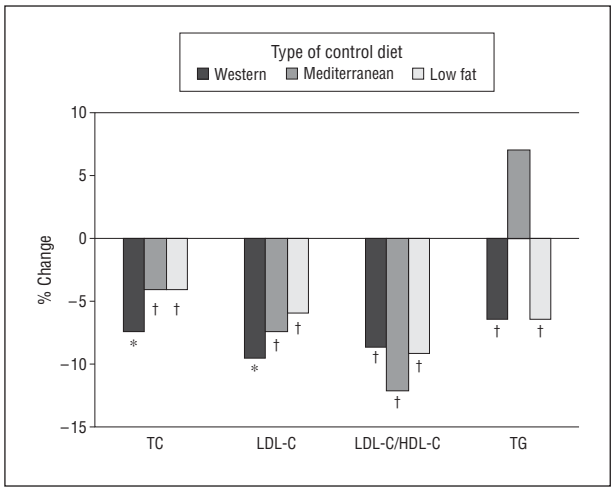

Figure 2. Estimated effects of nut consumption on blood lipid and lipoprotein levels by type of control diet. *$P<.001$ and †$P<.05$ for difference between type of control diet. HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; and TG, triglycerides.

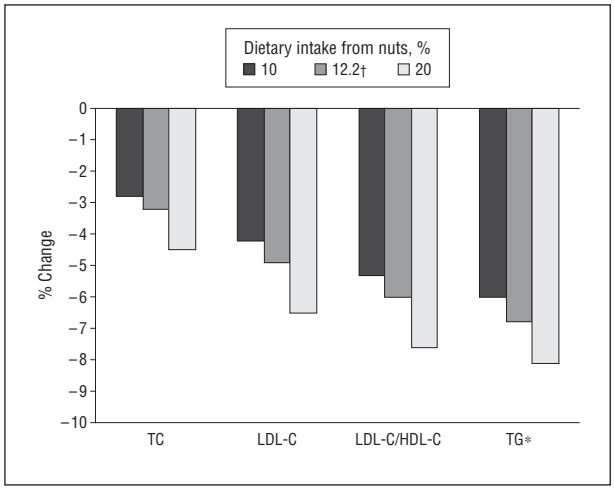

Figure 3. Estimated effects of nut consumption on blood lipid and lipoprotein levels by percentage of dietary energy from nuts. *Estimated using values from participants with triglyceride levels of at least 150 mg/dL (to convert triglyceride level to millimoles per liter, multiply by 0.0113). Dietary intakes from nuts of 10%, 12.2%, and 20% are equivalent to 35, 43, and 71 g, respectively, based on a 2000-kcal diet. †Recommended by the US Food and Drug Administration[10]; 12.2% is equivalent to 43 g/d (1.5 oz/d). HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; and TG, triglycerides.

While the blood lipid level and lipoprotein results corroborate those of previous clinical trials, the observed effect of a nut diet × BMI interaction on blood lipid level responses is a novel finding. In agreement with this observation, Mukuddem-Peterson et al[40] recently reported that high consumption of neither walnuts nor cashews was associated with blood lipid level changes in subjects with obesity and metabolic syndrome. It is well established that obese subjects have an attenuated cholesterol-lowering response to dietary reduction of saturated fatty acids compared with lean individuals, probably because obesity is characterized by elevated endogenous production of cholesterol in relation to insulin resistance.[41] However, in most of the nut consumption trials in our pooled analysis, nut diets and

control diets were matched for saturated fat content. Obesity and metabolic syndrome are each associated with reduced intestinal cholesterol absorption.[42,43] Nuts are rich in plant sterols, natural compounds that might contribute to cholesterol lowering by interfering with cholesterol absorption,[44] and this effect would be blunted when cholesterol absorption rates are low. More research is needed to answer the important question of why nuts are less effective in lowering blood cholesterol concentration among subjects with obesity.

When the effects of diets incorporating increasing amounts of nuts are compared with those of nut-free control diets, a dose-response effect is manifested. These findings are consistent with results from 2 clinical trials specifically designed to assess dose response between nut consumption and blood lipid levels. Sabaté et al[30] found proportionally greater reductions in LDL-C with a 20% energy (68 g [2.4 oz]) replacement of almonds into the usual diet (9.0% reduction) than a 10% energy (34 g [1.2 oz]) replacement (3.3% reduction). Jenkins et al[27] found graded decreases in LDL-C with a "full dose" (73 g [2.6 oz]) of almonds (9.4% decrease) compared with a "half dose" (37 g [1.3 oz]) (4.4% decrease). To achieve a clinically relevant reduction in blood lipid levels, patients with hyperlipidemia may benefit from higher amounts of nut consumption than that recommended by the US Food and Drug Administration[10] for the general public.

Incorporating nuts into the diet of patients with hyperlipidemia provides cardiovascular benefits beyond lowering blood cholesterol concentration. The 7.4% estimated mean reduction of LDL-C observed in this pooled analysis is modest compared with the effect of statin drugs.[45] However, the value of regular nut consumption for CHD prevention is unlikely due to the blood cholesterol–lowering effect alone, as the 37% summary estimate risk reduction from frequent nut consumption in epidemiological investigations[5] is more than double that attributable to lowering LDL-C by 7.4%.[44] Nut consumption exerts beneficial effects by improving endothelial function,[33] lowering oxidative stress,[20,27,37] and reducing lipoprotein(a) level.[21,24,27] In addition, nut consumption is associated with lower risk of developing type 2 diabetes mellitus,[46] and research has shown that frequent nut consumption does not lead to weight gain.[47-49]

As expected, nut consumption led to more pronounced reduction of TC and LDL-C compared with a Western diet vs Mediterranean or low-fat diet. Greater cholesterol-lowering effect is found when nuts replace saturated fat than when olive oil or carbohydrates are replaced. This finding has important clinical and public health applications. For patients with dyslipidemia and for the general population consuming a Western diet, the incorporation of nuts into their daily diet will result in greater improvement of blood lipid levels than for individuals already following a healthy Mediterranean or low-fat diet.

Although duration of the dietary intervention trials pooled herein ranged from 3 to 8 weeks, other investigators have found that favorable lipid levels resulting from nut consumption are sustainable. One-year findings from the Prevención con Dieta Mediterránea trial[50] evaluating the effects of nut consumption in the context of a Mediterranean diet on metabolic syndrome status showed that mixed nut consumption of 30 g/d significantly reduced the prevalence of high waist circumference, hypertriglyceridemia, and hypertension compared with a control group receiving a nut-free low-fat diet. Tapsell et al[51] found significantly decreased LDL-C and significantly increased HDL-C and ratio of TC to HDL-C in patients with type 2 diabetes mellitus consuming 30 g/d of walnuts for 6 months as part of a modified low-fat diet compared with those receiving nut-free, low-fat, or modified low-fat diets.

Our findings confirm the results of epidemiological studies showing that nut consumption lowers CHD risk and support the inclusion of nuts in therapeutic dietary interventions for improving blood lipid levels and lipoproteins and for lowering CHD risk. Nuts are a whole food that have been consumed by humans throughout history. Increasing the consumption of nuts as part of an otherwise prudent diet can be expected to favorably affect blood lipid levels (at least in the short term) and have the potential to lower CHD risk.

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Author Contributions: Mr Oda had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Sabaté. *Acquisition of data:* Sabaté and Ros. *Analysis and interpretation of data:* Sabaté, Oda, and Ros. *Drafting of the manuscript:* Sabaté. *Critical revision of the manuscript for important intellectual content:* Sabaté, Oda, and Ros. *Statistical analysis:* Oda. *Obtained funding:* Sabaté. *Study supervision:* Sabaté.
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