Nutrition, Metabolism and Cardiovascular Diseases 35 (2025) 103771

Contents lists available at ScienceDirect

Nutrition, Metabolism and Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Effect of nut consumption on blood lipids: An updated systematic review and meta-analysis of randomized controlled trials

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ARTICLE INFO

Handling Editor: Dr. A. Siani

Keywords:
Nuts
Peanuts
Blood lipids
LDL-C
Cholesterol
Dyslipidemia
Cardiovascular health

ABSTRACT

Aims: Nuts are nutrient-dense foods touted for their health-promoting effects, especially regarding cardiovascular health, yet inconsistencies in the literature remain in relation to their effect on blood lipids. Hence, a systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to determine the effect of nut intake on blood lipids.

Data synthesis: MEDLINE-PubMed and Cochrane databases were searched. 113 unique trials met eligibility criteria (n = 8060 adults with various health status) assessing the effect of a median daily dose of 45.5 g/d of nuts compared to a non-nut control on blood lipid outcomes met inclusion criteria. Overall, nut consumption resulted in moderate reductions in total cholesterol (mean difference, −0.14 mmol/L [95 % confidence interval, −0.18 to −0.10 mmol/L]) and LDL-C (−0.12 mmol/L [-0.14 to −0.09 mmol/L]), with small reductions in triglycerides (−0.05 mmol/L [-0.07 to −0.03 mmol/L]), TC:HDL-C (−0.11 [-0.16 to −0.06]), LDL-C:HDL-C (−0.19 [-0.24 to −0.12]), and apolipoprotein B (−0.04 g/L [-0.06 to −0.02 g/L]). There was no significant impact on HDL-cholesterol or other assessed measures. Certainty of evidence was high for apolipoprotein A, and generally moderate/low for all other outcomes. Sensitivity analysis did not change the evidence on the main outcomes. Significant effect modifications in subgroup analysis were shown for most of the lipid parameters assessed. None of these subgroup effects altered the evidence of heterogeneity for any primary outcome.

Conclusions: Current evidence provides a good indication that consuming nuts may advantageously affect blood lipids in adults with a mix of health status.

Prospero registration: PROSPERO identifier, CRD42022358688.

Abbreviations: CI, confidence interval; FFQ, Food Frequency Questionnaire; HDL-C, high-density lipoprotein-cholesterol; IQR, interquartile range; LDL, low-density lipoprotein; MD, mean difference; PICOTS, Population, Intervention, Comparison, Outcome, Time, Setting; RCT, randomized controlled trials; SD, standard deviation; SE, standard error of the mean; TC, total cholesterol; TG, triglycerides.

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https://doi.org/10.1016/j.numecd.2024.10.009
Received 14 July 2024; Received in revised form 4 October 2024; Accepted 9 October 2024
Available online 17 October 2024

1. Introduction

According to the World Health Organization (WHO), in 2019, more than seventeen million people died due to cardiovascular diseases (CVDs) [1]. Collectively, these health conditions are considered leading causes of morbidity and mortality worldwide and are a serious public health concern [2]. Scientific evidence has shown that by addressing modifiable lifestyle factors such as diet and physical activity, CVDs can be prevented, as well as intermediate health conditions such as overweight/obesity, hypertension, and dyslipidaemia, which impact the quality of life and contribute to the burden on the health system [3,4]. In this sense, an abnormal blood lipid profile, mainly characterized by elevated plasma levels of low-density lipoprotein-cholesterol (LDL-C) and lower levels of high-density lipoprotein-cholesterol (HDL-C), has been recognized as an early risk factor for CVDs and the onset of other non-communicable diseases [3]. Therefore, one of the main intervention targets of current cardiovascular clinical practice guidelines is the improvement of the blood lipid profile [5].

Dietary interventions have been recognized as a first step in blood lipid management for the prevention and treatment of CVD [3]. Most of the current dietary and clinical practice guidelines recommend adherence to a healthy dietary pattern with high consumption of whole grains, fruits and vegetables, legumes, fish, and nuts while reducing the intake of saturated and trans fatty acid–rich foods for blood cholesterol management and heart disease prevention [3,5]. As such, due to their complex nutritional matrix rich in unsaturated fatty acids, soluble fiber, magnesium, antioxidants, and phytosterols, the impact of nut consumption on blood lipids and cardiovascular health has been an object of research interest [6,7]. Results from several systematic reviews and meta-analyses (SRMA) have demonstrated that nut consumption (including walnuts, macadamia nuts, almonds, cashews, pistachios, Brazil nuts, and peanuts or a mixture) decreases total and LDL-C, or triglycerides [8–12]. Further, it has been suggested that nut consumption might contribute to a reduction in apolipoprotein B blood levels and improvements in HDL-C function, yet the evidence is limited [8].

Given their purported cardiovascular health-promoting properties, especially related to the blood lipid profile, in the last two decades nut consumption has been recognized by several international health organizations to be useful for cardiovascular risk reduction for both primary and secondary prevention [13–17], and regulated disease risk reduction health claims have been approved for cardiovascular disease by the United States Food and Drug Administration [18–20].

Nonetheless, a meta-analysis of randomized controlled trials has recently reported that, contrary to previous meta-analyses, nut consumption has no beneficial effects on the lipid profile [21]. However, methodological concerns were raised about this report [22], highlighting the difficulties in the interpretation and confidence of the results. To address the limitations of this meta-analysis as well as build upon other previously published meta-analyses to update the scientific evidence a comprehensive SRMA of randomized controlled trials investigating the effect of nut consumption on the blood lipid profile has been conducted with assessment of the certainty of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.

2. Methods

This SRMA was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3)[23] with the results reported following the PRISMA guidelines [23] (Supplemental Table S1). The study protocol was registered in PROSPERO (CRD42022358688).

2.1. Data sources and search criteria

A systematic search in the PubMed and Cochrane Central Register of Controlled Studies databases was conducted from inception through to September 11, 2022. These searches were supplemented with manual searches of the reference lists from the included trials.

Table 1 presents the PICOTS (population, intervention, comparator, outcome, time, and study design) framework used to define the question being addressed. Randomized controlled trials were included if they were conducted in adults (aged 18 years and older), involving participants of all health backgrounds with intervention periods of at least 3 weeks duration (as changes in blood lipids and lipoproteins with diet have been shown to stabilize within 2–3 weeks [24]), investigating the effect of nuts compared with control diets free of nuts on blood lipids including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1 (apoA1), apolipoprotein B (apoB), and blood lipid ratios when reported. For the context of the present research, the term “nuts” will include tree nuts [almonds, Brazil nuts, cashews, hazelnuts, macadamia, pecans, pistachios, walnuts, and mixed nuts] as well as pine nuts and peanuts. Even though the latter are not technically a “nut”, but instead a “seed” and “legume”, respectively; since pine nuts and peanuts share similar nutritional profiles to tree nuts and, in the case of peanuts, are often included in “mixed nut” formulations, further justifying their inclusion as part of the intervention analysed. Studies with whole nuts (in any form, such as chopped, slivered, sliced) or whole (100 %) nut butters were included, whereas trials only assessing nut oils or other nut derivatives were excluded. Supplemental Table S2 presents the full inclusion and exclusion criteria, with the search strategy for each database indicated in Supplemental Table S3. Reports were initially excluded based on a review of their titles and abstracts by two independent reviewers (JN and CVH or NK). Reports that remained were then assessed for inclusion based on a review of the full text by at least two independent reviewers (JN, CVH, or NK), leaving the final set of reports to be included in the present syntheses. For studies with more than one publication, the one with the relevant outcome information, followed by longest duration, and largest study population were selected. In reports containing more than 1 eligible trial comparison, each available trial comparison was included separately.

2.2. Data extraction

Two reviewers independently (JN and CVH or NK) extracted data from each of the eligible studies. Relevant extracted information included nut type and amount, number of participants, participant characteristics (e.g., sex, age, health status), study design and duration, comparator, background diet, funding source, and applicable outcome data. Authors were contacted for missing data where applicable. Graphically presented data were extracted from figures using the program Plot Digitizer [25]. If lipids were measured via multiple different methods (e.g., standard enzymatic methods and Friedewald formula vs. nuclear magnetic resonance spectroscopy), the method providing a direct measurement as opposed to relying on formula determination was utilized. Differences were resolved via discussion by means of consultation with senior authors (SKN, IPG, JFGG, NB, JSS).

2.3. Risk of bias assessment

Risk of bias was assessed for each of the included studies by reviewers independently and in duplicate (JN and CVH or NK) using the Cochrane Risk of Bias tool [26]. Assessment was performed across 5 domains of bias (sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting). The risk of bias for each domain was assessed as “low” (proper methods taken to reduce bias), “high” (improper methods taken, possibly creating bias), or “unclear” (insufficient information provided to properly assess). Assessor discrepancies were resolved by consensus and arbitration by senior authors (SKN, IPG, JFGG, NB, JSS).

Table 1
PICOTS framework for the search strategy.

PICOTS framework defined in the present systematic review and meta-analysis					
Participants	Interventions	Comparators	Outcomes	Time	Study design
Adults ≥18 years of age and of all health backgrounds.	Tree nuts, pine nuts, and peanuts (whole nuts and 100 % nut butters). [Almonds, Brazil nuts, cashews, hazelnuts, macadamia, mixed nuts, peanuts, pecans, pine nuts, pistachios, walnuts.]	Any control or placebo.	Blood lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, non-HDL-cholesterol). Apolipoproteins (Apolipoprotein A1, apolipoprotein B). Blood lipids ratios (total cholesterol-to-HDL-cholesterol ratio, LDL-cholesterol-to-HDL-cholesterol ratio, HDL-cholesterol-to-LDL-cholesterol ratio, triglyceride-to-HDL-cholesterol ratio).	≥3 weeks	Controlled trials conducted in humans.

HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; PICOTS, population, intervention, comparator, outcome, time, and study design.

2.4. Outcomes

The main outcomes of interest related to the blood lipid profile including TC, LDL-C, HDL-C, TG, and non-HDL-C. Additional secondary outcomes of interest comprised of other blood lipid-related biomarkers including apoA1, apoB, and blood lipid ratios.

Mean differences (MDs) between the intervention and control arm and their standard errors of the mean (SEMs) were extracted for each eligible trial comparison. If unavailable, this data was derived from available data using published formulas [27].

Mean pairwise differences in change-from-baseline values were preferred over end values, when available. When median data were provided, they were converted to mean data with corresponding variances using established methods [28,29]. When no variance data was available, the standard deviation from a trial with a similar size, participants, and nature of intervention, including nut type and dose was applied [30]. Non-HDL-C values that were not reported were derived by subtracting HDL-C from total cholesterol values with standard errors derived from HDL-C and total cholesterol variance data using the inverse variance law [31].

2.5. Data syntheses and analyses

Stata software (version 17.0; StataCorp) was used for all analyses. Separate pooled analyses of study trial comparisons were conducted for each outcome using the generic inverse variance method with the DerSimonian and Laird random-effects model when ≥5 trial comparisons were available, even in the absence of statistically significant between-study heterogeneity, as they yield more conservative summary effect estimates in the presence of residual heterogeneity [27,32,33]. A fixed-effects model was used when <5 trial comparisons were available [34]. Paired analyses were applied to all crossover trials and for within-arm changes in parallel trials, using a correlation coefficient of 0.5 to calculate standard errors [35–37]. To mitigate a unit of analysis error, when arms of trials with multiple interventions or control arms were used more than once, the corresponding sample size was divided accordingly [27].

Data were expressed as MDs with 95 % confidence intervals (CIs). Inter-study heterogeneity was assessed by visual inspection of the forest plot and the Cochran Q statistic ($p < 0.10$ was considered significant) and quantified by the I^2 statistic (≥50 % indicated substantial heterogeneity) [27]. Sources of heterogeneity were explored via sensitivity and subgroup analyses.

Sensitivity analyses assessing individual trial influence and altering the pairwise comparison correlation coefficient were conducted. The individual trial influence analysis was performed by systematically removing each individual trial comparison from the meta-analysis and recalculating the summary effect size to determine whether a single trial comparison exerted an undue influence. When the removal of a trial comparison explained the heterogeneity, changed the significance, direction, or magnitude of the effect by more than the minimally important difference (MID), it was considered an influential trial comparison. Sensitivity analyses were also performed using correlation coefficients of 0.25 and 0.75 to determine whether the overall results were robust to the use of different correlation coefficients. Subgroup analyses were conducted when 10 or more trial comparisons were available using meta-regression (significance at $P_Q < 0.05$). *A priori* subgroups included nut type, dosage, comparator, intervention duration, participant health status, age, sex, baseline weight (e.g., BMI category), study quality, where the study was conducted (continent), and funding sources. Meta-regression analyses were used to assess the significance of subgroup analyses.

Linear and nonlinear (restricted cubic splines) dose-response relationships were assessed if ≥ 6 trial comparisons were available using meta-regression (significance at $p < 0.05$) [38]. Non-linear dose-response threshold effects with 2 prespecified spline knots at important cardiovascular health-related recommendations of 28 g/d were also assessed.

Publication bias was assessed by visual inspection of funnel plots for the presence of small-study effects and formal testing with the Egger and Begg's tests (significance at $p < 0.10$) when at least 10 trial comparisons were available [39–41]. If there was evidence of publication bias, the size of the potential publication bias or other causes of asymmetry was quantified by adjusting for the funnel plot asymmetry and assessing the effect of small-study effects by imputing the missing study data using the Duval and Tweedie trim and fill method [42].

2.6. Certainty of the evidence

The certainty of the evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and software (GRADEpro GDT, McMaster University and Evidence Prime) [43]. Three reviewers (JN, CVH, and NK) independently performed GRADE assessments for each outcome. Discrepancies were resolved by consensus or arbitration by senior authors (SKN, IPG, JGG). The evidence was rated as high, moderate, low, or very low certainty. Randomized controlled trials initially receive a high certainty by default and then may be downgraded or upgraded based on prespecified criteria [43–45]. Downgrading the certainty of the evidence may occur due to the following reasons: risk of bias (Cochrane Risk of Bias Tool assessment <6), inconsistency (substantial unexplained interstudy heterogeneity), indirectness (presence of factors that limit the generalizability of the results), imprecision (the 95 % confidence interval for the effect estimate overlaps the MID for benefit or harm), and publication bias (significant evidence of small-study effects). The certainty of the evidence was upgraded when a significant dose-response gradient existed. The importance of the magnitude of the pooled estimates was assessed using the prespecified MIDs and the effect

size categories according to the GRADE guidance as follows: a large effect (≥5 times the MID), moderate effect (≥2 times the MID), small important effect (≥1 time the MID), and trivial/unimportant effect (<1 MID) [45].

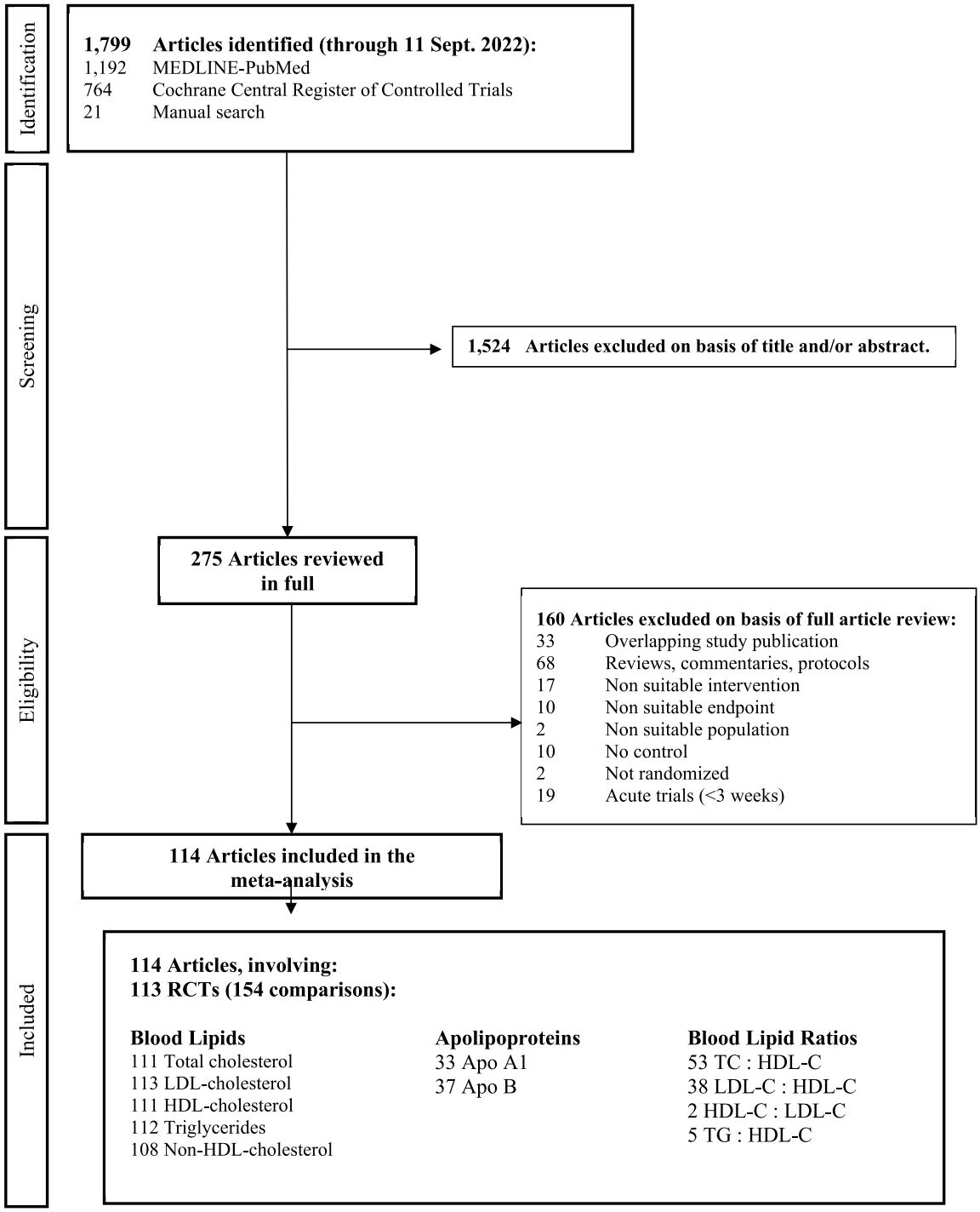
3. Results

3.1. Search results

Fig. 1 shows the flow of the literature. The search strategy identified 1977 reports, of which 275 were reviewed in full and 114 articles involving 113 unique trials (n = 8060) comprising of 154 relevant comparisons were included in the final meta-analysis [46–157]. Of the authors contacted with requests for additional information [67,68,121,125,136,137,158–163], 4 replied with the ability to provide applicable data [66,121,136,159].

3.2. Trial characteristics

Table 2 summarizes the characteristics of the included trials.



Apo, apolipoprotein; HDL-cholesterol, high-density lipoprotein-cholesterol; LDL-cholesterol, low-density lipoprotein-cholesterol; RCT, randomized controlled trial; TC, total cholesterol; TG, triglycerides.

Fig. 1. Summary of evidence search and selection.

Table 2
Summary of trial characteristics.

Trial characteristic	Summary
Trial comparisons (*n*)	154
No. of participants (*n*)	7905
Study size, median *n* (range)	35 (10–625)
Sex, % women (range)	57 % (0–100 %)
Age (years), mean (range)	46.8 (18–86)
Health Status (No. of comparisons)	CVD = 2, DM = 19, HL = 28, HTN = 2, Healthy = 36, MetS = 14, Multiple = 3, OW/OB = 41, Other = 9.
Study design (%) (crossover: parallel)	42:58
Duration (weeks), median (range)	8 (3–104)
Country (No. of comparisons)	Africa = 2, Australia = 10, Brazil = 12, Canada = 4, China = 7, Germany = 2, Hawaii = 2, India = 3, Iran = 9, Japan = 3, Korea = 4, Mexico = 2, Multiple (United States & Spain) = 1, New Zealand = 8, Nigeria = 2, Norway = 2, Pakistan = 2, Spain = 10, Sweden = 1, Tunisia = 1, Turkey = 2, United Kingdom = 2, United States = 63.
Nut dose (g/d), median (range)	45.5 (5–100)
Nut type (No. of comparisons)	Almonds = 44, Brazil Nuts = 3, Cashews = 4, Hazelnuts = 7, Macadamia Nuts = 7, Mixed Nuts = 13, Peanuts = 12, Pecans = 8, Pistachios = 12, Walnuts = 44.
Comparator[a] (No. of comparisons)	Carbohydrate = 20, Carbohydrate + Fat = 5, Carbohydrate + Protein = 9, Fat = 16, Fat + Protein = 10, Habitual Dietary Pattern = 55, Healthy Dietary Pattern = 37, Not Specified = 2.
Funding[b] (No. of comparisons)	Agency = 121, Agency-Industry = 19, Industry = 5, None = 2, Not Reported = 7.

CVD, cardiovascular disease; DM, diabetes; HL, hyperlipidemia; HTN, hypertension; MetS, metabolic syndrome; OW/OB, overweight and/or obesity.

[a] Healthy dietary pattern refers to a dietary pattern based on country or disease specific guidelines, such as the American Heart Association dietary recommendations; NCEP Diet, National Cholesterol Education Program diet.

[b] Agency funding is that from government, university, or not-for-profit sources. Industry funding is that from trade organizations that obtain revenue from the sale of products.

Supplementary Table S4 provides the details of the characteristics of each of the included trials separately. All trial comparisons were conducted in outpatient settings, with most in the United States (41 %) then Brazil (8 %), Australia (6 %), Spain (6 %), and the rest across European, Asian, and African countries. Trials had a median follow-up duration of 8 weeks (range 3–104), a slightly higher proportion of women (median percentage women 57 %, range 0–100 %), and 42 % had a crossover design (17 [34 %] of 50 crossover trials had no washout period between interventions). Most participants were middle-aged (approximate mean age of 46.8 years, range 18–86 years), had overweight/obesity or hyperlipidaemia (with 26 % and 18 % of the studies recruiting for participants with these health statuses, respectively). Most trials studied almonds (29 %) or walnuts (29 %) with a median dose of 45.5 g/day (range 5–100 g/day) with most compared to a habitual dietary pattern free of nuts (36 %), healthy dietary patterns, such as the National Cholesterol Education Program (NCEP) Step 2 diet, American Heart Association dietary recommendations, or other dietary guidelines (24 %), or nuts were exchanged for a control carbohydrate-based food (13 %).

3.3. Risk of bias

Supplemental Figs. S1–S11 show the Cochrane Risk of Bias assessments for the included trials by outcome. Most trials were judged as having low or unclear risk of bias across domains.

3.4. Effect of nut consumption on main outcomes

Fig. 2 and Supplemental Fig. S12 show the effect of nut consumption on total cholesterol. In 111 trials (150 comparisons) involving 7,138 participants, (28 comparisons in those with hyperlipidaemia), nut consumption led to a small important reduction in total cholesterol compared with control diets (MD -0.14 mmol/L [95 % CI: −0.18 to −0.10 mmol/L], $P < 0.001$; substantial heterogeneity, $I^2 = 76$ %, $P < 0.001$).

Fig. 2 and Supplemental Fig. S13 show the effect of nut consumption on LDL-C. In 112 trials (152 comparisons) involving 7,237 participants, (28 comparisons in those with hyperlipidaemia), nut consumption led to a small important reduction in LDL-C compared to the control (−0.12 mmol/L [-0.14 to −0.09 mmol/L], $P < 0.001$; substantial heterogeneity, $I^2 = 90$ %, $P < 0.001$).

Fig. 2 and Supplemental Fig. S14 show the effect of nut consumption on HDL-C. In 111 trials (150 comparisons) involving 7,446 participants, (28 comparisons in those with hyperlipidaemia), nut consumption did not significantly affect HDL-C compared to the control (0.02 mmol/L [-0.00 to 0.04 mmol/L], $P = 0.101$; substantial heterogeneity, $I^2 = 99$ %, $P < 0.001$).

Fig. 2 and Supplemental Fig. S15 show the effect of nut consumption on triglycerides. In 112 trials (152 comparisons) involving 7,489 participants, (28 comparisons in those with hyperlipidaemia), nut consumption led to a trivial reduction in triglycerides compared to the control (−0.05 mmol/L [-0.07 to −0.03 mmol/L], $P < 0.001$; substantial heterogeneity, $I^2 = 52$ %, $P < 0.001$).

Fig. 2 and Supplemental Fig. S16 show the effect of nut consumption on non-HDL-C. In 108 trials (145 comparisons) involving 6,609 participants, (28 comparisons in those with hyperlipidaemia), nut consumption led to a small important reduction in non-HDL-C compared to the control (−0.16 mmol/L [-0.20 to −0.12 mmol/L], $P < 0.001$; no substantial heterogeneity, $I^2 = 21$ %, $P < 0.001$).

3.5. Effect of nut consumption on secondary outcomes

Fig. 2 and Supplemental Figs. S17–S18 show the effect of nut consumption on apolipoproteins. Nut consumption showed a small important reduction in apoB (−0.04 g/L [-0.06 to −0.02 g/L], $P < 0.001$; substantial heterogeneity, $I^2 = 88$ %, $P < 0.001$) and no effect on apoA1.

Fig. 2 and Supplemental Figs. S19–S22 show the effect of nut consumption on blood lipids. Nut consumption showed small important reductions in TC:HDL ratio (−0.11 mmol/L [-0.16 to −0.06 mmol/L], $P < 0.001$; substantial heterogeneity, $I^2 = 0$ %, $P < 0.001$) and LDL:HDL ratio (−0.19 mmol/L [-0.24 to −0.12 mmol/L], $P < 0.001$; substantial heterogeneity, $I^2 = 70$ %, $P < 0.001$). Non-significant improvements were shown for other ratios assessed.

3.6. Sensitivity and subgroup analyses

Supplemental Figs. S23–S33 show differing the model utilized (i.e., fixed for effect estimates originally assessed via random effects model and vice versa) did not significantly alter findings.

Supplemental Figs. S34–S43 show influence analyses, in which systematic removal of individual trials altered the results. Removal of single trial comparisons did not result in significant changes in pooled effect estimates and hence did not explain the observed heterogeneity.

Supplemental Table S6 shows sensitivity analyses in which different correlation coefficients (0.25 and 0.75) for paired analyses to calculate standard errors were utilized. None of the correlation coefficients altered the conclusions for any outcome.

Additional sensitivity analyses were conducted which included the PREDIMED study [164], comparing a Mediterranean diet plus nuts group with a Mediterranean diet plus olive oil group and a low-fat control diet group, did not significantly alter the findings for any of the outcomes with relevant data available (TC, LDL-C, HDL-C, TG,

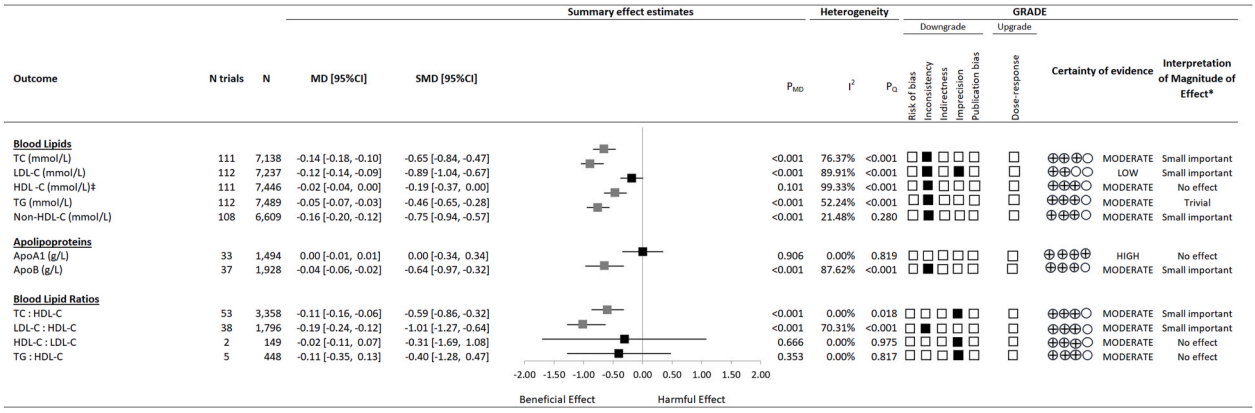


Figure 2. Summary plot of the effect of nut consumption on blood lipid outcomes in randomized controlled trials. Data are expressed as weighted mean differences with 95% confidence intervals using the generic inverse variance method modelled by random effects meta-analyses for all outcomes except for HDL-C to LDL-C ratio where a fixed effects model was utilized due to there being less than 5 trial comparisons. To allow the pooled effect estimates for each end point to be displayed on the same axis, mean differences were transformed to standardised mean differences (SMDs). Pseudo-95% confidence intervals for each transformed SMD were derived directly from the original mean difference and 95% confidence intervals. Between study heterogeneity was assessed by the Cochran Q statistic, where P<0.10 is considered statistically significant, and quantified by the I^2 statistic, where I^2 ≥50% is considered evidence of substantial heterogeneity. The grading of recommendations, assessment, development, and evaluation (GRADE) of randomized controlled trials are rated as "high" certainty of evidence and can be downgraded by five domains and upgraded. The filled black squares indicate downgrade or upgrade for each outcome. *For interpretation of the magnitude, we used the minimally important differences (MIDs) for each outcome and dose-response analyses to assess the importance of magnitude of our point estimate using the effect size categories according to new GRADE guidance.

‡Owing to the difference in directionality of HDL-cholesterol compared with the other outcomes with regards to signal for benefit or harm, the sign for the SMD was changed.

Grey coloured squares mean the result is statistically significant and beneficial (p<0.05).

To convert LDL-C, non-HDL-C, and HDL-C to mg/dL, multiply by 38.67; to convert triglycerides to mg/dL, multiply by 88.57.

Apo A1, apolipoprotein A1; Apo B, apolipoprotein B; CI, confidence interval; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; MD, mean difference; non-HDL-C=non-high-density lipoprotein-cholesterol; P_{MD}, P value of the mean difference; P_Q, P value of the heterogeneity; SMD, standardised mean difference; TC, total cholesterol; TG, triglycerides.

Fig. 2. Summary plot of the effect of nut consumption on blood lipid outcomes in randomized controlled trials.

non-HDL-C, and TC:HDL ratio).

Supplemental Figs. S44–S70 present the subgroup analyses conducted for all outcomes except for the ratios of HDL:LDL and TG:HDL (<10 trial comparisons). For total cholesterol, evidence of significant effect modifications were seen in categorical analyses, by BMI category (P = 0.01), where significantly greater reductions were observed in total cholesterol in those trials with participants on average having a BMI between 18.5 and 29.9 kg/m^2; in health status (P < 0.01), where recruited participants had hyperlipidaemia, hypertension, overweight/obesity, or were considered in good health showed greater reductions than other categories; nut type (P < 0.01), where almond pecan, pistachio, and walnut interventions showed greater reductions; in comparator (P < 0.01), where nut consumption compared to carbohydrate and healthy dietary pattern controls resulted in greater reductions; and allocation concealment (P < 0.01), where those studies rated as unclear and low had greater reductions than those rated as high. For LDL-cholesterol, evidence of significant effect modifications by study design (P = 0.02), where crossover trials showed greater reductions than parallel trials, although both categories were significant; by BMI category (P < 0.01), where significantly greater reductions were observed in total cholesterol in those trials with participants on average having a BMI between 18.5 and 29.9 kg/m^2; in health status (P < 0.01), where recruited participants had hyperlipidaemia, hypertension, or were considered in good health showed greater reductions than other categories; nut type (P < 0.01), where almond and walnut interventions showed greater reductions; in comparator (P < 0.01), where nut consumption compared to carbohydrate-protein and healthy dietary pattern controls resulted in greater reductions; by funding, (P < 0.01), where those reporting no funding received showed the greatest reductions; and sequence generation (P = 0.01), blinding (P = 0.01), and incomplete outcome data (P < 0.01), where those studies rated as unclear had greater reductions than those rated as high or low, yet both unclear and low categories were significant. For the remaining outcomes, significant effect modification was observed by at least one of the following: sex distribution, age group, BMI category, health status, continent, nut type, comparator, funding, allocation concealment, incomplete outcome reporting, and selective outcome reporting. None of these subgroup effects altered the evidence of heterogeneity for any outcome. No effect modification was found by duration except for apoB where a duration of ≤8 weeks showed a significant reduction.

No effect modification was found by dose except for TC:HDL ratio where a dose of ≥45.5 g/d weeks showed a significant reduction. No effect modification was found by the presence or absence of a washout phase in crossover trials on any outcome.

3.7. Dose-response analyses

Supplemental Figs. S71–S86 present linear and non-linear dose-response analyses. No significant dose-response findings were observed.

3.8. Publication bias

Supplemental Figs. S87–S102 show the assessment for publication bias for all outcomes. Evidence of funnel plot asymmetry was observed, with either Egger's and/or Begg's tests showing evidence of small study effects (P < 0.05) for TC, LDL-C, HDL-C, TG, apoB, and TC:HDL ratio. The trim and fill method showed either no evidence of small study effects (TC, HDL-C, apoB) or that the imputation of trials did not alter the significance of the findings (LDL-C, TG, TC:HDL ratio). Publication bias was not assessed for the ratios of HDL-cholesterol to LDL-cholesterol and triglycerides to HDL-cholesterol (<10 trial comparisons).

3.9. GRADE assessment

Fig. 2 and Supplemental Tables S7–S8 present the GRADE assessments of the overall certainty of the evidence for the effect of nut consumption on blood lipids. The evidence was graded as moderate for all outcomes owing to a downgrade for either inconsistency or imprecision, except for LDL-C which was graded as low owing to downgrades for inconsistency and imprecision and apoA1 graded as high certainty.

4. Discussion

4.1. Summary of findings

The present SRMA of nut consumption and blood lipids involving 114 articles (113 unique trials comprising of 154 relevant comparisons, n = 8060) substantiates the beneficial effect on TC, LDL-C, and non-HDL-C, as well as apoB, TC:HDL, and LDL:HDL ratios without impacting HDL-C compared to a non-nut control in adults. These favourable

findings remained regardless of the duration (whether nut intake was more or less than 8 weeks) or dose (whether nut intake was more or less than 45.5 g/d).

4.2. Findings in the context of existing literature

While there have been inconsistencies in the literature, the majority of past meta-analysis evidence aligns with the present results [9,10,165–171]. Of note, Houston and colleagues conducted a meta-analysis assessing nut intake and cardiovascular risk factors, including blood lipids, with findings paralleling present results [172]. Nonetheless, the present findings provide greater clarification and certainty, after conducting different sensitivity and subgroup analyses. There have been notable differences in conduct among past meta-analyses which have brought about uncertainties in interpretation and generalizability of the application of the results. Differences in observed findings may be due to varying attributes of the included studies, for instance, some previous meta-analyses assessed seeds and nuts in combination, or only individual nut types or compared nut types instead of having a nut-free comparator [9,10,165,168–170,173–177]. Additionally, the form of nut consumption has also previously included both whole nuts and nut oils or other nut components in some studies [21], which may attenuate the actual effectiveness of consuming whole nuts on blood lipids due to the lack of fiber in oil and other nutrients in the food matrix of nuts. Thus, the present results provide a more comprehensive and clear assessment of nuts as a whole compared to a non-nut control on the blood lipid profile of adults of various health status.

Furthermore, the present findings support current and proposed health claims as well as clinical practice guidelines. In the United States, the Food and Drug Association (FDA) has qualified health claims for macadamia nuts, walnuts, and nuts in relation to coronary heart disease [18–20]. Similarly, the European Food Safety Authority (EFSA) has noted a number of health claims related to nuts and health, yet all except one are not authorized [178–182]. While most of the proposed health claims have supported daily consumption of 1–1.5 oz (28–42.5 g/d) of nuts in aiding heart health or more specifically the maintenance of normal blood LDL-C concentrations, the claims have not been granted with statements akin to there being “supportive but not conclusive research”. The present work adds to the body of evidence in support of such health claims, specifically for nuts in reducing the risk of cardiovascular disease via reducing LDL-C. This more closely aligns with recommendations from cardiovascular and diabetes associations for the incorporation of nuts into healthy dietary patterns for the promotion of heart health [13,15,16,183]. Additionally, the present SRMA identifies circumstances where nut consumption may be particularly impactful for blood lipids, such as for individuals with hyperlipidaemia or hypertension; those in good health and/or with a BMI between 18.5 and 29.9 kg/m^2; and when incorporating into healthy dietary patterns and/or substituting carbohydrate-protein foods.

4.3. Potential mechanisms of action

The favourable changes in blood lipid profiles observed with nut consumption may be attributed to various factors, including their unsaturated fat, dietary fiber, plant sterol, and satiating properties. Nuts tend to be rich in unsaturated fats, including monounsaturated and polyunsaturated fats. These fats have been shown to lower LDL-C levels without negatively affecting HDL-C [184]. The unsaturated fats in nuts may contribute to a more favourable lipid profile compared to saturated fat and low-fat dietary intakes [185,186]. Nuts are also a good source of dietary fiber, including soluble fiber. Soluble fiber has been shown to lower LDL-C levels by binding to cholesterol in the digestive system, preventing its absorption into the bloodstream [187]. This process can lead to increased excretion of cholesterol from the body. Nuts contain plant sterols, which structurally resemble cholesterol. Plant sterols, similar to fiber, can compete with cholesterol for absorption in the digestive system, reducing the overall absorption of cholesterol, in addition, it has been suggested that plant sterols may regulate proteins implicated in cholesterol metabolism in both enterocytes and hepatocytes, hence contributing to a lowering of TC and LDL-C levels [188,189]. Regular nut consumption has been associated with better weight management [190]. Maintaining a healthy weight is important for overall cardiovascular health, and nuts, despite being considered “calorie-dense” may contribute to satiety and reduce the likelihood of overeating, especially less nutritive foods. Lastly, nuts may influence the size and function of lipid particles. Some studies suggest that nut consumption can lead to a shift in LDL particle size from smaller, more dense particles, which are associated with a higher risk of cardiovascular disease, to larger, less dense particles, potentially reducing cardiovascular risk [191–193]. Hence, nuts can be a nutritious part of a balanced dietary pattern.

4.4. Strengths and limitations

The analyses have notable strengths, such as a thorough search that enabled the identification of eligible studies comprehensively. The inclusion criteria prioritized high-quality randomized controlled trials, offering maximum protection against bias. Intention-to-treat data, when accessible, was utilized to generate more conservative pooled estimates [194]. Additionally, the GRADE approach was used to assess the overall certainty of evidence.

Limitations were also present in the synthesis. First, there was evidence of serious inconsistency in several pooled estimates owing to unexplained heterogeneity. There was also evidence of imprecision in a number of pooled analyses owing to crossing of the prespecified MID, which indicates that clinically important benefits may not be guaranteed.

Weighing the strengths and limitations, the certainty of evidence indicated small yet important beneficial effects of nut consumption on TC, LDL-, and non-HDL-C, as well as apoB and the TC:HDL and LDL:HDL ratios.

4.5. Implications

The present findings support the recommendation that incorporating nuts into one’s diet could have beneficial effects on blood lipid profiles. This may be particularly significant for individuals at risk of cardiovascular disease (e.g., those with hyperlipidaemia) or those aiming to improve their overall cardiovascular health. Recommending the inclusion of nuts in dietary plans could contribute to a more holistic approach to the prevention or management of cardiovascular risk factors through dietary interventions.

5. Conclusions

In conclusion, this synthesis supports existing recommendations for the consumption of nuts for cardiovascular risk reduction by favourably affecting the blood lipid profile in adults. These findings substantiate the current health claims and support health professionals and dietary guidelines in recommending nuts as part of a nutrient-dense dietary pattern for cardiovascular health.

Author contributions

S.K.N., N.B., J.S.-S.: conceptualization; S.K.N., I.P.G., J.N., N.K., C.V.H. and J.F.G.G.: data curation; S.K.N., I.P.G., J.N., N.K., C.V.H. and J.F.G.G.: formal analysis; investigation; S.K.N., N.B., and J.S.-S.: methodology; S.K.N. and J.S.-S.: project administration and resources; S.K.N. N.B. and J.S.-S.: supervision; S.K.N., N.B., and J.S.-S.: validation; S.K.N.: writing—original draft; and S.K.N., I.P.G., J.N., N.K., C.V.H., J.F.G.G., N.B., and J.S.-S.: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Funding sources

This work was supported by a grant from the INC International Nut and Dried Fruit Council Foundation. S.K.N. was supported by a post-doctoral fellowship from the Canadian Institutes of Health Research (CIHR, MFE-171207). J.N. was supported by a predoctoral grant from Ministerio de Ciencia, Innovación y Universidades (FPU 20/00385). C. V.-H. received a predoctoral grant from the Generalitat de Catalunya (2022 FI_B100108). N.K. was funded by a research grant from the Agència de Gestió d'Ajuts Universitaris de Recerca (AGAUR FI, record number: 2021FI_B 00145). None of the funding sources provided any input into the design, collection, analysis, interpretation of the data, or manuscript writing.

Declaration of competing interest

S.K.N. is a volunteer member of the not-for-profit group Plant-Based Canada. J.S.-S. reported receiving research support from the Instituto de Salud Carlos III, Ministerio de Educación y Ciencia, the European Commission, the USA National Institutes of Health; receiving consulting fees or travel expenses from Instituto Danone and Abbott Laboratories, receiving nonfinancial support from Patrimonio Comunal Olivarero, the Almond Board of California, Pistachio Growers and Borges S.A; serving on the board of and receiving grant support through his institution from the International Nut and Dried Foundation; and personal fees from Instituto Danone; Serving in the Board of Danone Institute International. None of these organizations had any role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results. All other authors declare no conflict of interest.

Acknowledgements

We would like to thank the authors who provided additional information and the scholarships, fellowships, and grant (described below) that enabled the conduct of this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2024.10.009.

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