Meta-Analysis

Effect of Nuts on Anthropometric and Glycemic Indexes and Blood Pressure in Secondary Cardiovascular Prevention: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Context: *Nut-enriched diets have a positive impact on cardiovascular risk factors, such as body mass, blood pressure, and fasting blood glucose. However, studies in individuals undergoing secondary cardiovascular prevention show controversial results.* ***Objective:*** *This systematic review with meta-analysis assessed the effect of nut supplementation on anthropometric, glycemic, and blood pressure indices in patients with atherosclerotic cardiovascular disease, as well as the frequency of adverse events.* ***Data Sources:*** *Six databases were used for the search—PubMed, Cochrane Library, EMBASE, BVS (Biblioteca Virtual da Saude), Web of Science, and ClinicalTrials.gov—until February 2023, with no language restrictions.* ***Data Extraction:*** *The Cochrane Handbook for Systematic Reviews of Interventions methodology and the PICOS (Population, Intervention, Comparison, Outcome, Setting/design) strategy were used. Seven independent reviewers were involved in data extraction and resolution of disagreements. Certainty of the evidence was evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.* ***Data Analysis:*** *From 5187 records identified, 6 publications containing data referring to 5 randomized clinical trials (n = 436) were included in the final analyses. The nuts evaluated were almonds, pecans, Brazil nuts, and mixed nuts, with portions that varied between 5 g and 85 g (median: 30 g/day). The intervention period varied between 6 and 12 weeks. The nuts had no effect on fasting glucose and anthropometric indices, although the certainty of the evidence for most of these outcomes was low or very low. They also had no effect on systolic (mean difference [MD]: -1.16 mmHg [95% CI, -5.68 to 3.35], I^2 = 0%—moderate certainty of evidence) or diastolic (MD: 0.10 mmHg [95% CI, -2.30 to 2.51], I^2 = 0%—high certainty of evidence) blood pressure. It was not possible to aggregate data on adverse events.* ***Conclusion:*** *Nut supplementation had no effect on blood pressure, fasting glucose, or anthropometric*

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profile in the context of atherosclerotic cardiovascular disease.
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Key words: *secondary prevention, nuts, body weight, blood pressure, blood glucose, meta-analysis [publication type].*

INTRODUCTION

Ischemic heart disease (IHD) is the leading cause of mortality worldwide.[1] Inadequate diet, changes in systolic blood pressure (SBP) and fasting blood glucose, and high body mass index (BMI) are among the main modifiable risk factors responsible for IHD-related mortality.[2] In addition to being a risk factor in itself, diet also plays a crucial role in managing other risk factors, including blood pressure levels, glucose metabolism, and body mass.[3] However, specific nutritional guidelines and strategies that improve cardiometabolic outcomes in patients already affected by IHD are still scarce,[4,5] and the recommendations referenced for individuals undergoing primary cardiovascular prevention are usually mixed.[6,7]

Nut-enriched diets have been widely studied and related to benefits on cardiometabolism.[8,9] In secondary cardiovascular prevention, diets rich in nuts have been shown to improve cardiometabolic indicators[10] and reduce cardiovascular events, including ischemic events.[11] Nuts are rich in unsaturated fatty acids, L-arginine, minerals, phenolic compounds, and phytosterols, which appears to explain their cardioprotective effects.[12] Studies have investigated the effect of nut supplementation as an adjunct to the treatment of IHD,[13–16] beyond the context of the Mediterranean diet (the most studied cardioprotective nut-enriched diet). However, the results on the effects that the intake of these foods has on cardiometabolic risk factors in this population are conflicting.

In primary cardiovascular prevention, systematic reviews assessing nut supplementation also present discordant results regarding its effects on blood pressure,[17–21] glycemic control,[17,18,20] and anthropometric parameters.[18,20–23] Considering that the intake of these foods has not yet been assessed in a more robust way in secondary cardiovascular prevention, in addition to presenting conflicting results in primary prevention, this study aimed to systematically review the effect of nut intake on blood pressure, glycemic profile markers, and anthropometric indicators in the context of secondary prevention of atherosclerotic cardiovascular disease. Systematic reviews with meta-analysis are necessary, as they synthesize the literature and inform best practices, therefore improving nutritional recommendations in this population.

METHODS

This systematic review and meta-analysis was conducted using the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3)[24] and reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table S1).[25] The protocol was registered in the PROSPERO database (CRD42020163456) and is presented at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020163456.

Search strategy and eligibility criteria

Table S2 shows the search strategy used. The research was conducted in the following electronic databases: PubMed, Cochrane Library, EMBASE, BVS (Biblioteca Virtual da Saude), Web of Science, and ClinicalTrials.gov. Manual searches based on the reference lists of included studies or direct searches on Google complemented these strategies. Standardized vocabulary, key words and their synonyms, and standardized filters to identify studies improved the search whenever possible (MeSH [Medical Subject Heading] terms), following the PICOS approach (Population, Intervention, Comparison, Outcome, Setting/design) (Table 1). The first search was carried out in August 2020 and updated in June 2021, April 2022, and February 2023.

Randomized clinical trials with a parallel or crossover design with a washout period of $\geq$3 weeks were included. Only studies with individuals $\geq$18 years of age and with known atherosclerotic cardiovascular disease (coronary artery disease, myocardial infarction, angina pectoris, stroke, revascularization, or peripheral vascular disease) defined according to the primary study were assessed. Studies in which participants were healthy, pregnant, lactating, or with a single health condition considered primary cardiovascular prevention (eg, type 2 diabetes [T2D], obesity, metabolic syndrome, hypertension, dyslipidemia) were excluded. Studies that did not report the outcomes of interest were also excluded. No restrictions were placed regarding language or publication dates.

For the intervention to be eligible, clinical trials had to evaluate supplementation (at any dosage, frequency, and run-in period) of different nuts (almonds, Brazil nuts, cashew nuts, hazelnuts, macadamia nuts, pecans,

Table 1. PICOS criteria for inclusion of intervention studies

Parameter	Criteria
Population	Individuals ≥18 y diagnosed with atherosclerotic cardiovascular disease
Intervention	Background diet supplemented with any type of nuts, with or without caloric restriction
Comparison	Nut-free background diet, with or without caloric restriction
Outcomes	Blood pressure (systolic and diastolic blood pressure), glycemic profile (fasting glucose, glycated hemoglobin, serum insulin, and homeostasis model assessment of insulin resistance), anthropometric indexes (body weight, body mass index, and waist circumference), and frequency of adverse events
Setting/design	Randomized controlled clinical trials (parallel or crossover design)

pine nuts, pistachios, walnuts) and/or "non-true" nuts according to their botanical classification (Baru nut, peanut) added to any dietary pattern (eg, low-fat diet, Mediterranean diet, low-carbohydrate diet) with or without energy restriction. Studies evaluating mixed nuts were also included. The quantity and frequency of nuts prescribed had to be clearly described in the article. The control treatment could be an isocaloric diet, with or without energy restriction, or any specific eating pattern without nut supplementation. Studies that tested non-nut parts of the plant, isolated nut oils, and/or extracts were excluded.

Data extraction

All citations retrieved from each database, titles, and abstracts were independently evaluated by 2 reviewers (A.C.B.-F. and R.H.V.M.). Whenever at least 1 of the authors considered a citation suitable for eligibility or if the title and abstract information was insufficient, the full text was obtained and evaluated for eligibility. Duplicate publications or sub-studies of the included trials were listed as the main reference if they provided additional relevant information that was not available in the original publication. Disagreements within the team were resolved by consensus.

Data from the selected articles were independently extracted by 2 reviewers (L.R.d.S. and E.S.) using a standardized form (available at https://data.mendeley.com/datasets/n9spjvd467/2) and disagreements were resolved by consensus or by a third reviewer (A.M.). Information was basically extracted regarding the identification and characteristics of the study, characteristics of the participants, details of the intervention and control group, and the outcomes. Authors were contacted by email if there were any missing data. Data were not considered in the analyses if outcomes were absent or if researchers were unable to obtain original data from the authors.

Risk-of-bias assessment

Two reviewers (A.M. and G.W.) independently assessed the risk of bias of the studies using the second version of the Cochrane Risk-of-Bias tool for randomized trials (RoB 2).[26] The following domains were assessed: randomization process, deviations from intended interventions, missing outcome data, outcomes measurement, and selection of reported outcomes. Overall risk of bias was assessed as low (if all domains were considered as low risk), as having some concerns (if at least 1 domain was considered as some concerns), or as high (if at least 1 domain was considered as high risk or if multiple domains were characterized with some concerns, substantially reducing confidence in the results). Discrepancies were resolved by consensus or by a third reviewer (E.O.d.A.-S.).

Outcomes

The prespecified outcomes were differences in anthropometric indicators (body mass [kg], BMI [kg/m^2], and waist circumference [cm]), SBP and diastolic blood pressure (DBP) (mmHg), glycemic profile (fasting blood glucose [mg/dL], glycated hemoglobin [%], serum insulin [μIU/mL], homeostasis model assessment of insulin resistance [HOMA-IR]), and frequency of adverse events.

Statistical analysis

All effect measures are presented as mean differences (MDs) and 95% CIs between the group who consumed nuts and the control group (no nuts) using a random-effects model and inverse-variance method. Note that the 95% CIs describe the uncertainty in the location of the mean of different effects in the studies and are not the most appropriate estimates for decision-making based on the results. Instead, the estimates of the 95% prediction interval (95% PI; ≥3 studies) were considered, as they reflect the expected effects in future studies. This approach aligns with the characteristics of the randomized clinical trials included in the meta-analysis.[27] Further, these estimates also reflect the range of potential effects (harmful or beneficial) that are useful for clinical decision-making.[27] Heterogeneity was measured using the Higgins statistic (I^2) and classified as follows: may not be important (0% to 40%), may represent moderate heterogeneity (30% to 60%), may represent substantial

heterogeneity (50% to 90%), and may represent considerable heterogeneity (75% to 100%).[28] In the presence of heterogeneity (P value for Cochran's Q test $< .10$) or when the range between the lower and upper limit of the 95% CI was above 30% for I^2, subgroup analyses were conducted[25] with potential effect modifiers being the type (almonds vs other nuts), the dosage of nuts consumed (<30 g vs ≥ 30 g/day), and the risk of bias of primary studies (high vs low). Furthermore, the inaccuracy of the effect estimate was also identified visually through the lack of overlapping 95% CIs in the forest plots to remove discrepant data from the meta-analysis.[25] Concomitantly, as recommended in the Cochrane Handbook version 6.3 (section 10–14), sensitivity analyses that involved removing individual studies from the meta-analysis were also performed. To avoid unit overlap in analyses, for randomized controlled trials with multiple intervention arms and a single control group, the sample size for the control group was weighted by the number of groups and participants with nut supplementation.[29,30] In these multi-arm trials, relevant intervention groups were determined to be included in the systematic review. Intervention groups with similar categories were grouped together for a single pairwise comparison using the equations recommended in the Cochrane Handbook version 6.3 (section 6–5-2–10). Crossover clinical trials were analyzed as parallel.[24] For all studies analyzed, the SD of differences was imputed using the correlation coefficient (CC) of 0.5.[31] To estimate the SD delta (Δ SD), the recommendations of the Cochrane Handbook version 6.3 (section 6–5-2–8) were used. Measures of dispersion expressed as standard errors or 95% CI were converted according to the Cochrane Handbook version 6.3 (section 6.5.2.2) before analysis. In cases of data expressed as median and interquartile range, for conversion into mean ± SD, the proposal by Wan et al[32] was used. To explore dose–response data for nuts and the outcomes analyzed, when the number of entries was ≥ 3 studies, meta-regression was performed for the total value in grams of nuts consumed, corrected for the most frequent intervention time among studies (12 weeks, standardized to 90 days). All statistical tests were 2-tailed, and the significance level was set at $P \leq .05$. Data analysis models were performed with R software (4.3.1; R Foundation for Statistical Computing) using the meta package (G.W.) (scripts are available at https://data.mendeley.com/datasets/n9spjvd467/2).

Assessing the certainty of the evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to assess the certainty of the evidence.[33,34] The level of certainty of the evidence generated by the meta-analysis was initially set as high and was downgraded when any of the following were present: study limitations, imprecision in estimates of effect, indirectness of evidence, inconsistency, or evidence of reporting bias.[33,34] Evidence generated by studies with limitations means that most of the included trials showed a high risk of bias. "Imprecision" in estimates of effect indicates that there was a non-acceptable level of random error in the estimate of effect generated by the meta-analysis. "Indirectness" of evidence occurred when there were differences between the population, intervention, comparator, and outcome of interest included in the relevant studies. "Inconsistency" indicates that the results of the individual trials were different from each other. Finally, "reporting bias" occurs when investigators failed to report studies (typically those that show no effect) or outcomes (typically those that may be harmful or for which no effect was observed).

RESULTS

Literature flow

Figure 1 shows the literature search and selection process. Of the 5187 records identified, 3173 were screened and 3090 were excluded based on titles and abstracts. Of the 83 publications reviewed in full, 77 were excluded based on eligibility criteria (complete list available at https://data.mendeley.com/datasets/n9spjvd467/2). A total of 6 publications containing data from 5 randomized clinical trials and involving 436 participants with established cardiovascular disease were included in the final analyses. Data from 4 publications ($n = 391$) were obtained for anthropometric profile analyses, 4 publications ($n = 397$) for blood pressure analysis, and 2 publications ($n = 172$) for glycemic profile analyses.

Characteristics of the studies

Table 2[13–16,35,36] and Table S3 show the characteristics of the included studies. All experiments were single center and conducted in an outpatient setting in Brazil, the United States, Pakistan, and Iran. Four studies had a parallel design, and 1 study had a crossover design. The time of follow-up ranged from 8 to 22 weeks. There was a higher proportion of men included in the studies than women (median, 55%; range between 40%[13] and 77%[14,15]), there was a median age of 60 years old (range between 59[16] and 63 years[35]), a majority were overweight patients (median BMI, 29.9 kg/m^2; ranging between 29.5[14,15] and 30.7 kg/m^2 [16]), and 93% (median) were taking lipid-lowering drugs (range between 96%[13] and 76%[35]; 100% using statins [no report of other lipid-lowering agents]). The median loss to follow-up

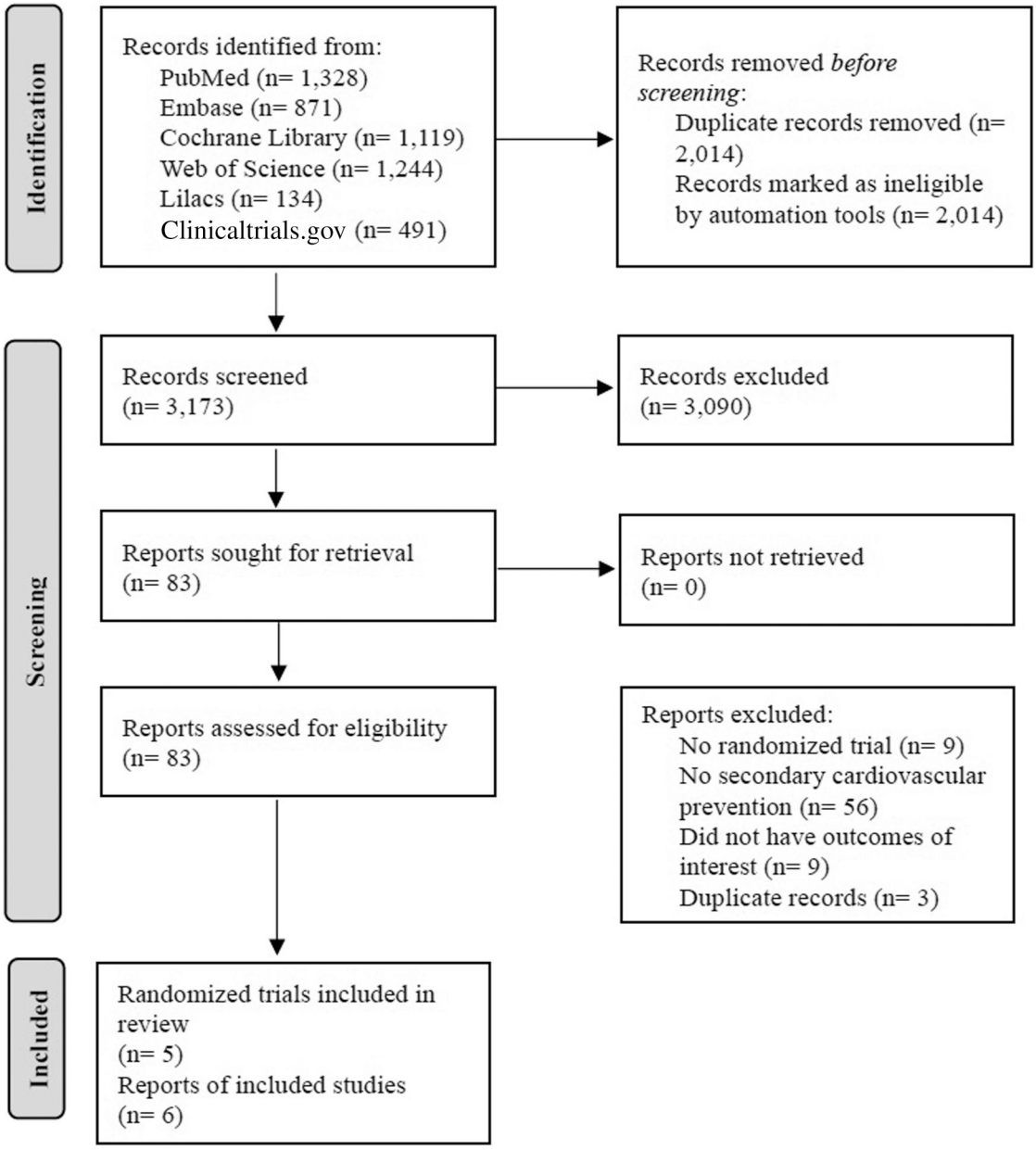

Figure 1. Flow Diagram of the Literature Search Process.

between studies was 21.3% (range between 4.3%[16] and 25.2%[14,15]). In 1 trial, an intention-to-treat approach was used to analyze the data.[14,15]

The intervention time varied between 6 and 12 weeks. The nuts evaluated were almonds ($n = 2$), pecans ($n = 1$), and Brazil nuts ($n = 1$), and 1 study evaluated a mix of nuts (almonds, pistachios, and peanuts). Daily doses varied between 5 g and 85 g (median, 30 g/day) and were provided to participants in all studies. No trials assessed co-interventions. A dietary survey method was used in all studies (food diary, 24-hour recall, food-frequency questionnaire) to evaluate compliance. Two trials collected nut packaging (consumed or not)[13,16] and Jamshed et al[36] used telephone calls (twice a week) to assess adherence to treatment. In 1 study[16], participants were instructed to ensure that total energy intake remained constant between groups (isocaloric diets), while in the other 4 studies, participants were instructed to add the nuts provided to the standardized diet for both treatment arms. The background diet was heterogeneous across studies. In 2 trials[35,36] maintenance of the usual eating pattern was recommended. One study[13] recommended the National Cholesterol Education Program (NCEP) Step 1 diet. The GENUTRI study[14,15] prescribed a healthy diet based on nutritional guidelines, calculated individually

Table 2. Characteristics of study design and interventions

First author (year); country	Type of RCT	No. randomized	Primary outcome	Enrollment period	Intervention period	Follow-up period	Frequency of visits	LFU, *n*	Experimental intervention	Control group
Chen et al (2015)[13]; USA	Crossover	T: 51 Eph: 26 Cph: 25	Brachial artery flow-mediated dilation	NR	6 wk	22 wk[a]	NR	Run-in phase: 4 Eph2: 1 Cph2: 1	Type of nut: almonds Dosage: 85 g/d Frequency: 2×/d Number of portions per day[b]: 3 Dietary pattern: National Cholesterol Education Program (NCEP) Step 1 diet	National Cholesterol Education Program (NCEP) Step 1 diet
Jamshed et al (2015)[36]; Pakistan	Parallel groups	T: 150 EG1: 50 EG2: 50 CG: 50	HDL cholesterol	NR	12 wk	12 wk	3 visits (baseline, 6 and 12 wk)	EG1: 12 EG2: 9 CG: 16	Type of nut: EG1: Pakistan almonds EG2: American almonds Dosage: 10 g/d Frequency: 1×/d Number of portions per day[b]: 0.36 Dietary pattern: habitual diet	Habitual diet
GENUTRI study; Brazil Campos et al (2019)[15] Dos Santos et al (2021)[14]	Parallel groups	T: 135 EG: 68 CG: 67	LDL cholesterol	August 2014 to January 2016	12 wk	12 wk	4 visits (baseline, 4, 8, and 12 wk)	EG: 11 CG: 23	Type of nut: pecan Dosage: 30 g/d Frequency: 1×/d Number of portions per day[b]: 1.1 Dietary pattern: healthy diet based on nutritional guidelines, calculated individually for weight reduction or maintenance	Healthy diet based on nutritional guidelines, calculated individually for weight reduction or maintenance
Coutinho-Wolino et al (2022)[35]; Brazil	Parallel groups	T: 47 EG: 26 CG: 21	Nrf2	June to November 2015	12 wk	12 wk	NR	EG: 3 CG: 7	Type of nut: Brazil nut Dosage: 5 g/d Frequency: 1×/d Number of portions per day[b]: 0.2 Dietary pattern: habitual diet	Habitual diet
Ghanavati et al (2020)[16]; Iran	Parallel groups	T: 70 EG: 35 CG: 35	C-reactive protein	NR	8 wk	8 wk	Bimonthly	EG: 0 CG: 3	Type of nut: almonds, pistachio, and peanuts Dosage: 39 g–60 g/d (20% of calculated total daily energy needs) Frequency: 1×/d Number of portions per day[b]: 1.4–2.15 Dietary pattern: low-calorie diet (75% of the ETEE including the mixed nuts)	Low-calorie diet (75% of the ETEE nut-free)

Abbreviations: CG, control group; Cph, control phase (individuals who started the trial with the control diet); Cph2, second control phase (individuals who finished the trial with the control diet); EG, experimental group; EG1, Pakistan nuts; EG2, American nuts; Eph, experimental phase (individuals who started the trial with the intervention diet); Eph2, second experimental phase (individuals who finished the trial with the intervention diet); ETEE, estimated total energy expenditure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LFU, lost to follow-up; NR, not reported; Nrf2, nuclear factor erythroid 2–related factor 2; T, total randomized; RCT, randomized clinical trial.

[a]Six-week run-in period and 4-week washout period between each intervention phase.

[b]One portion = 28 g.

to reduce, or maintain, body weight. Finally, Ghanavati et al[16] recommended an individualized low-calorie diet comprising 75% of daily energy needs. Table 3[13–16,35,36] shows the energy and macronutrient composition of the standardized diets at baseline for each study. Only the GENUTRI study[14,15] showed residual nutrient (energy-adjusted intake).

Risk of bias

The assessment of the risk of bias for the studies included in the analyses according to Cochrane is shown in Figures S1 and S2. Three studies[13–15] showed a low risk of bias. One study showed some concerns of general risk of bias due to the lack of a clear description of the randomization process.[35] One was classified as high risk due to the non-random interpretation of the allocation,[16] and another study[36] was classified as high risk because it presented some concerns in more than 1 domain (the randomization process was not clearly described and more than 1 type of analysis was possible to evaluate the outcomes).

Outcomes

Anthropometric profile. Table S4 shows the baseline and final values and the main results of the primary studies according to each outcome. Nut intake had no statistically significant effect on body mass (3 studies,[14,16,36] $n = 315$; MD: -1.53 kg [95% CI, −4.53 to 1.47], $I^2 = 44.7\%$; Figure 2A), BMI (3 studies,[14,16,35] $n = 202$; MD: −0.04 kg/m^2 [95% CI, −1.10 to 1.02], $I^2 = 0\%$; Figure 2B), or waist circumference (2 studies,[14,16] $n = 241$; MD: -1.29 cm [95% CI, -4.14 to 1.55], $I^2 = 0\%$; Figure 2C) in comparison to the control group.

Blood pressure. Compared with nut-free diets, nut intake did not show a statistically significant effect on SBP values (4 studies,[13,14,16,36] $n = 405$; MD: −1.16 mmHg [95% CI, -5.68 to 3.35], $I^2 = 0\%$; Figure 3A) or DBP (4 studies,[13,14,16,36] $n = 405$; MD: 0.10 mmHg [95% CI, -2.30 to 2.51], $I^2 = 0\%$; Figure 3B).

Glycemic profile. Two articles[14,35] ($n = 172$) provided data on fasting glucose. The descriptions of both baseline and final values are described in Table S4; considering that each study pointed to a different direction when performing an exploratory metanalysis—suggesting inconsistent results—it was decided to show only the pooled analysis (MD: 4.55 mg/dL [95% CI, -40.05 to 49.14], $I^2 = 85.6\%$) and not the forest plot. The study by Dos Santos et al[14] (sub-analysis of the GENUTRI study) evaluated the values of glycated hemoglobin,

Table 3. Dietary composition at baseline according to study groups.

First author (year)	Energy, kcal/d	CHO	Dietary fiber, g	Protein	Total fats	SFAs	MUFAs	PUFAs	Cholesterol, mg	AE
Chen et al (2015)[13,a]	1732.9 ± 859.1	232.0 ± 28.7[c] 53.4 ± 7.3[d]	19.7 ± 11.2	70.5 ± 32.3[c] 16.8 ± 3.6[d]	59.9 ± 37.3[c] 30.5 ± 6[d]	19.7 ± 13.2[c] 9.9 ± 2.8[d]	21.6 ± 13.3[c] 11.2 ± 2.5[d]	12.9 ± 8.3[c] 6.6 ± 1.7[d]	201.8 ± 148.6	NR
Jamshed et al (2015)[36,b]	EG1: 2050 ± 350 EG2: 2310 ± 390 CG: 2070 ± 370	EG1: 25 ± 6[d] EG2: 31 ± 7[d] CG: 39 ± 9[d]	EG1: 36 ± 6[d] EG2: 46 ± 9[d] CG: 24 ± 12[d]	EG1: 54 ± 11[d] EG2: 61 ± 12[d] CG: 46 ± 14[d]	EG1: 12 ± 2[d] EG2: 16 ± 3[d] CG: 38 ± 4[d]	EG1: 13 ± 2[d] EG2: 17 ± 3[d] CG: 15 ± 4[d]	EG1: 8 ± 1[d] EG2: 10 ± 2[d] CG: 14 ± 3[d]	EG1: 15 ± 2[d] EG2: 18 ± 4[d] CG: 8 ± 3[d]	EG1: 340 ± 120 EG2: 120 ± 38 CG: 250 ± 42	NR
GENUTRI study										Yes
Campos et al (2019)[15]	EG: 1721 ± 740	EG: 59.3 ± 31.2[d]	EG: 13.7 ± 7.3	EG: 22.3 ± 11.5[d]	EG: 40.7 ± 23.7[d]	EG: 10.9 ± 7.0[d]	EG: 10.6 ± 7.3[d]	EG: 4.9 ± 4[d]	EG: 203 ± 119	
Dos Santos et al (2021)[14]	CG: 1719 ± 638	CG: 56.3 ± 27.6[d]	CG: 13.1 ± 5.7	CG: 23.6 ± 10.6[d]	CG: 36.6 ± 17.3[d]	CG: 10.7 ± 5.9[d]	CG: 9.9 ± 6.6[d]	CG: 4.9 ± 3.1[d]	CG: 233 ± 134	
Coutinho-Wolino et al. (2022)[35]	EG: 1862.7 ± 663.1 CG: 1692.7 ± 626.5	NR	EG: 30. 5 ± 16.5 CG: 24.3 ± 15.7	EG: 1.28 ± 0.81[e] CG: 0.96 ± 0.2[e]	NR	NR	NR	NR	NR	NR
Ghanavati et al. (2020)[16]	EG: 1742.1 ± 936 CG: 1640.1 ± 649.2	EG: 273.5 ± 147.8[c] CG: 270.4 ± 113.3[c]	EG: 15.4 ± 7.6 CG: 16.3 ± 9.8	EG: 60.1 ± 26[c] CG: 66 ± 20.7[c]	EG: 48.8 ± 39.1[c] CG: 41.3 ± 15.8[c]	EG: 12.9 ± 5.9[c] CG: 14 ± 7.3[c]	EG: 13.6 ± 15.8[c] CG: 10.4 ± 6.2[c]	EG: 8.6 ± 9.6[c] CG: 9.6 ± 8[c]	EG: 249.2 ± 310.9 CG: 160.8 ± 168.1	NR

Abbreviations: AE, adjusted for energy intake; CG, control group; CHO, carbohydrate; EG, experimental group; EG1, Pakistan nuts; EG2, American nuts; MUFA, monounsaturated fatty acid; NR, not reported; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.
[a]Dietary intake before run-in phase for all individuals included.
[b]Data expressed as mean ±SE instead of SD.
[c]g/d.
[d]Percentage of total daily energy intake.
[e]g/kg per day.

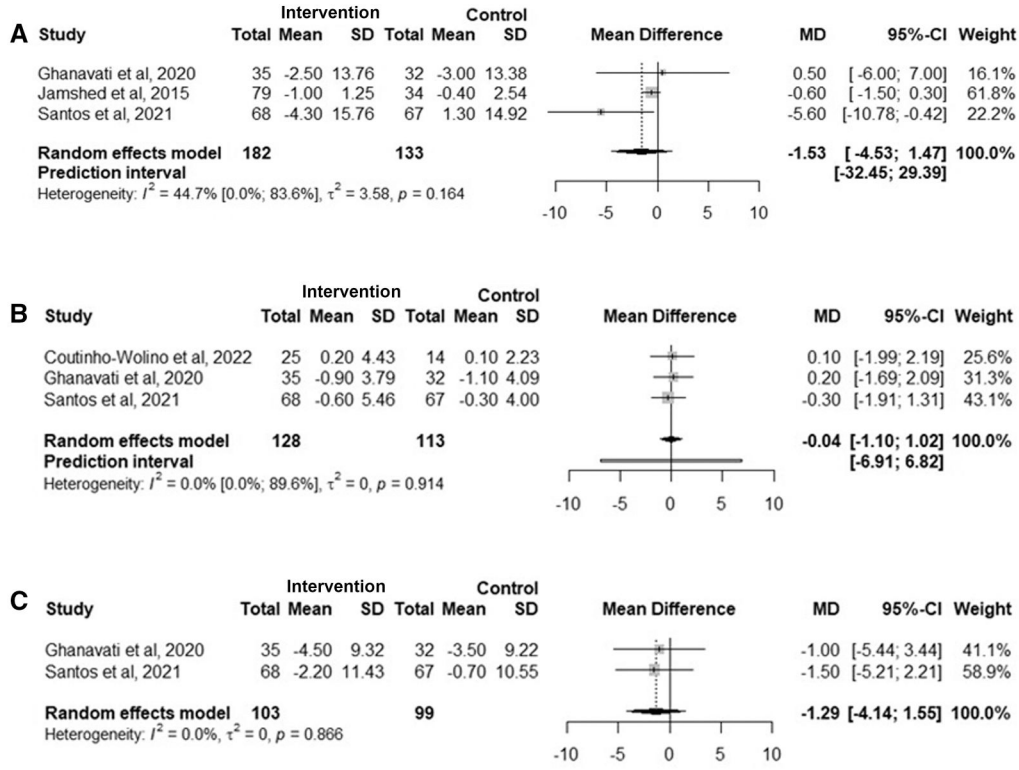

Figure 2. Meta-analysis on the Effect of Nut Supplementation in Anthropometric Indices. (A) Body mass; (B) body mass index; and (C) waist circumference. Abbreviation: MD, mean difference

insulinemia, and HOMA-IR, and showed no significant difference between the final means of these markers when comparing the group with and without pecan nut supplementation, even after adjusting for baseline data and the use of glucose-lowering agents (data not shown).

Subgroup and sensitivity analysis, publication bias, and meta-regression. Prespecified subgroup analyses according to the type of nut supplemented and the risk of bias were performed for SBP and DBP and did not indicate any deviation from the main results (Figures S3–S6). Analysis of the dosage of nuts consumed was not possible because only 1[36] of the 4 studies included in the polled analysis evaluated <30 g of nuts per day, which precludes the comparison.

After individual studies were excluded, sensitivity analyses for results with heterogeneity ≥0% showed no differences in the main results (Figures S7 and S8). Due to the small number of studies included in the meta-analyses, it was not possible to assess whether there was evidence of publication bias. Meta-regression analysis (figures available at https://data.mendeley.com/datasets/n9spjvd467/2) did not suggest an association between the dosage of nuts consumed and SBP, DBP, and BMI after adjusting for the intervention time.

Adverse events. Two studies[35,36] presented no reports of adverse events related to nut intake, and the study by Jamshed et al[36] reported 3 angioplasties during follow-up (1 in each study arm). In the GENUTRI study,[14,15] 2 participants reported adverse events related to the intervention (nausea and constipation). With regard to the occurrence of other events in this trial, 1 myocardial infarction followed by percutaneous intervention and 1 death were reported in the control group. The other studies[13,16] did not report the occurrence of adverse events.

Grade. When comparing the groups consuming nuts with the control groups, the certainty of the evidence for body weight was downgraded by the risk of bias, indirect evidence, and imprecision of the trials included in this meta-analysis, resulting in very low quality of the evidence. The certainty of the evidence for fasting glucose was rated as low due to inconsistencies and imprecision, which contributed to its low quality. With regard to the outcome of waist circumference, both the risk of bias and indirect factors had an impact on the certainty of the evidence. As for body weight, its certainty was downgraded due to concerns related to bias, indirectness, and imprecision. The SBP outcome showed a moderate quality of the evidence (the imprecision had an impact on it) and the certainty of the evidence was

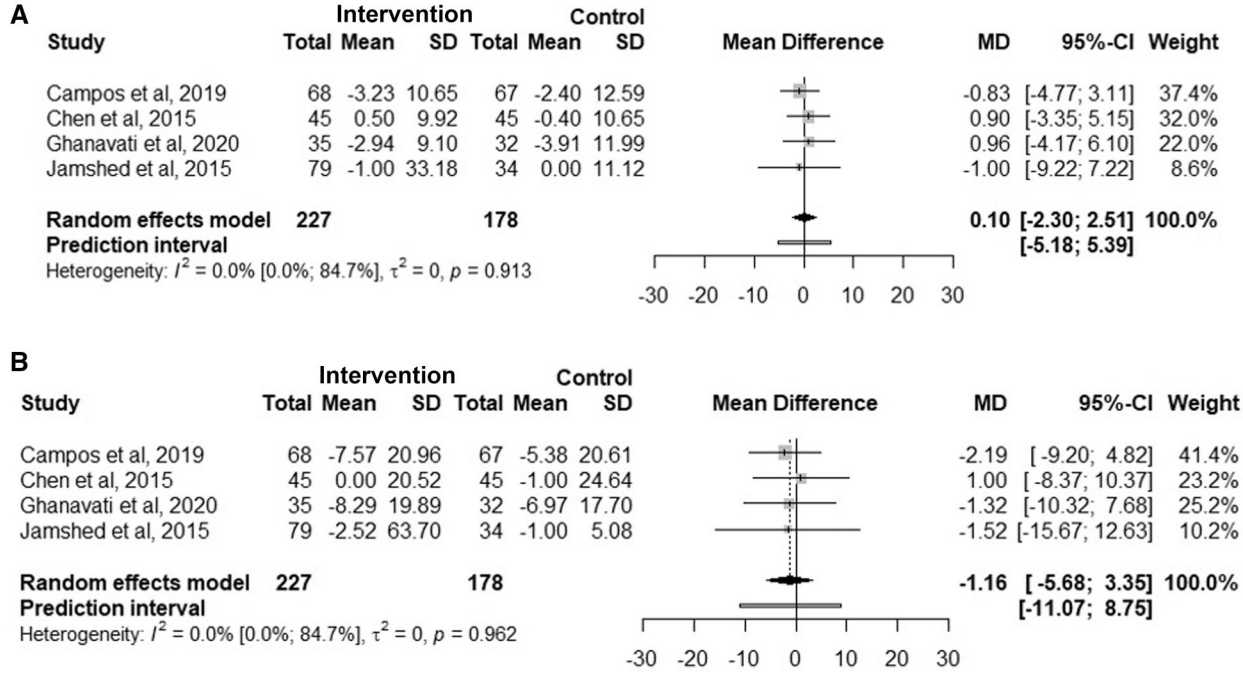

Figure 3. Meta-analysis on the Effect of Nut Supplementation in Systolic (A) and Diastolic (B) Blood Pressure. Abbreviation: MD, mean difference

high for DBP and BMI. Furthermore, publication bias cannot be ruled out. A summary of the certainty of the evidence, along with the reasons for downgrading, is presented in Table S5.

DISCUSSION

This systematic review and meta-analysis included 6 studies (including 5 randomized clinical trials) with a total of 436 participants. The findings demonstrated that nut intake did not change body mass, BMI, waist circumference, fasting glucose, or blood pressure in patients with established IHD. Furthermore, it was not possible to obtain aggregated results regarding glycated hemoglobin, serum insulin, and HOMA-IR, as well as the frequency of adverse events. The sample sizes grouped by outcomes in this study are small and therefore the results should be interpreted with caution. In addition, the quality of the evidence for most outcomes was low.

Nuts are often linked to increased body mass because they contain a high level of lipids and, consequently, energy. However, in this study, it was observed that nut intake did not modify this parameter in patients with established IHD, a result that is consistent with the literature across various populations.[18,23,37] In a previous systematic review of randomized clinical trials conducted in the general population, nut intake even resulted in a small reduction in body mass (mean difference: -0.37 kg; 95% CI, -0.72 to -0.01).[22] Nuts have a hunger-suppressing effect despite not promoting satiety.[38] Further, they are associated with energy compensation, especially when consumed as stand-alone snacks.[39] However, this energy compensation differs according to nutritional status: Overweight individuals may experience increased energy intake following a nut-containing meal, whereas this is not typically observed in normal-weight individuals.[40] In contrast, regular intake of nuts could increase the basal metabolic rate and diet-induced thermogenesis, influenced by the nutritional composition of these foods (high content of unsaturated fatty acids, proteins, and dietary fiber).[41,42] Furthermore, the polyphenol content present in different nuts positively modulates gut microbiota, stimulating the growth of beneficial bacteria that can influence weight management.[40]

The type of nut consumed, nutritional status, and the duration of nut supplementation seem to influence the waist circumference results. In a network meta-analysis conducted by Fernández-Rodriguez et al[43] only diets enriched with almonds significantly reduced waist circumference compared with the control diet (standardized mean difference: −0.15; 95% CI, −0.27 to −0.02) and with diets enriched with pistachios, mixed nuts, and hazelnuts. However, in subgroup analysis, this effect remained significant only in overweight individuals with supplementation >12 weeks.[43] In this meta-analysis, only 2 studies that assessed the effect of different nuts in different dosages and with a maximum

follow-up period of 12 weeks were included, which hindered the comparison of the results shown.

Considering the heterogeneity of the background diets in the primary studies evaluated, it is not possible to conclude whether the neutral effect of nut intake on anthropometric indicators could be attributed to a specific dietary pattern or to the incorporation of nuts into an energy-restricted diet. Also noteworthy is the fact that statins (used by >75% of participants) are associated with increased energy and lipid intake[44] (probably due to the false perception that the medication replaces the diet), as well as increased mass and redistribution of body fat through direct inhibition of 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A reductase[45] (mainly when using low- and medium-potency therapeutic regimens).

Abundant in nuts, the amino acid L-arginine serves as the substrate for the synthesis of nitric oxide in the endothelium, a potent regulator of vascular tone and blood pressure.[46] This mechanism appears to explain the positive effects of nut consumption on blood pressure values.[47] The L-arginine content of almonds (2.47 g/100 g) and peanuts (3.1 g/100 g) stand out compared with that of other nuts (pistachios, 2.03 g/100 g; pecans, 1.18 g/100 g).[48] Li et al[49] conducted a dose–response meta-analysis to assess the effect of almonds on blood pressure and identified reductions in SBP (-0.90; 95% CI, -1.74 to -0.06) but not in DBP. In this study, meta-regression results indicated that the dose of almonds used contributed to the heterogeneity of the results regarding DBP. Similarly, the primary studies included in this meta-analysis evaluated heterogeneous amounts of almonds (high doses [85 g/d] in the study by Chen et al[13] and low doses [10 g/d] according to the protocol of Jamshed et al[36]). However, it was not possible to identify a specific effect of almonds in the subgroup analysis, as well as a dose–response effect on SBP/DBP in the meta-regression. Compared with the study by Li et al,[49] the population included in this meta-analysis was more homogeneous (only secondary cardiovascular prevention and, on average, overweight). Furthermore, it is worth noting that statins negatively impact the synthesis of leptin—a potent regulator of blood pressure[50]—as well as adipose tissue, through extracellular signal–regulated kinases 1/2 and peroxisome proliferator-activated receptor-gamma.[51]

Studies in primary cardiovascular prevention have shown contradictory results regarding nuts and glycemic control. The meta-analysis conducted by Tindall et al,[52] who assessed the effect of different nuts and peanuts on markers of glycemic control in different populations (healthy individuals, with T2D, hyperlipidemia, or at cardiovascular risk), did not identify an effect of nut supplementation on fasting glucose. Similarly, almond intake did not improve blood glucose in a meta-analysis conducted in the general population.[53] Another study that evaluated pistachio intake among individuals with T2D, prediabetes, or metabolic syndrome, however, indicated an improvement in fasting glucose (OR = 1.7; 95% CI, 1.2 to 2.4; $P = .002$, $I^2 = 0.0\%$).[54] Nut intake as a carbohydrate replacement appears to improve glycemic control among individuals with dysglycemia, particularly favoring this population.[55] The small number of trials included in this study showing different directions, combined with the heterogeneity of interventions, hinders comparisons with other results. Still, the use of statins is known to increase glycemic parameters such as glycated hemoglobin and fasting blood glucose.[56]

Endothelial dysfunction is the pivotal mechanism of the atherosclerotic process and, consequently, IHD. Elements related to a dysfunctional endothelium have a direct or indirect impact on the modulation of risk factors, such as altered fasting glucose (by compromising the activity of NADPH oxidase 4, a crucial regulator of glucose homeostasis),[57] high blood pressure (mainly due to reduced nitric oxide and increased reactive oxygen species, increasing vascular tone),[58] or excess adiposity (due to impaired function of endothelial leptin receptors, deregulating energy homeostasis).[59] Therefore, considering the complex interaction between atherosclerosis mechanisms and specific drug therapy (frequently, polypharmacy), it may be difficult to observe any isolated effect of nut supplementation, especially in the short term, in the secondary prevention setting. It is noteworthy that, in primary cardiovascular prevention, individuals are not necessarily using medications (preventing the onset of some disease can be achieved by adopting a healthy lifestyle). Still, nuts (mainly heat-treated and roasted) are naturally rich in glyoxal and methylglyoxal due to their high lipid and protein content[60]; these reactive α-dicarbonyl compounds are precursors of dietary advanced glycation end products—which are related to impaired cardiometabolic markers.[61] Considering that metabolic changes and oxidative stress mechanisms are exacerbated in individuals in secondary cardiovascular prevention,[62] nut consumption might not exert the expected positive effects.

This systematic review with meta-analysis contains several strengths and limitations. The study contains the most up-to-date results of the few randomized clinical trials examining the effect of nuts on anthropometric profile, glucose profile, and blood pressure in patients at the secondary prevention level. Possible sources of heterogeneity (although low) were explored, as well as dose–response relations. The GRADE approach was used to assess the certainty of the evidence. A notable strength was that current guidelines for conducting the review and analyses were followed. The exclusivity of the population group covered in this study (patients with IHD) can be considered both a strength and a

limitation, as it is a population that lacks specific scientific evidence but limits the generalizability of the results to other populations. Due to the small number of included trials, the group and subgroup analyses were probably not sufficiently substantiated, and the results should be investigated further; in addition, an inaccurate estimation of heterogeneity might have resulted in biased effect estimates and narrow 95% CIs, due to the difficulty in estimating both between-study heterogeneity and variance when few trials are included. Furthermore, it was not possible to perform both publication bias and robust meta-regression analyses due to the small number of studies included, as well the 95% PI for all outcomes—which provides the range within which the results of a new trial might lie.[63] The intervention time of the included studies was short (between 6 and 12 weeks), and the dosages of nuts assessed, as well as the types, were quite heterogeneous. The background diets were different among the studies, which hindered standardization of the control groups. In this regard, the long-term impact of consuming standardized portions of nuts on the assessed outcomes remains uncertain, as does the best background diet to be added in scenarios outside the Mediterranean region. The robustness of the results observed with the Mediterranean diet is probably due to the synergy between foods, and not to the specific intake of any nutrient. It is important to note that, apart from the use of statins, which directly impact the outcomes assessed in this meta-analysis, the study participants were taking multiple drugs. This extensive medication regimen may have introduced confounding factors that potentially influenced the results of the primary studies. Notably, only in the GENUTRI study were all results adjusted for covariates. Another limitation is the fact that some studies included in this meta-analysis were sub-analyses of other clinical trials, and the sample size calculation was not specifically designed to assess the outcomes of interest. Most studies also showed high rates of loss to follow-up. Finally, the quality of the evidence for most outcomes was considered low/very low, which impacted the methodological quality of the primary studies. These above-mentioned points need to be considered when interpreting the results of this study.

CONCLUSION

This systematic review and meta-analysis of 5 randomized clinical trials showed that the intake of nuts did not change anthropometric and blood pressure parameters in patients with established IHD, when compared with non–nut-enriched diets. However, the sample size was small, the interventions were short-term and ranged from 5 to 85 g per day of different nuts, and the certainty of the evidence was generally low. Well-designed, long-term clinical trials investigating the effect of the consumption of different nuts in individuals with IHD are needed in the future to elucidate the role of these foods in the cardiometabolism of this specific population.

List of contributors

A.C.B.-F. and A.M. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. A.C.B.-F., L.R.d.S., R. V.M., E.S., M.F.F., E.A.S., R.H.N.S., G.B.S.D., M.M.R., E.O. d.A.-S., A.B.C., and A.M. developed the study protocol. A. C.B.-F., G.W., L.R.d.S., R.V.M., M.F.F., R.H.N.S., E.O.d.A.-S., and A.M. executed the search strategy, extracted the data, and analyzed and interpreted the data. A.C.B.-F., C. W., G.W., L.R.d.S., E.S., M.F.F., and A.M. wrote the first draft of the manuscript. R.V.M., E.A.S., R.H.N.S., G.B.S.D., M.M.R., E.O.d.A.-S., and A.B.C. participated in the analysis and interpretation of data and critically revised the manuscript for important intellectual content. A.C.B.-F. and A.M. obtained the funding and were responsible for the original concept, design, and supervision of the work. All authors read and approved the final version of the manuscript.

Supplementary material

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Conflicts of interest

The authors have no relevant interests to declare.

Data availability

The datasets generated during the current study and the supplementary material (Standardized form for data collection; Main RStudio script; Complete articles read in full and reasons for exclusion; Meta-regression analysis for systolic [A] and diastolic [B] blood pressure and

body mass index [C] results) are available at https://data.mendeley.com/datasets/n9spjvd467/2.

REFERENCES

1. World Health Organization (WHO). Global health estimates: leading causes of death. Accessed March 5, 2022. https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death.
2. Dai H, Much AA, Maor E, et al. Global, regional, and national burden of ischaemic heart disease and its attributable risk factors, 1990-2017: results from the Global Burden of Disease Study 2017. *Eur Heart J Qual Care Clin Outcomes*. 2022;8(1):50-60. https://doi.org/10.1093/ehjqcco/qcaa076
3. Lacroix S, Cantin J, Nigam A. Contemporary issues regarding nutrition in cardiovascular rehabilitation. *Ann Phys Rehabil Med*. 2017;60(1):36-42. https://doi.org/10.1016/j.rehab.2016.07.262
4. Ibanez B, James S, Agewall S, et al.; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39(2):119-177. https://doi.org/10.1093/eurheartj/ehx393
5. Virani SS, Newby LK, Arnold SV, et al.; Peer Review Committee Members. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2023;148(9):e9-e119. https://doi.org/10.1161/CIR.0000000000001168
6. Piepoli MF, Hoes AW, Agewall S, et al.; ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37(29):2315-2381. https://doi.org/10.1093/eurheartj/ehw106
7. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Circulation*. 2019;140(11):e596-e646. https://doi.org/10.1161/CIR.0000000000000678
8. Diab A, Dastmalchi LN, Gulati M, Michos ED. A heart-healthy diet for cardiovascular disease prevention: where are we now? *Vasc Health Risk Manag*. 2023;19:237-253. https://doi.org/10.2147/VHRM.S379874
9. Chen W, Zhang S, Hu X, Chen F, Li D. A review of healthy dietary choices for cardiovascular disease: from individual nutrients and foods to dietary patterns. *Nutrients*. 2023;15(23):4898. https://doi.org/ 10.3390/nu15234898.
10. Djekic D, Shi L, Brolin H, et al. Effects of a vegetarian diet on cardiometabolic risk factors, gut microbiota, and plasma metabolome in subjects with ischemic heart disease: a randomized, crossover study. *J Am Heart Assoc*. 2020;9(18):e016518. https://doi.org/ 10.1161/JAHA.120.016518.
11. Delgado-Lista J, Alcala-Diaz JF, Torres-Peña JD, et al.; CORDIOPREV Investigators. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. *Lancet*. 2022;399(10338):1876-1885. https://doi.org/10.1016/S0140-6736(22)00122-2
12. Bitok E, Sabaté J. Nuts and cardiovascular disease. *Prog Cardiovasc Dis*. 2018;61(1):33-37. https://doi.org/10.1016/j.pcad.2018.05.003
13. Chen CY, Holbrook M, Duess MA, et al. Effect of almond consumption on vascular function in patients with coronary artery disease: a randomized, controlled, crossover trial. *Nutr J*. 2015;14:61. https://doi.org/10.1186/s12937-015-0049-5
14. Dos Santos JL, Portal VL, Markoski MM, de Quadros AS, Bersch-Ferreira Â, Marcadenti A. Effect of pecan nuts and extra-virgin olive oil on glycemic profile and nontraditional anthropometric indexes in patients with coronary artery disease: a randomized clinical trial. *Eur J Clin Nutr*. 2022;76(6):827-834. https://doi.org/10.1038/s41430-021-01045-7
15. Campos VP, Portal VL, Markoski MM, et al. Effects of a healthy diet enriched or not with pecan nuts or extra-virgin olive oil on the lipid profile of patients with stable coronary artery disease: a randomised clinical trial. *J Hum Nutr Diet*. 2020;33(3):439-450. https://doi.org/10.1111/jhn.12727
16. Ghanavati M, Hosseinabadi SM, Parsa SA, Safi M, Emamat H, Nasrollahzadeh J. Effect of a nut-enriched low-calorie diet on body weight and selected markers of inflammation in overweight and obese stable coronary artery disease patients: a randomized controlled study. *Eur J Clin Nutr*. 2021;75(7):1099-1108. https://doi.org/10.1038/s41430-020-00819-9
17. Arnesen EK, Thorisdottir B, Bärebring L, et al. Nuts and seeds consumption and risk of cardiovascular disease, type 2 diabetes and their risk factors: a systematic review and meta-analysis. *Food Nutr Res*. 2023;67:8961. https://doi.org/10.29219/fnr.v67.8961
18. Moosavian SP, Rahimlou M, Rezaei Kelishadi M, Moradi S, Jalili C. Effects of almond on cardiometabolic outcomes in patients with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Phytother Res*. 2022;36(5):1839-1853. https://doi.org/10.1002/ptr.7365
19. Jalali M, Karamizadeh M, Ferns GA, Zare M, Moosavian SP, Akbarzadeh M. The effects of cashew nut intake on lipid profile and blood pressure: a systematic review and meta-analysis of randomized controlled trials. *Complement Ther Med*. 2020;50:102387. https://doi.org/10.1016/j.ctim.2020.102387
20. Lee-Bravatti MA, Wang J, Avendano EE, King L, Johnson EJ, Raman G. Almond consumption and risk factors for cardiovascular disease: a systematic review and meta-analysis of randomized controlled trials. *Adv Nutr*. 2019;10(6):1076-1088. https://doi.org/10.1093/advances/nmz043
21. Guasch-Ferré M, Li J, Hu FB, Salas-Salvadó J, Tobias DK. Effects of walnut consumption on blood lipids and other cardiovascular risk factors: an updated meta-analysis and systematic review of controlled trials. *Am J Clin Nutr*. 2018;108(1):174-187. https://doi.org/10.1093/ajcn/nqy091
22. Jayedi A, Ge L, Johnston BC, et al. Comparative effectiveness of single foods and food groups on body weight: a systematic review and network meta-analysis of 152 randomized controlled trials. *Eur J Nutr*. 2023;62(3):1153-1164. https://doi.org/10.1007/s00394-022-03046-z
23. Nishi SK, Viguiliouk E, Blanco Mejia S, et al. Are fatty nuts a weighty concern? A systematic review and meta-analysis and dose-response meta-regression of prospective cohorts and randomized controlled trials. *Obes Rev*. 2021;22(11):e13330. https://doi.org/10.1111/obr.13330
24. Higgins J, Thomas J, Chandler J, et al., eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 6.4 (updated February 2022). Cochrane; 2022. Accessed April 20, 2022. https://training.cochrane.org/handbook/current
25. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. https://doi.org/10.1136/bmj.n71
26. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898
27. IntHout J, Ioannidis JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open*. 2016;6(7):e010247. https://doi.org/10.1136/bmjopen-2015-010247
28. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity—subgroups, meta-regression, bias, and bias-adjustment. *Med Decis Making*. 2013;33(5):618-640. https://doi.org/10.1177/0272989X13485157
29. Cortes MB, da Silva RSN, de Oliveira PC, et al. Effect of aerobic and resistance exercise training on endothelial function in individuals with overweight and obesity: a systematic review with meta-analysis of randomized clinical trials. *Sci Rep*. 2023;13(1):11826. https://doi.org/10.1038/s41598-023-38603-x
30. Gualberto PIB, Benvindo VV, Waclawovsky G, Deresz LF. Acute effects of energy drink consumption on cardiovascular parameters in healthy adults: a systematic review and meta-analysis of randomized clinical trials [manuscript published online ahead of print, September 11, 2023]. *Nutr Rev*. 2023. https://doi.org/10.1093/nutrit/nuad112
31. Balk EM, Earley A, Patel K, Trikalinos TA, Dahabreh IJ. *Empirical Assessment of Within-Arm Correlation Imputation in Trials of Continuous Outcomes*. Rockville, MD: Agency for Healthcare Research and Quality; 2012.
32. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135. https://doi.org/10.1186/1471-2288-14-135
33. Schünemann H, Brozek J, Oxman A, eds. GRADE handbook for grading quality of evidence and strength of recommendation. Version 3.2 [updated March 2009]. The GRADE Working Group; 2009. Accessed April 20, 2022. http://www.cc-ims.net/gradepro
34. Guyatt GH, Oxman AD, Vist GE, et al.; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. https://doi.org/10.1136/bmj.39489.470347.AD
35. Coutinho-Wolino KS, da Cruz BO, Cardozo LFMF, et al. Brazil nut supplementation does not affect trimethylamine-n-oxide plasma levels in patients with coronary artery disease. *J Food Biochem*. 2022;46(8):e14201. https://doi.org/10.1111/jfbc.14201
36. Jamshed H, Sultan FA, Iqbal R, Gilani AH. Dietary almonds increase serum HDL cholesterol in coronary artery disease patients in a randomized controlled trial. *J Nutr*. 2015;145(10):2287-2292. https://doi.org/10.3945/jn.114.207944
37. Fernández-Rodríguez R, Martínez-Vizcaíno V, Garrido-Miguel M, Martínez-Ortega IA, Álvarez-Bueno C, Eumann Mesas A. Nut consumption, body weight, and adiposity in patients with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Nutr Rev*. 2022;80(4):645-655. https://doi.org/10.1093/nutrit/nuab053
38. Akhlaghi M, Ghobadi S, Zare M, Foshati S. Effect of nuts on energy intake, hunger, and fullness, a systematic review and meta-analysis of randomized clinical trials. *Crit Rev Food Sci Nutr*. 2020;60(1):84-93. https://doi.org/10.1080/10408398.2018.1514486
39. Nikodijevic CJ, Probst YC, Tan SY, Neale EP. The effects of tree nut and peanut consumption on energy compensation and energy expenditure: a systematic review and meta-analysis. *Adv Nutr*. 2023;14(1):77-98. https://doi.org/10.1016/j.advnut.2022.10.006

40. Lamuel-Raventos RM, Onge MS. Prebiotic nut compounds and human microbiota. *Crit Rev Food Sci Nutr*. 2017;57(14):3154-3163. https://doi.org/10.1080/10408398.2015.1096763
41. Agebratt C, Ström E, Romu T, et al. A randomized study of the effects of additional fruit and nuts consumption on hepatic fat content, cardiovascular risk factors and basal metabolic rate. *PLoS One*. 2016;11(1):e0147149. https://doi.org/10.1371/journal.pone.0147149
42. Casas-Agustench P, López-Uriarte P, Bulló M, Ros E, Gómez-Flores A, Salas-Salvadó J. Acute effects of three high-fat meals with different fat saturations on energy expenditure, substrate oxidation and satiety. *Clin Nutr*. 2009;28(1):39-45. https://doi.org/10.1016/j.clnu.2008.10.008
43. Fernández-Rodríguez R, Mesas AE, Garrido-Miguel M, Martínez-Ortega IA, Jiménez-López E, Martínez-Vizcaíno V. The relationship of tree nuts and peanuts with adiposity parameters: a systematic review and network meta-analysis. *Nutrients*. 2021;13(7):2251. https://doi.org/10.3390/nu13072251
44. Sugiyama T, Tsugawa Y, Tseng CH, Kobayashi Y, Shapiro MF. Different time trends of caloric and fat intake between statin users and nonusers among US adults: gluttony in the time of statins? *JAMA Intern Med*. 2014;174(7):1038-1045. https://doi.org/10.1001/jamainternmed.2014.1927
45. Swerdlow DI, Preiss D, Kuchenbaecker KB, et al.; InterAct Consortium. HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. *Lancet*. 2015;385(9965):351-361. https://doi.org/10.1016/S0140-6736(14)61183-1
46. Moncada S, Higgs A. The L-arginine-nitric oxide pathway. *N Engl J Med*. 1993;329(27):2002-2012. https://doi.org/10.1056/NEJM199312303292706
47. Ros E. Nuts and CVD. *Br J Nutr*. 2015;113(Suppl 2):S111-S120. https://doi.org/10.1017/S0007114514003924
48. Ros E. Nuts and novel biomarkers of cardiovascular disease. *Am J Clin Nutr*. 2009;89(5):1649S-1656S. https://doi.org/10.3945/ajcn.2009.26736R
49. Li Z, Bhagavathula AS, Batavia M, et al. The effect of almonds consumption on blood pressure: a systematic review and dose-response meta-analysis of randomized control trials. *J King Saud Univ Sci*. 2020;32(2):1757-1763. https://doi.org/10.1016/j.jksus.2020.01.013
50. Ma D, Feitosa MF, Wilk JB, et al. Leptin is associated with blood pressure and hypertension in women from the National Heart, Lung, and Blood Institute Family Heart Study. *Hypertension*. 2009;53(3):473-479. https://doi.org/10.1161/HYPERTENSIONAHA.108.118133
51. Singh P, Zhang Y, Sharma P, et al. Statins decrease leptin expression in human white adipocytes. *Physiol Rep*. 2018;6(2):e13566. https://doi.org/10.14814/phy2.13566
52. Tindall AM, Johnston EA, Kris-Etherton PM, Petersen KS. The effect of nuts on markers of glycemic control: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2019;109(2):297-314. https://doi.org/10.1093/ajcn/nqy236
53. Nowrouzi-Sohrabi P, Hassanipour S, Sisakht M, Daryabeygi-Khotbehsara R, Savardashtaki A, Fathalipour M. The effectiveness of pistachio on glycemic control and insulin sensitivity in patients with type 2 diabetes, prediabetes and metabolic syndrome: a systematic review and meta-analysis. *Diabetes Metab Syndr*. 2020;14(5):1589-1595. https://doi.org/10.1016/j.dsx.2020.07.052
54. Asbaghi O, Moodi V, Neisi A, et al. The effect of almond intake on glycemic control: a systematic review and dose-response meta-analysis of randomized controlled trials. *Phytother Res*. 2022;36(1):395-414. https://doi.org/10.1002/ptr.7328
55. Jenkins DJA, Kendall CWC, Lamarche B, et al. Nuts as a replacement for carbohydrates in the diabetic diet: a reanalysis of a randomised controlled trial. *Diabetologia*. 2018;61(8):1734-1747. https://doi.org/10.1007/s00125-018-4628-9
56. Mach F, Ray KK, Wiklund O, et al.; European Atherosclerosis Society Consensus Panel. Adverse effects of statin therapy: perception vs. the evidence—focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. *Eur Heart J*. 2018;39(27):2526-2539. https://doi.org/10.1093/eurheartj/ehy182
57. Meza CA, La Favor JD, Kim DH, Hickner RC. Endothelial dysfunction: is there a hyperglycemia-induced imbalance of NOX and NOS? *Int J Mol Sci*. 2019;20(15):3775. https://doi.org/10.3390/ijms20153775
58. Konukoglu D, Uzun H. Endothelial dysfunction and hypertension. *Adv Exp Med Biol*. 2017;956:511-540. https://doi.org/10.1007/5584_2016_90
59. Gogiraju R, Witzler C, Shahneh F, et al. Deletion of endothelial leptin receptors in mice promotes diet-induced obesity. *Sci Rep*. 2023;13(1):8276. https://doi.org/10.1038/s41598-023-35281-7
60. Catak J, Yaman M, Ugur H, Servi EY, Mizrak ÖF. Investigation of the advanced glycation end products precursors in dried fruits and nuts by HPLC using pre-column derivatization. *J Food Nutr Res*. 2022;61:1-8.
61. Khan MI, Ashfaq F, Alsayegh AA, et al. Advanced glycation end product signaling and metabolic complications: dietary approach. *World J Diabetes*. 2023;14(7):995-1012. https://doi.org/10.4239/wjd.v14.i7.995.
62. Park JY, Lee SH, Shin MJ, Hwang GS. Alteration in metabolic signature and lipid metabolism in patients with angina pectoris and myocardial infarction. *PLoS One*. 2015;10(8):e0135228. https://doi.org/10.1371/journal.pone.0135228.
63. Lin L. Use of prediction intervals in network meta-analysis. *JAMA Netw Open*. 2019;2(8):e199735. https://doi.org/10.1001/jamanetworkopen.2019.9735.

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https://doi.org/10.1093/nutrit/nuae054
Meta-Analysis