

Nut consumption and incidence of cardiovascular diseases and cardiovascular disease mortality: a meta-analysis of prospective cohort studies

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Context: Previous meta-analyses evaluating the association between nut consumption and the risk of cardiovascular disease (CVD) had substantial methodological limitations and lacked recently published large prospective studies; hence, making an updated meta-analysis highly desirable. **Objective:** To update the clinical guidelines for nutrition therapy in relation to the European Association for the Study of Diabetes (EASD), a systematic review and meta-analysis of prospective studies was conducted using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to summarize the evidence of the association between total nuts, specific types of nuts, and the incidence of, and mortality from, CVD outcomes. **Data sources:** Relevant articles were identified by searching the PubMed and Cochrane databases. **Data extraction:** Two independent researchers screened the articles to identify those that met the inclusion criteria. **Data analysis:** The inverse variance method with fixed-effect or random-effects models was used to pool data across studies (expressed as risk ratio [RR] and 95% confidence interval [CI]). Heterogeneity was tested and quantified using the Cochrane Q test and I^2 -statistic, respectively. The GRADE system was used to assess the quality of the evidence. **Results:** Nineteen studies were included in the analyses. The results revealed an inverse association between total nut consumption (comparing highest vs lowest categories) and CVD incidence (RR, 0.85; 95%CI, 0.800-0.91; I^2 , 0%), CVD mortality (RR, 0.77; 95%CI, 0.72-0.82; I^2 , 3%), coronary heart disease (CHD) incidence (RR, 0.82; 95%CI, 0.69-0.96; I^2 , 74%), CHD mortality (RR, 0.76; 95%CI, 0.67-0.86; I^2 , 46%), stroke mortality (RR, 0.83; 95%CI, 0.75-0.93; I^2 , 0%), and atrial fibrillation (RR, 0.85; 95%CI,

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0.73–0.99; I^2 , 0%). No association was observed with stroke incidence and heart failure. The certainty of the evidence ranged from moderate to very low. **Conclusions:** This systematic review and meta-analysis revealed a beneficial role of nut consumption in reducing the incidence of, and mortality from, different CVD outcomes.

INTRODUCTION

Cardiovascular disease (CVD) is an important public health issue. According to the World Health Organization (WHO), it is the leading cause of death worldwide, affecting approximately 17.7 million people in 2015.¹ Importantly, CVDs are susceptible to behavior modifications. In this sense, a healthy diet is one of the lifestyle components that could be promoted to help address this global health concern.² Different healthy dietary patterns, such as the Mediterranean diet (MedDiet),³ the DASH diet⁴ or a vegetarian diet⁵ have nuts as a key food component. Nuts, despite their high fat content (mainly unsaturated fatty acids),⁶ are also rich in minerals, vitamins, fiber, and bioactive compounds.⁷ Given this exceptional nutritional profile, frequent nut consumption has been inversely associated with a lower risk of CVD in large prospective cohort studies, which have been summarized in several meta-analyses.^{8–20} Nonetheless, some of the previous meta-analyses had methodological limitations, such as the inclusion of studies with nuts plus seeds or legumes as exposure; the inclusion of studies combining different outcomes across analyses (eg, inclusion of studies with only fatal CHD [coronary heart disease] outcome in the CVD mortality analysis); and the inclusion of studies without the first category of exposure as reference. Moreover, since publication of the last meta-analyses, the results of two new large prospective cohort studies evaluating the association between nut consumption and CVD outcomes have been published.^{21,22} One study reported updated results from the Nurses' Health Study I (NHSI), Nurses' Health Study II (NSHII), and Health Professionals Follow-up Study (HPFS) comprising up to 32 years of follow-up and a large number of cases.²¹ Another reported the association between nut consumption and the incidence of 7 CVD outcomes in a population of 32 911 males.²² Importantly, most of the previous meta-analyses have focused on total nut intake, and only a few have taken into account the potential associations between specific types of nut consumption and the risk of CVD outcomes, which may vary considerably.

Therefore, taking into consideration the aforementioned issues and in order to develop evidence-based recommendations, the Diabetes and Nutrition Study

group (DNSG) of the EASD (European Association for the Study of Diabetes) commissioned a systematic review and meta-analysis (SRMA) of prospective cohort studies using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to summarize the evidence of the association between the consumption of total nuts or specific types of nuts, and the incidence of, and mortality from, certain CVD outcomes. The shape of the associations with linear and non-linear dose-response analysis was also evaluated.

METHODS

The current systematic review and meta-analysis followed the methodological guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions*.²³ Results are reported according to Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.²⁴ The protocol is available at <http://www.crd.york.ac.uk/PROSPERO/> (identifier, PROSPERO 2018 CRD42018103360).

Search strategy

A systematic search, limited to human studies with no language restrictions, was conducted of the MEDLINE (PubMed) and Cochrane Library databases through 5 June 2018. An updated search was then performed on March 19, 2019. **Table 1** shows the PICOS (participants, interventions/exposures, comparators, outcomes and study design) criteria used to identify studies eligible for inclusion. The electronic search was supplemented with a manual review of the reference lists of the retrieved articles. **Figure 1** and **Table S1** in the Supporting Information online summarize the search and selection process.

Study selection

An initial screening of all titles and abstracts of the retrieved articles was performed to evaluate compliance with the eligibility criteria. Inclusion criteria were prospective cohort studies with at least 1 year of follow-up, conducted in an adult population; with total nuts or specific types of nuts as exposure; with the incidence of,

Table 1 PICOS criteria for inclusion and exclusion of studies

Parameter	Inclusion criteria	Exclusion criteria
Participants	General population of adults	Aged <18 years
Intervention/exposure	Nut consumption (including total nuts, or subtypes of nuts, eg, walnuts, almonds, peanuts, peanut butter, hazelnuts)	Dietary intakes do not include total nut consumption or different subtypes of nut consumption
Comparison	Extreme quantiles	Risk estimate on continuous scale
Outcome	Incidence of, or mortality from, cardiovascular disease, coronary heart disease, stroke, heart failure, atrial fibrillation	Other cardiovascular disease outcomes
Study design	Prospective cohort studies	Cross-sectional, case-control, ecological, retrospective observational studies, clinical trials, and non-human studies

or mortality from, CVD, CHD, stroke, heart failure (HF), or atrial fibrillation (AF) as the outcome; and reporting effect estimators as odds ratios (ORs), risk ratios (RRs), or hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs). When more than 1 article from the same study was revealed, both papers were included if the end points were different (ie, AF in one article and stroke in the other). When multiple publications from the same study reported the same outcome, the study with the longest follow-up was selected for inclusion. Proceedings or published abstracts were not included in the present systematic review and meta-analysis.

Two publications were identified for the Nurses' Health Study I and Health Professionals Follow-up Study, which evaluated the association between nut consumption and CVD outcomes in a whole population cohort study²¹ and in individuals with diabetes only.²⁵ Therefore, for the present meta-analysis the study conducted in the whole cohort, where participants with diabetes were also included, was selected. Similarly, for The Netherlands Cohort Study, two different articles were also identified: one published in 2015²⁶ and another one in 2019.²⁷ However, in both cases the total sample size and the period of follow-up were the same. Therefore, the 2015 publication²⁶ was included because its main aim fitted better with the objective of the present systematic review and meta-analysis.

Data extraction

Two independent reviewers (N.B.-T. and I.P.-G.) reviewed the full text of the articles that were selected in the first phase of the screening process. Using a standardized proforma, the following relevant information was extracted from those studies that met all of the inclusion criteria: authors, journal and year of publication, study design, cohort name, country or study location, total sample size, characteristics of subjects, follow-up duration, sources of findings, type of exposure and method used for its assessment, outcome and method assessment, effect estimators

(OR, RR, or HR and 95% confidence intervals), and statistical analyses. When necessary, authors were contacted by email to obtain additional information relevant to the analyses. Any disagreement was resolved by discussion or, if necessary, by a third author (J.S.-S.).

Quality of the included studies

The Newcastle-Ottawa scale (NOS) was utilized to assess the quality of the included studies.²⁸ It is a rating scale from 0 to 9, where points are allocated according to 3 different domains: population selection, outcome assessment, and comparability of the groups. A maximum of 4, 3, and 2 points were allotted to each study after evaluation of the aforementioned domains. High-quality studies were considered those studies with a total score of at least 7 points. Disagreements in grading the quality of the studies were resolved through consensus between the reviewers.

Outcomes

The primary outcomes were CVD incidence (including only nonfatal or a combination of nonfatal and fatal outcomes of a composite of different CVD outcomes) and CVD mortality, which only included a composite of different fatal CVD end points. Secondary outcomes included incidence of nonfatal or a combination of nonfatal and fatal outcomes, and mortality from fatal outcomes, ie, CHD, stroke, AF, and HF.

Studies that reported fatal CHD and nonfatal myocardial infarction separately were combined using a fixed-effects model to generate an overall estimate for CHD incidence.^{29,30} In the same way, following the same procedure, ischemic stroke and intracerebral hemorrhage outcomes,²² and fatal ischemic stroke and fatal hemorrhagic stroke³¹ end points, were combined to obtain an overall estimate for stroke incidence and stroke mortality, respectively.

Statistical analyses

The generic inverse variance method with a random-effects model (≥ 5 comparisons) or fixed-effects model (< 5 comparisons) was used to pool the natural log-transformed RRs for CVD incidence and mortality outcomes, to compare highest vs lowest categories of nut consumption. For one study³² that reported results using the second category of nut consumption, rather than the lowest one, as the reference, the RR and its corresponding 95%CI were recalculated following the Hamling et al³³ method, using the first category as the reference.

Heterogeneity among studies was estimated using Cochran's *Q* test and quantified by the *I*² statistic. Statistical significance was set at $P < 0.10$, and an *I*² value $\geq 50\%$ was considered to reflect substantial heterogeneity.

Meta-regression analysis was performed in order to assess whether a priori specified study characteristics (ie, sex, follow-up, geographical area, NOS scale and its individual domains) may have affected the overall effect estimates. This subgroup analysis was only conducted if at least 10 study comparisons were available.²³

Sensitivity analysis, excluding 1 study at a time and recalculating the summary estimates, was performed to ascertain the influence of individual studies on the summary estimates. If the removal of a study yielded a change in the level of significance, magnitude (by $> 10\%$), or direction of the pooled risk estimates, or changed the evidence of heterogeneity, then it was considered as influential.

Linear dose-response analysis for total nut consumption and different CVD outcomes was conducted following the 2-stage generalized least-squares trend (GLST) estimation method developed by Greenland and Longnecker³⁴ and Orsini et al.³⁵ In the first stage, the method fits the dose-response model within each study, and in the second stage it combines study-specific trends. Data on RRs and the corresponding 95%CIs, total number of participants, cases, and doses for at least 3 categories of nut consumption were needed to carry out this method. The mean or median of nut consumption from each exposure category was used if it was directly reported. For those studies that did not report this information, the midpoint between the upper and lower boundaries was assigned when ranges of nut consumption were available. For studies that reported open-ended extreme categories, a width equal to the adjacent category was assumed in order to estimate the upper or lower cutoff value. Some studies reported the information on nut consumption in grams, and others in servings. Therefore, servings were

converted to grams, where 1 serving equated to 28 g, unless authors specified other serving sizes.

Potential nonlinear association between nut consumption and CVD outcomes was assessed using restricted cubic splines (MKSPLINE procedure), which were combined using multivariate meta-analysis. The departure from linearity was assessed by the Wald test constraining the regression coefficient for the second spline equal to zero.³⁶

Publication bias was tested by the visual inspection of the funnel plots for asymmetry and statistically Begg's test and Egger's test. When few studies are included in the analysis, the power of the tests is too low; therefore, publication bias was only examined if more than 10 study comparisons were included in the analysis.²³ Statistical significance was set at $P < 0.05$.

Data analysis was performed using Review Manager (RevMan) software version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014 and STATA version 15 software (StataCorp LP, College Station, Texas).

Grading the evidence

The GRADE system was used to rate the overall quality and the strength of the evidence. The quality of evidence for each outcome was categorized as high, moderate, low, or very low. This system regards observational studies as low-quality evidence.³⁷ The level of evidence can be upgraded or downgraded according to different specified criteria. Determinants to downgrade included study design and execution limitations,³⁸ inconsistency,³⁹ indirectness,⁴⁰ imprecision,⁴¹ and publication bias.⁴² Determinants to upgrade included large magnitude effect, dose-response gradient, and attenuation by plausible confounding effects.⁴³ Discrepancies in ratings of the evidence quality were resolved by consensus between N.B.-T. and I.P.-G.

RESULTS

Study selection process

The present systematic review and meta-analysis included 19 prospective studies from the 2992 identified articles (Figure 1). Three study comparisons (1 report) were included in the meta-analysis for total CVD,²¹ 14 study comparisons (9 reports) for CVD mortality,^{21,26,31,44-49} 7 study comparisons (5 reports) for CHD,^{21,22,29,30,50} 12 study comparisons (8 reports) for CHD mortality,^{21,22,26,30,31,44,48,51} 7 study comparisons (5 reports) for stroke,^{21,22,32,52,53} 11 study comparisons (7 reports) for stroke mortality,^{21,26,31,32,47,48,51} 5 study comparisons (4 reports) for hemorrhagic stroke,^{22,52-54}

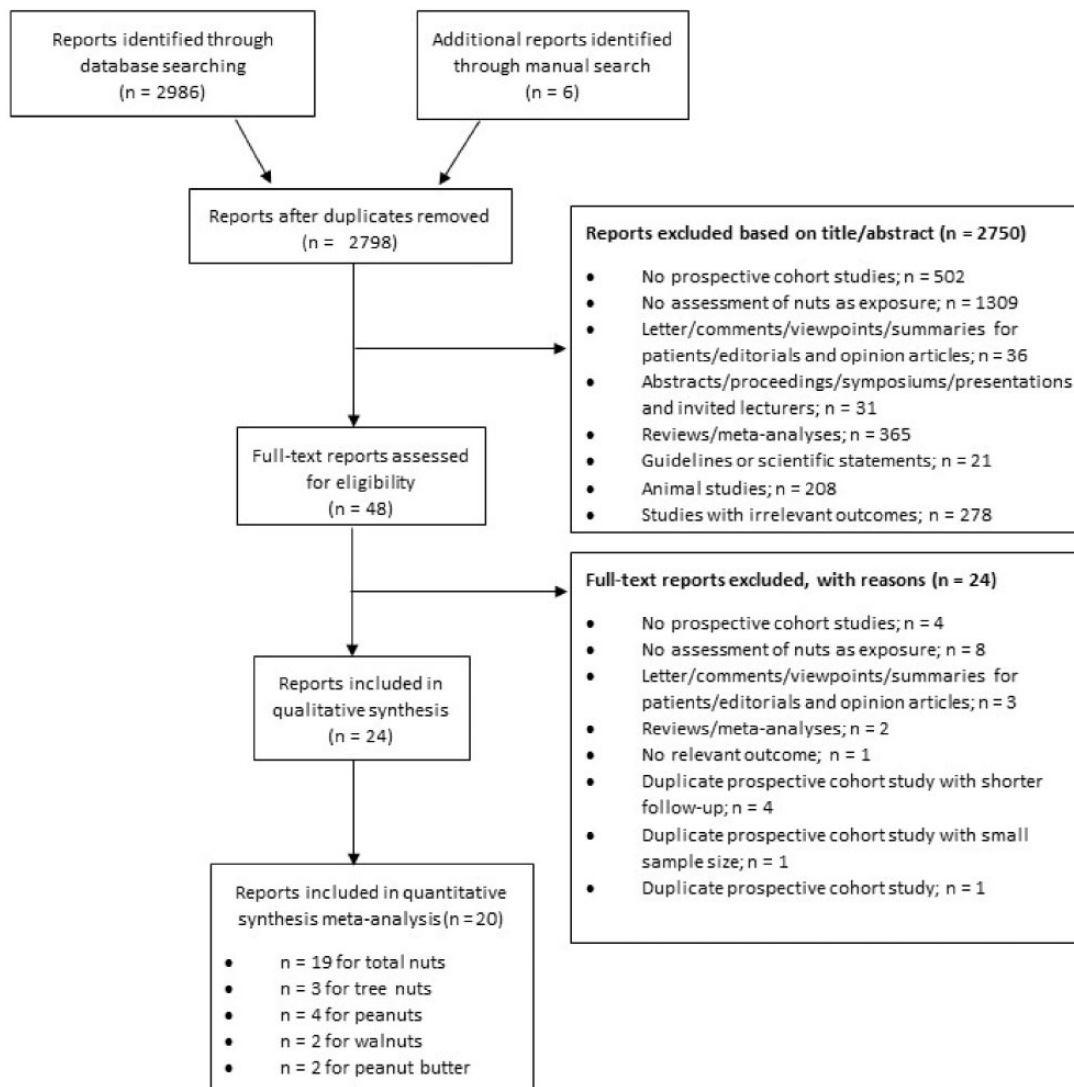


Figure 1 Flow diagram of the literature search and selection process

7 study comparisons (5 reports) for ischemic stroke,^{21,22,32,52,53} 2 study comparisons for AF,^{22,55} and 2 study comparisons for HF.^{22,56}

Four studies^{57–60} that reported the risk estimate on continuous scale instead of categories of nut consumption were identified and therefore were not included in the high vs low categories of consumption analyses and the dose-response analyses.

Study characteristics

The characteristics of the included studies are presented in Table 2^{21,22,26,29–32,44,46–60}. Publication date ranged from 1992 to 2018. Six of the studies originated from Europe, 13 from America, 1 from Asia, 1 from Australia, 1 from both China and the USA, and 1 from both China and Germany. The duration of follow-up ranged from 4.3 to 28.7 years. All the studies assessed

nut intake via a food frequency questionnaire. The vast majority of studies (70.9%) were of high quality according to the NOS scale. Tables S1–S5 in the Supporting Information online describe the characteristics of the included studies by type of nut consumption.

High vs low categories of consumption analyses

Nuts and cardiovascular disease incidence. Three cohort comparisons, involving 210 836 participants and 14 136 cases, analyzed the association between nut consumption and the risk of CVD incidence. The summary RR (95%CI) for high vs low categories of nut consumption was 0.85 (0.80–0.91) with no evidence of interstudy heterogeneity ($I^2 = 0\%$; $P_{\text{heterogeneity}} = 0.81$) (Figure 2 and Figure S1 in the Supporting Information online). Regarding specific types of nuts, consumption of tree nuts ([RR, 0.85; 95%CI, 0.79–0.91]; $I^2 = 0\%$;

Table 2 Characteristics of the included studies evaluating the association between nuts and risk of cardiovascular disease outcomes

Study	Country	Study name	Population	Nut consumption assessment method	Type of nuts	Nut intake	Age, y	Follow-up (mean, median, or range), y	Outcome	Incident cases	Funding source	NOS score
Fraser et al (1992) ²⁹	USA	Seventh-day Adventists	26 473 M/F	Self-administered semi-quantitative FFQ	Not specified	≥51 servings/wk vs <1 serving/wk	≥25	6	Nonfatal MI CHD mortality	134 463	Agency	7
Albert et al (2002) ³⁰	USA	Physicians' Health Study	21 454 M	Self-administered semi-quantitative FFQ	Not specified	≥2 servings/wk vs <1 serving/mo	40–84	17	CHD mortality Nonfatal MI	566 1037	Agency	7
Blomhoff et al (2006) ⁴⁴	USA	Iowa Women's Health Study	31 778 F	Self-administered FFQ	Nuts plus peanut butter	7 servings/wk vs 0.5 servings/wk	55–69	15	CVD mortality CHD mortality	1675 948	Agency	6
Djoussé et al (2008) ⁵⁶	USA	Physicians' Health Study	20 976 M	Unvalidated, self-administered FFQ	Not specified	≥2 servings/wk vs <1 serving/wk	40–84	19.6	Heart failure	1093	NR	6
Nettleton et al (2008) ⁵⁷	USA	Atherosclerosis Risk in Communities Study	14 153 M/F	Interview-administered FFQ	Nuts plus peanut butter	Continuous: 1 serving/d	45–64	13	Heart failure	1140	Agency	8
Djoussé et al (2010) ⁵²	USA	Physicians' Health Study	21 078 M	Unvalidated, self-administered FFQ	Not specified	7 servings/wk vs <1 serving/wk	40–84	21.1	Stroke Ischemic stroke Hemorrhagic stroke	1424 1189 219	Agency	6
Bernstein et al (2012) ⁵⁴	USA	Nurses' Health Study I Health Professionals Follow-Up Study	80 010 F 43 150 M	Validated, self-administered FFQ	Not specified	0.34 servings/d vs 0.60 servings/d vs 0 servings/d	30–55 40–75	26 22	Hemorrhagic stroke Hemorrhagic stroke	1383 829	Agency	6
Khawaja et al (2012) ⁵⁵	USA	Physicians' Health Study	21 054 M	Unvalidated, self-administered FFQ	Not specified	≥6 servings/wk vs 0 servings/wk	40–84	24	Atrial fibrillation	3317	Agency	7
Yaemhiri et al (2012) ⁵⁸	USA	Women's Health Initiative Observational Study	87 025 F	Self-administered FFQ	Not specified	Continuous: 1 serving/d	50–79	7.6	Ischemic stroke	1049	Agency	8
von Ruesten et al (2013) ⁵⁹	Germany	EPIC-Potsdam study	23 531 M/F	Self-administered semi-quantitative FFQ	Peanuts, walnuts, brazil nuts	Continuous: 1 serving/d	35–65	8	CVD	363	Agency	8

(continued)

Table 2 Continued

Study	Country	Study name	Population	Nut consumption assessment method	Type of nuts	Nut intake	Age, y	Follow-up (mean, median, or range), y	Outcome	Incident cases	Funding source	NOS score
Guasch-Ferré et al (2013) ⁴⁶	Spain	PREDIMED study	7216 M/F	Interview-administered, validated, semi-quantitative FFQ	Almonds, peanuts, hazelnuts, pistachios, pine nuts	>3 servings/wk vs never	55–80	4.8	CVD mortality	81	Agency-Industry	9
Bonaccio et al (2015) ⁴⁸	Italy	Moli-sani study	10 509 F 8877 M	Validated, self-administered FFQ	Walnuts, hazelnuts, almonds, peanuts	Intake vs no intake	>35	4.3	CVD mortality CHD mortality Stroke	104 39 19	Agency	6
di Giuseppe et al (2015) ³²	Germany	EPIC-Potsdam study	25 997 M/F	Validated, self-administered FFQ	Peanuts, walnuts, brazil nuts	14.2 g/d vs 0 g/d	F: 49.2M: 52.5	8.3	Stroke Ischemic stroke Stroke	288 235 36	Agency	8
Gopinath et al (2015) ⁵¹	Australia	Blue Mountains Eye Study	1312 F 1581 M	Validated, self-administered FFQ	Not specified	4.90 to 100 g/d vs 0 to 0.50 g/d	≥49	15	CVD mortality IHD mortality Stroke	258 188 101	Agency	7
Haring et al (2014) ⁵⁰	USA	Atherosclerosis Risk in Communities Study	12 066 M/F	Interview-administered FFQ	Not specified	0.6 servings/d vs 0.1 servings/d	45–64	22	mortality CVD mortality IHD mortality Stroke	1147	Agency	9
Haring et al (2015) ⁵³	USA	Atherosclerosis Risk in Communities Study	11 601 M/F	Interview-administered FFQ	Nuts plus peanut butter	1 servings/d vs 0 servings/d	45–64	22.7	Stroke Hemorrhagic stroke	699 114	Agency	8
Hsieh et al (2015) ⁴⁷	USA	Physicians' Health Study	20 742 M	Unvalidated, self-administered FFQ	Not specified	≥5 servings/wk vs <1 serving/wk	40–84	9.6	Ischemic stroke CVD mortality Stroke	598 760 143	Agency	6
Luu et al (2015) ³¹	USA	Southern Community Cohort Study	71 764 M/F	Semi-quantitative FFQ	Total nuts and peanut butter	≥18.45 g/d vs <0.95 g/d	40–79	5.4	mortality CVD mortality IHD mortality Ischemic stroke mortality Hemorrhagic stroke	1857 793 121 96	Agency	8

(continued)

Table 2 Continued

Study	Country	Study name	Population	Nut consumption assessment method	Type of nuts	Nut intake	Age, y	Follow-up (mean, median, or range), y	Outcome	Incident cases	Funding source	NOS score
	China	Shanghai Women's Health Study and Shanghai Men's Health Study	134 265 M/F		Peanut	≥2.54 g/d vs <0.14 gram/day	40–70 and 40–74	12.2 and 6.5	CVD mortality IHD mortality Ischemic stroke mortality Hemorrhagic stroke mortality	2587 631 588 597		
van den Brandt and Schouten (2015) ²⁶	Netherlands	Netherlands Cohort Study	3202 M/F (subcohort)	Self-administered validated FFQ	Tree nuts, peanuts	19.6 g/d vs 0 g/d	55–69	9	CVD mortality IHD mortality Stroke mortality	2985 1488 565	NR	7
Wang et al (2016) ⁶⁰	China	Linxian NIT cohort	2445 M/F	FFQ	Peanuts, chest-nuts, walnuts	Continuous: 3 servings/mo	40–69	26	Heart disease mortality Stroke mortality	355 452	Agency	6
Germany												
Eslamparast et al (2017) ⁴⁹	Iran	Golestan Cohort Study	28 257 F 20 855 M	Validated, self-administered, semi-quantitative FFQ	Peanuts, tree nuts	≥3 servings/wk vs never	40–87	7	CVD mortality	911 1105	Agency	7
Guasch-Ferré et al (2017) ²¹	USA	Nurses' Health Study I	76 364 F	Validated, self-administered FFQ	Peanuts, other nuts, and walnuts (if available)	≥5 servings/wk vs never or almost never	30–55	28.7	CVD mortality CVD mortality CHD mortality CHD mortality Stroke mortality Stroke mortality	6727 1770 3552 996 3322 773	Agency	7
		Nurses' Health Study II	92 946 F				25–42	21.5	Ischemic stroke mortality CVD mortality CVD mortality CHD mortality CHD mortality Stroke mortality Stroke mortality	1635 1915 82 670 46 1262 36		
		Health Professionals Follow-Up Study	41 526 M				40–75	22.5	Ischemic stroke mortality CVD mortality CVD mortality CHD mortality CHD mortality Stroke mortality Stroke mortality	220 5494 2599 4168 1921 1326 367		
									Ischemic stroke mortality	742		

(continued)

Table 2 Continued

Study	Country	Study name	Population	Nut consumption assessment method	Type of nuts	Nut intake	Age, y	Follow-up (mean, median, or range), y	Outcome	Incident cases	Funding source	NOS score
Larsson et al (2018) ²²	Sweden	Cohort of Swedish Men	32 911 M	FFQ	Nuts (not including coconut or chestnuts)	≥3 servings/wk vs never	45–83	17	MI MI mortality Heart failure Atrial fibrillation Ischemic stroke Intracerebral hemorrhage	4983 917 3160 7550 3782 543	Agency	8

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; EPIC, European Prospective Investigation into Cancer and Nutrition; F, females; FFQ, food frequency questionnaire; IHD, ischemic heart disease; M, males; MI, myocardial infarction; NIT, Nutrition Intervention Trials; NOS, Newcastle-Ottawa scale; NR, Not reported; PREDIMED, Prevención con Dieta Mediterránea.

$P_{\text{heterogeneity}}$, 0.70), peanuts ([RR, 0.87; 95%CI, 0.81–0.93]; I^2 , 0%; $P_{\text{heterogeneity}}$, 0.67), and walnuts ([RR, 0.81; 95%CI, 0.71–0.92]; I^2 , 73%; $P_{\text{heterogeneity}}$, 0.03) was associated with a lower risk of CVD incidence after comparing highest vs lowest categories of consumption (Table 3 and Figures S2–S4 in the Supporting Information online). No association was reported between peanut butter consumption and the risk of CVD incidence ([RR, 0.98; 95%CI, 0.93–1.03]; I^2 , 89%; $P_{\text{heterogeneity}}$, <0.01) (Table 3 and Figure S5 in the Supporting Information online).

Nuts and cardiovascular disease mortality. Fifteen cohort comparisons analyzed the association between nut consumption and CVD mortality, including 413 727 participants and 14 475 cases. The summary RR (95%CI) for high vs low categories of nut consumption was 0.77 (0.72–0.82) with no evidence of interstudy heterogeneity (I^2 , 3%; $P_{\text{heterogeneity}}$, 0.42) (Figure 2 and Figure S6 in the Supporting Information online). Regarding specific types of nuts, only peanuts have been studied in relation to CVD mortality, showing a summary RR of 0.77 (95%CI, 0.70–0.85) for high vs low categories of consumption, with no evidence of interstudy heterogeneity (I^2 , 0%; $P_{\text{heterogeneity}}$, 0.81) (Table 3 and Figure S7 in the Supporting Information online).

Nuts and coronary heart disease incidence. Seven cohort comparisons analyzed the association between nut consumption and CHD incidence, including 275 812 participants and 12 654 cases. The summary RR (95%CI) for high vs low categories of nut consumption was 0.82 (0.69–0.96) with evidence of substantial interstudy heterogeneity (I^2 , 74%; $P_{\text{heterogeneity}}$ <0.01) (Figure 2 and Figure S8 in the Supporting Information online). Regarding specific types of nuts, consumption of tree nuts ([RR, 0.77; 95%CI, 0.70–0.84]; I^2 , 61%; $P_{\text{heterogeneity}}$, 0.08), peanuts ([RR, 0.85; 95%CI, 0.79–0.92]; I^2 , 0%; $P_{\text{heterogeneity}}$, 0.55), and walnuts ([RR, 0.791; 95%CI, 0.66–0.94]; I^2 , 69%; $P_{\text{heterogeneity}}$, 0.04) was associated with a lower risk of CHD incidence after comparing highest vs lowest categories of consumption (Table 3 and Figures S9–S11 in the Supporting Information online). No association was reported between peanut butter consumption and the risk of CHD incidence ([RR, 1.00; 95%CI, 0.94–1.07]; I^2 , 43%; $P_{\text{heterogeneity}}$, 0.17) (Table 3 and Figure S12 in the Supporting Information online).

Nuts and coronary heart disease mortality. Thirteen cohort comparisons analyzed the association between nut consumption and CHD mortality, including 396 041 participants and 7877 cases. The summary RR (95%CI)

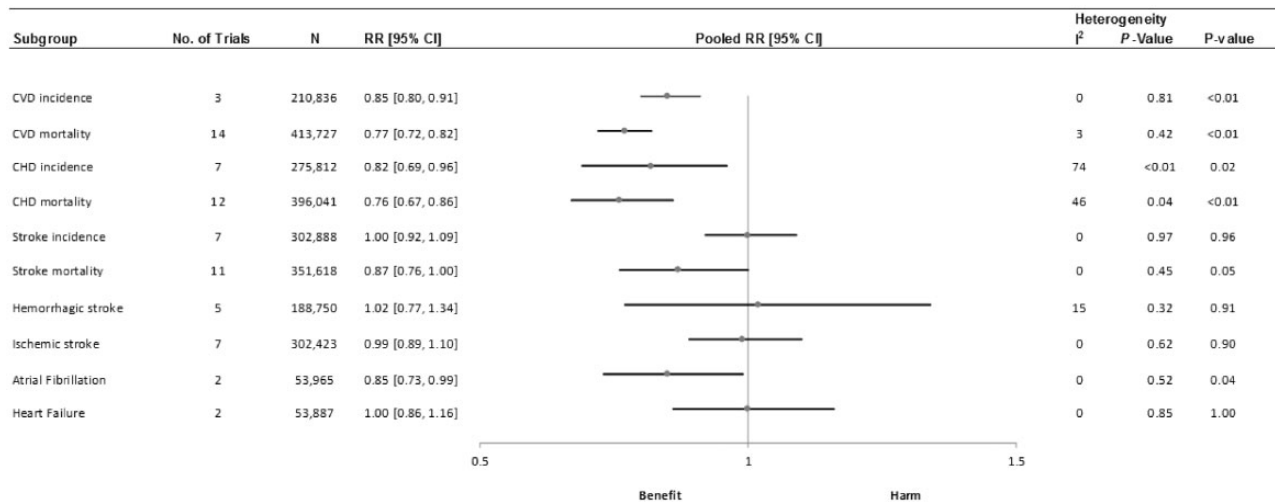


Figure 2 Summary plots of effect estimates from prospective cohort studies evaluating the association between nut consumption and the risk of different cardiovascular outcomes. Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; RR, risk ratio

Table 3 Summary RR of cardiovascular disease outcomes by different types of nut consumption (comparing highest vs lowest categories)

	No. of cohorts	No. of participants	No. of cases	RR (95%CI)	P for heterogeneity	I^2 (%)
Tree nuts						
CVD	3	210 836	14 136	0.85 (0.79, 0.91)	0.70	0
CVD mortality	–	–	–	–	–	–
Stroke	3	210 836	5910	1.00 (0.89, 1.11)	0.93	0
Stroke mortality	3	118 962	1851	0.93 (0.77, 1.13)	0.44	0
CHD	3	210 836	8390	0.77 (0.70, 0.84)	0.08	61
CHD mortality	–	–	–	–	–	–
Peanuts						
CVD	3	210 836	14 136	0.87 (0.81, 0.93)	0.67	0
CVD mortality	2	134 265	5572	0.77 (0.70, 0.85)	0.81	0
Stroke	3	210 836	5910	0.90 (0.81, 0.99)	0.32	13
Stroke mortality	4	253 227	3036	0.83 (0.73, 0.95)	0.07	57
CHD	3	210 836	8390	0.85 (0.79, 0.92)	0.55	0
CHD mortality	2	134 265	2119	0.75 (0.64, 0.88)	0.46	0
Walnuts						
CVD	3	144 021	5255	0.81 (0.71, 0.92)	0.03	73
CVD mortality	–	–	–	–	–	–
Stroke	3	144 021	5910	0.85 (0.71, 1.02)	0.19	39
Stroke mortality	–	–	–	–	–	–
CHD	3	144 021	2685	0.79 (0.66, 0.94)	0.04	69
CHD mortality	–	–	–	–	–	–
Peanut butter						
CVD	3	210 836	14 136	0.98 (0.93, 1.03)	<0.01	89
CVD mortality	–	–	–	–	–	–
Stroke	3	210 836	5910	0.94 (0.87, 1.02)	<0.01	86
Stroke mortality	–	–	–	–	–	–
CHD	3	210 836	8390	1.00 (0.94, 1.07)	0.17	43
CHD mortality	–	–	–	–	–	–

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; RR, risk ratio.

for high vs low categories of nut consumption was 0.76 (0.67–0.86) with evidence of moderate interstudy heterogeneity (I^2 , 46%; $P_{\text{heterogeneity}}$, 0.04) (Figure 2 and Figure S13 in the Supporting Information online). Regarding specific types of nuts, peanut consumption

was inversely associated with the risk of CHD mortality after comparing high vs low categories of consumption ([RR, 0.75; 95%CI, 0.64–0.88]; I^2 , 0%; $P_{\text{heterogeneity}}$, 0.46) (Table 3 and Figure S14 in the Supporting Information online).

Nuts and stroke incidence. Seven cohort comparisons analyzed the association between nut consumption and stroke incidence, including 302 888 participants and 12 646 cases. The summary RR (95%CI) for high vs low categories of nut consumption was 1.00 (0.92–1.09) with no evidence of interstudy heterogeneity (I^2 , 0%; $P_{\text{heterogeneity}}$, 0.97) (Figure 2 and Figure S15 in the Supporting Information online). Regarding specific types of nuts, peanut consumption was associated with a lower risk of stroke incidence after comparing highest vs lowest categories of consumption ([RR, 0.90; 95%CI, 0.81–0.99]; I^2 , 13%; $P_{\text{heterogeneity}}$, 0.32) (Table 3 and Figure S16 in the Supporting Information online). No association was observed between tree nut, walnut, and peanut butter consumption and the risk of stroke incidence (Table 3 and Figures S17–S19 in the Supporting Information online).

Nuts and stroke mortality. Twelve cohort comparisons analyzed the association between nut consumption and stroke mortality, including 351 618 participants and 2332 cases. The summary RR (95%CI) for high vs low categories of nut consumption was 0.83 (0.75–0.93) with no evidence of interstudy heterogeneity (I^2 , 0%; $P_{\text{heterogeneity}}$, 0.45) (Figure 2 and Figure S20 in the Supporting Information online). Regarding specific types of nuts, peanut consumption was associated with a lower risk of stroke mortality after comparing highest vs lowest categories of consumption ([RR, 0.85; 95%CI, 0.79–0.92]; I^2 , 0%; $P_{\text{heterogeneity}}$, 0.55) (Table 3 and Figure S21 in the Supporting Information online). No association was reported between tree nut consumption and the risk of stroke death (Table 3 and Figure S22 in the Supporting Information online).

Nuts and hemorrhagic stroke. Five cohort comparisons analyzed the association between nut consumption and hemorrhagic stroke incidence, involving 188 750 participants and 3088 cases. The summary RR (95%CI) for high vs low categories of nut consumption was 1.02 (0.77–1.34) with no evidence of interstudy heterogeneity (I^2 , 15%; $P_{\text{heterogeneity}}$, 0.32) (Figure 2 and Figure S23 in the Supporting Information online). No study analyzed the association between different types of nuts and the risk of hemorrhagic stroke.

Nuts and ischemic stroke. Seven cohort comparisons analyzed the association between nut consumption and ischemic stroke incidence, involving 302 423 participants and 8401 cases. The summary RR (95%CI) for high vs low categories of nut consumption was 0.99 (0.89–1.10) with no evidence of interstudy heterogeneity (I^2 , 0%; $P_{\text{heterogeneity}}$, 0.62) (Figure 2 and Figure S24 in

the Supporting Information online). No study analyzed the association between different types of nuts and the risk of hemorrhagic stroke.

Nuts and atrial fibrillation. Two cohort comparisons analyzed the association between nut consumption and AF, involving 53 965 participants and 10 867 cases. The summary RR (95%CI) for high vs low categories of nut consumption was 0.85 (0.73–0.99) with no evidence of interstudy heterogeneity (I^2 , 0%; $P_{\text{heterogeneity}}$, 0.52) (Figure 2 and Figure S25 in the Supporting Information online). No study analyzed the association between different types of nuts and the risk of AF.

Nuts and heart failure. Two cohort comparisons analyzed the association between nut consumption and HF, involving 53 887 participants and 4253 cases. The summary RR (95%CI) for high vs low categories of nut consumption was 1.00 (0.86–1.16) with no evidence of interstudy heterogeneity (I^2 , 0%; $P_{\text{heterogeneity}}$, 0.85) (Figure 2 and Figure S26 in the Supporting Information online). No study analyzed the association between different types of nuts and the risk of HF.

Dose-response analyses

Figures S27–S34 in the Supporting Information online show the linear and non-linear dose-response analyses between total nut consumption and CVD outcomes. The summary RR (95%CI) for a 28-g/d increment was 0.87 (0.81–0.93) for CVD incidence, 0.71 (0.61–0.84) for CVD mortality, 0.75 (0.64–0.88) for CHD incidence, 0.67 (0.52–0.87) for CHD mortality, 1.06 (0.97–1.15) for stroke incidence, 1.01 (0.88–1.18) for stroke mortality, 1.05 (0.77–1.43) for hemorrhagic stroke, and 1.06 (0.86–1.31) for ischemic stroke.

Total nut consumption and the risk of CVD incidence (Figure S27 in the Supporting Information online), CVD mortality (Figure S28 in the Supporting Information online), stroke mortality (Figure S32 in the Supporting Information online), and hemorrhagic stroke (Figure S33 in the Supporting Information online) showed a non-linear association ($P_{\text{non-linearity}} < 0.01$). The reduction in the risk of CVD incidence was observed up to a consumption of 10 g/d, with no further reduction with higher consumptions (Table S6 in the Supporting Information online). For CVD mortality and CHD mortality, there was a steeper reduction in the risk at approximately 15–20 g/d, with no further reduction with a higher consumption (Table S6 in the Supporting Information online). The reduction in the risk of stroke mortality was observed up to a consumption of 5 g/d, with no significant reductions above this amount (Table S6 in the Supporting Information

online). The association between total nuts and hemorrhagic stroke appeared to be J-shaped with a risk reduction up to 5 g/d, but there was a slight non-significant positive association at intakes of 25 g/d (Table S6).

There was no evidence of non-linear association for the other outcomes.

Sensitivity analyses

Table S7 in the Supporting Information online shows the sensitivity analysis by the removal of one study at a time. Regarding total nut consumption, no trial modified the magnitude, direction, or significance of the pooled estimates or the evidence for heterogeneity for total CVD incidence and mortality, stroke incidence and mortality, HF, or AF. Removal of the Guasch-Ferré et al study (NHSI)²¹ changed the pooled estimates of total CHD incidence from significant to nonsignificant. Removal of the Larsson et al²² study explained the heterogeneity for CHD death (I^2 , 16%; $P_{\text{heterogeneity}}$, 0.28). With regard to different types of nuts, removal of the Guasch-Ferré et al study (HPFS) and Guasch-Ferré study (NHSII)²¹ modified the significance of the pooled RR for peanut consumption and total stroke from significant to nonsignificant, and removal of the Bao et al⁴⁵ study explained the heterogeneity (I^2 , 0%; $P_{\text{heterogeneity}}$, 0.77). In the case of peanut butter, removal of the Guasch-Ferré et al study (NHSII)²¹ explained the heterogeneity for total CVD (I^2 , 0%; $P_{\text{heterogeneity}}$, 0.60) and for total stroke (I^2 , 0%; $P_{\text{heterogeneity}}$, 0.53). Furthermore, removal of the Guasch-Ferré et al study (NHSI)²¹ changed the significance of the pooled estimates for total stroke from nonsignificant to significant. Regarding walnuts, removal of the Guasch-Ferré et al study (HPFS)²¹ changed the magnitude of the RR for total CVD and CHD and the pooled estimates became significant for total stroke. Removal of the Guasch-Ferré et al study (NHSI)²¹ changed the significance of the pooled estimates for total CVD and CHD from significant to nonsignificant. Finally, removal of the Guasch-Ferré et al study (NHSII)²¹ explained the heterogeneity (I^2 , 0%; $P_{\text{heterogeneity}}$, 0.53) for CHD and changed the significance of the pooled estimates from significant to nonsignificant.

Subgroup analyses

Subgroup analyses could only be conducted for CVD, CHD, and stroke death. Figures S35–S40 in the Supporting Information online show the a priori subgroup analyses for the aforementioned outcomes. The meta-regression analysis revealed no evidence of effect modification by sex, duration of follow-up, or NOS

quality score and its individual domains. However, the risk of CVD death was modified by geographical area ($P=0.03$). In studies conducted in America, nut consumption was inversely associated with the risk of CVD mortality (RR, 0.68; 95%CI, 0.61–0.77), whereas no association was observed in those studies conducted in Europe (RR, 0.91; 95%CI, 0.72–1.14) or Oceania (RR, 0.95; 95%CI, 0.71–1.28). Geographical area explained 38.9% of the total heterogeneity (I^2 , 47%; $P_{\text{heterogeneity}}$, 0.04). No effect modification by geographical area was observed for CHD mortality and stroke mortality.

Publication bias

Figures S41–S43 in the Supporting Information online show the funnel plots used to assess publication bias for death from CVD, CHD, and stroke (the only outcomes with more than 10 study comparisons in the analyses). There was no statistical evidence of small study effects based on visual inspection of the funnel plots with either Egger's test or Begg's test (all $P > 0.05$).

Grading of the evidence

Table 4 shows the GRADE assessment for the certainty of the evidence for the association between total nut consumption and the risk of CVD outcomes. The evidence was rated as moderate for CVD mortality and CHD mortality; low for CVD incidence and stroke mortality; and very low for CHD incidence, stroke incidence, hemorrhagic stroke, ischemic stroke, AF, and HF. Tables S8–S11 in the Supporting Information online show the GRADE assessment for the association between subtypes of nut consumption and the risk of CVD outcomes. The overall certainty of the evidence was graded as very low for all subtypes of nut consumption and CVD outcomes.

DISCUSSION

The results of the present systematic review and meta-analysis of prospective cohort studies showed a significant inverse association between total nut consumption and the risk of CVD incidence and mortality, CHD incidence and mortality, and AF. There was no association between total nut consumption and stroke incidence or mortality, hemorrhagic stroke, ischemic stroke, and HF. Regarding specific types of nuts, tree nut consumption was associated with a lower risk of CVD and CHD incidence, while peanut consumption was associated with a lower incidence of, and mortality from, CVD, stroke, and CHD, and walnut consumption with a lower incidence of CVD, stroke, and CHD. No

Table 4 GRADE assessment of the systematic review and meta-analysis of prospective cohort studies assessing the association between total nut consumption and cardiovascular disease outcomes

Outcome	No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations ^a	Relative (95%CI)	Quality
CVD incidence	3	Observational studies	Not serious	Not serious	Serious ^b	Not serious	Dose-response gradient ^c	RR 0.85 (0.80 to 0.91)	⊕⊕⊕○○ LOW
CVD mortality	14	Observational studies	Not serious	Not serious	Not serious	Not serious	Dose-response gradient ^d	RR 0.77 (0.72 to 0.82)	⊕⊕⊕○○ MODERATE
CHD incidence	7	Observational studies	Not serious	Serious ^e	Serious ^f	Serious ^g	Dose-response gradient ^h	RR 0.82 (0.69 to 0.96)	⊕○○○○ VERY LOW
CHD mortality	12	Observational studies	Not serious	Not serious	Not serious	Not serious	Dose-response gradient ⁱ	RR 0.76 (0.67 to 0.86)	⊕⊕⊕○○ MODERATE
Stroke incidence	7	Observational studies	Not serious	Not serious	Serious ^j	Serious ^k	None	RR 1.00 (0.92 to 1.09)	⊕○○○○ VERY LOW
Stroke mortality	11	Observational studies	Not serious	Not serious	Not serious	Serious ^l	Dose-response gradient ^m	RR 0.87 (0.76 to 1.00)	⊕⊕⊕○○ LOW
Hemorrhagic stroke	5	Observational studies	Serious ⁿ	Not serious	Serious ^o	Serious ^p	Dose-response gradient ^q	RR 1.02 (0.77 to 1.34)	⊕○○○○ VERY LOW
Ischemic stroke	7	Observational studies	Not serious	Not serious	Serious ^r	Serious ^s	None	RR 0.99 (0.89 to 1.10)	⊕○○○○ VERY LOW
Atrial fibrillation	2	Observational studies	Not serious	Not serious	Serious ^t	Serious ^u	None	RR 0.85 (0.73 to 0.99)	⊕○○○○ VERY LOW
Heart failure	2	Observational studies	Serious ^v	Not serious	Serious ^w	Serious ^x	None	RR 1.00 (0.86 to 1.16)	⊕○○○○ VERY LOW

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; GLST, generalized least squares trend; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; NOS, Newcastle-Ottawa scale, RR, risk ratio.

^aPublication bias could not be assessed in meta-analyses that included <10 trial comparisons. Therefore, for these outcomes, no downgrades were made for publication bias.

^bSerious indirectness for CVD incidence, as the included studies were conducted among health professionals and >50% of the weight (69.30%) was contributed by studies conducted among males.

^cUpgrade for a dose-response gradient, as the MKSPLINE dose-response analyses showed a significant nonlinear inverse relationship between total nut consumption and CVD incidence ($P < 0.01$); see Figure S27 in the Supporting Information online.

^dUpgrade for a dose-response gradient, as the MKSPLINE dose-response analyses showed a significant nonlinear inverse relationship between total nut consumption and CVD mortality ($P < 0.01$); see Figure S28 in the Supporting Information online.

^eSerious inconsistency for CHD incidence due to high degree of unexplained heterogeneity ($I^2 = 74%$, $P = 0.001$).

^fSerious indirectness for CHD incidence, as >50% of the weight (55.4%) was contributed by studies conducted among health professionals.

^gSerious imprecision for CHD incidence, as the 95%CI (0.69–0.96) overlapped with the minimally important difference for clinical benefit (RR 0.95).

^hUpgrade for a dose-response gradient, as the GLST dose-response analyses revealed a significant linear inverse relationship between total nut consumption and CHD incidence ($P < 0.01$); see Figure S29 in the Supporting Information online.

ⁱUpgrade for a dose-response gradient, as the MKSPLINE dose-response analyses showed a significant nonlinear inverse relationship between total nut consumption and CHD mortality ($P < 0.01$); see Figure S30 in the Supporting Information online.

^jSerious indirectness for stroke incidence, as >50% of the weight (72.7%) was contributed by studies conducted among health professionals.

^kSerious imprecision for stroke incidence as the 95%CI (0.92–1.09) overlapped with the minimally important difference for clinical benefit (RR 0.95) and harm (RR 1.05).

^lSerious imprecision for stroke mortality, as the 95%CI (0.76–1.00) overlapped with the minimally important difference for clinical benefit (RR 0.95).

^mUpgrade for a dose-response gradient, as the MKSPLINE dose-response analyses showed a significant nonlinear inverse relationship between total nut consumption and stroke mortality ($P = 0.029$); see Figure S32 in the Supporting Information online.

ⁿSerious risk of bias for hemorrhagic stroke, as >50% of the weight (68.7%) was contributed by studies considered to be at high risk of bias (NOS < 7).

^oSerious indirectness for hemorrhagic stroke, as >50% of the weight (68.7%) was contributed by studies conducted among health professionals and >50% of the weight (55.7%) was contributed by studies conducted among males.

^pSerious imprecision for hemorrhagic stroke as the 95%CI (0.77–1.34) overlapped with the minimally important difference for clinical benefit (RR 0.95) and harm (RR 1.05).

^qUpgrade for a dose-response gradient, as the MKSPLINE dose-response analyses showed a significant nonlinear inverse relationship between total nut consumption and hemorrhagic stroke ($P = 0.01$); see Figure S33 in the Supporting Information online.

^rSerious indirectness for ischemic stroke, as >50% of the weight (66.1%) was contributed by studies conducted among health professionals.

^sSerious imprecision for ischemic stroke, as the 95%CI (0.89–1.10) overlapped with the minimally important difference for clinical benefit (RR 0.95) and harm (RR 1.05).

^tSerious indirectness for atrial fibrillation, as only 2 available studies were conducted among males.

^uSerious imprecision for atrial fibrillation, as the 95%CI (0.73–0.99) overlapped with the minimally important difference for clinical benefit (RR 0.95).

^vSerious risk of bias for heart failure, as >50% of the weight (65.40%) was contributed by a study considered to be at high risk of bias (NOS < 7).

^wSerious indirectness for heart failure, as only 2 available studies were conducted among males.

^xSerious imprecision for heart failure, as the 95%CI (0.86–1.16) overlapped with the minimally important difference for clinical benefit (RR 0.95) and harm (RR 1.05).

association was observed between peanut butter consumption and CVD outcomes.

Several previous meta-analyses have focused on summarizing data regarding nut consumption and different CVD outcomes.^{8–20} It is important to highlight that some limitations in terms of methodology were present, such as the inclusion of studies with nuts plus seeds or fruits as exposure^{9,10,16,17} or the arbitrary combination of different end points across the analyses (eg, the inclusion of studies with a cause-specific CVD outcome in CVD).^{9,14,18–20} The present meta-analysis attempted to deal with these methodological issues by including exclusively those studies that reported only nut consumption as exposure. Additionally, in the analyses of CVD incidence, only those studies evaluating a composite of non-fatal, or a combination of nonfatal and fatal CVD events, were included. Similarly, for CVD mortality, only studies that evaluated a composite of fatal CVD events were considered. For secondary outcomes, the same definition criteria as in the primary outcomes were applied.

The results of the present study, regarding total nut consumption, are highly consistent with one of the most recent meta-analyses in this field,¹⁵ which showed an inverse association between nut consumption and different CVD outcomes, and which also took into account the aforementioned methodological issues at the time of performing their analyses. Recently, one study conducted only among individuals with diabetes observed similar results. Those individuals consuming ≥ 5 servings of total nuts per week presented a lower risk of CVD incidence (HR, 0.83; 95%CI, 0.71–0.98), CHD incidence (HR, 0.80; 95%CI, 0.67–0.96), and CVD mortality (HR, 0.66; 95%CI, 0.52–0.84) than those consuming less than 1 serving per month.²⁵

Results regarding specific types of nuts are in line with those of previous meta-analyses, which also showed an inverse association between tree nut consumption and peanut consumption and the risk of CVD incidence, CVD mortality, CHD incidence, and CHD mortality,^{9,11,15} and no association with stroke incidence.^{9,15} In a recent analysis conducted only among individuals with diabetes, the results were similar for tree nut consumption, which was also associated with a lower risk of CVD incidence and mortality and CHD incidence. However, the findings revealed no association between peanut consumption and CVD outcomes.²⁵ Although the present meta-analysis also evaluated the association between walnut consumption and peanut butter consumption and the risk of CVD, CHD, and stroke incidence, the data was sourced from only one report, which included information from three different cohorts: the NHSI, NHSII, and HPFS.²¹ The lack of association between peanut butter consumption

and the risk of CVD outcomes may be due to the addition of salt and hydrogenated fats, which could counteract the beneficial effect of other nutrients present in raw peanuts. At present, owing to the limited number of studies included in previous meta-analyses and in the present analyses, and considering the high degree of interstudy heterogeneity, it is unclear whether different types of nuts are associated with CVD outcomes.

Different potential mechanisms have been proposed to explain the beneficial association observed between nut consumption and different CVD outcomes. Nuts are rich in unsaturated fatty acids, proteins, different minerals (including potassium and magnesium), vitamins (including vitamin C and E), and phenolic compounds. This unique nutritional profile means that nuts possess different properties that beneficially modify CVD risk factors and therefore reduce the risk of CVD. In fact, the ability to lower total cholesterol and low-density lipoprotein (LDL)-cholesterol levels is probably one of the best-known properties of nuts, as was demonstrated by a pooled analysis of 25 intervention trials,⁶¹ and more recently in one meta-analysis of 61 randomized controlled trials.⁶² Other possible mechanisms include a reduction in circulating levels of inflammatory cytokines (especially C-reactive protein), the modulation of nitric oxide production, an improvement in endothelial function, and a reduction in oxidative stress.^{63,64}

The present analysis has some strengths that should be elucidated. First, a comprehensive systematic search strategy was used to identify all available prospective cohort studies. Second, studies reporting only nut consumption as exposure were included. Third, the certainty of the evidence was assessed using the GRADE approach.

However, the present systematic review and meta-analysis also has some limitations. Subgroup analyses for most of the outcomes could not be performed because less than 10 study comparisons were available. Measurement error in the evaluation of nut consumption could not be ruled out because all included studies used food frequency questionnaires for this purpose. Because of this limitation, along with the possibility of residual confounding because of the observational nature of the included studies, GRADE-assessed prospective cohort studies tend to be of lower quality than other types of prospective studies. Another important limitation is that the certainty of the evidence in the effect estimates, regarding total nut consumption, was moderate only for two outcomes (CVD mortality and CHD mortality), and it was considered as low and very low for the others, mainly owing to downgrading for indirectness and imprecision. Therefore, future research is very likely to change the confidence in the effect estimates.

CONCLUSION

The present systematic review and meta-analysis provides the most updated and comprehensive summary estimates of the association between total nut consumption, different subtypes, and CVD outcomes. The results suggest a beneficial role of total nut consumption in reducing the incidence of, and mortality from, different CVD outcomes. Future research should focus on specific types of nuts in order to better clarify their effect on CVD outcomes.

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Declaration of interest. J.S.-S. reports serving on the board of the International Nut and Dried Fruit Council, and the Eroski Foundation, and receiving grant support from these entities through his institution. He also reports serving on the Executive Committee of the Instituto Danone, Spain. He has received research funding from the Instituto de Salud Carlos III, Spain;

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Zucker e.V. He is a member of the European Fruit Juice Association Scientific Expert Panel. He is on the Clinical Practice Guidelines Expert Committees of Diabetes Canada, European Association for the study of Diabetes (EASD), Canadian Cardiovascular Society (CCS), and Obesity Canada. He serves or has served as an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Technical Committee on Carbohydrates of the International Life Science Institute (ILSI) North America. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD, and Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His wife is an employee of Sobeys Inc. C.W.C.K. has received grants or research support from the Advanced Food Materials Network, Agriculture and Agri-Foods Canada (AAFC), Almond Board of California, American Pistachio Growers, Barilla, Calorie Control Council, Canadian Institutes of Health Research (CIHR), Canola Council of Canada, International Nut and Dried Fruit Council, International Tree Nut Council Research and Education Foundation, Loblaw Brands Ltd, Pulse Canada, Saskatchewan Pulse Growers, and Unilever. He has received in-kind research support from the Almond Board of California, American Peanut Council, Barilla, California Walnut Commission, Kellogg Canada, Loblaw Companies, Quaker (PepsiCo), Primo, Unico, Unilever, and WhiteWave Foods. He has received travel support and/or honoraria from the American Peanut Council, American Pistachio Growers, Barilla, California Walnut Commission, Canola Council of Canada, General Mills, International Nut and Dried Fruit Council, International Pasta Organization, Loblaw Brands Ltd, Nutrition Foundation of Italy, Oldways Preservation Trust, Paramount Farms, Peanut Institute, Pulse Canada, Sabra Dipping Co., Saskatchewan Pulse Growers, Sun-Maid, Tate & Lyle, Unilever, and WhiteWave Foods. He has served on the scientific advisory board for the International Tree Nut Council, International Pasta Organization, McCormick Science Institute, Oldways Preservation Trust, Paramount Farms, and Pulse Canada. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD), is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the EASD, and is a director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. D.R. is the president of the Croatian

Society for Diabetes and Metabolic Disorders of the Croatian Medical Association. He serves as an Executive Committee member of the Croatian Endocrine Society, Croatian Society for Obesity, and Croatian Society for Endocrine Oncology. He was a board member and secretary of IDF Europe and currently he is the chair of the IDF YLD Program. He has served as an Executive Committee member of the Diabetes and Nutrition Study Group of the EASD and currently he serves as a Executive Committee member of Diabetes and Cardiovascular Disease Study Group of the EASD. He has served as principal investigator or coinvestigator in clinical trials of AstraZeneca, Eli Lilly, MSD, Novo Nordisk, Sanofi Aventis, Solvay, and Trophos. He has received honoraria for speaking or advisory board engagements and consulting fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Lifescan – Johnson & Johnson, Novartis, Novo Nordisk, MSD, Merck Sharp & Dohme, Pfizer, Pliva, Roche, Salvus, Sanofi Aventis, and Takeda. No competing interests were declared by N.B.-T., I.P.-G., and H.K.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Table S1 Search strategy

Table S2 Characteristics of the included studies evaluating the association between tree nut consumption and the risk of cardiovascular disease outcomes, comparing highest vs lowest categories

Table S3 Characteristics of the included studies evaluating the association between peanut consumption and the risk of cardiovascular disease outcomes, comparing highest vs lowest categories

Table S4 Characteristics of the included studies evaluating the association between walnut consumption and the risk of cardiovascular disease outcomes, comparing highest vs lowest categories

Table S5 Characteristics of the included studies evaluating the association between peanut butter consumption and the risk of cardiovascular disease outcomes, comparing highest vs lowest categories

Table S6 Risk ratio and 95%CI from non-linear dose-response analysis of total nuts and cardiovascular disease, coronary heart disease, and stroke

Table S7 Sensitivity analysis by systematic exclusion of one study at a time^a

Table S8 GRADE assessment of the systematic review and meta-analysis of prospective cohort studies

assessing the association between tree nut consumption and cardiovascular disease outcomes

Table S9 GRADE assessment of the systematic review and meta-analysis of prospective cohort studies assessing the association between peanut consumption and cardiovascular disease outcomes

Table S10 GRADE assessment of the systematic review and meta-analysis of prospective cohort studies assessing the association between walnut consumption and cardiovascular disease outcomes

Table S11 GRADE assessment of the systematic review and meta-analysis of prospective cohort studies assessing the association between peanut butter consumption and cardiovascular disease outcomes

Figure S1 Association between nut consumption (highest vs lowest categories) and the risk of cardiovascular disease

Figure S2 Association between tree nut consumption (highest vs lowest categories) and the risk of cardiovascular disease

Figure S3 Association between peanut consumption (highest vs lowest categories) and the risk of cardiovascular disease

Figure S4 Association between walnut consumption (highest vs lowest categories) and the risk of cardiovascular disease

Figure S5 Association between peanut butter consumption (highest vs lowest categories) and the risk of cardiovascular disease

Figure S6 Association between nut consumption (highest vs lowest categories) and the risk of cardiovascular disease mortality

Figure S7 Association between peanut consumption (highest vs lowest categories) and the risk of cardiovascular disease mortality

Figure S8 Association between nut consumption (highest vs lowest categories) and the risk of coronary heart disease

Figure S9 Association between tree nut consumption (highest vs lowest categories) and the risk of coronary heart disease

Figure S10 Association between peanut consumption (highest vs lowest categories) and the risk of coronary heart disease

Figure S11 Association between walnut consumption (highest vs lowest categories) and the risk of coronary heart disease

Figure S12 Association between peanut butter consumption (highest vs lowest categories) and the risk of coronary heart disease

Figure S13 Association between nut consumption (highest vs lowest categories) and the risk of coronary heart disease mortality

Figure S14 Association between peanut consumption (highest vs lowest categories) and the risk of coronary heart disease mortality

Figure S15 Association between nut consumption (highest vs lowest categories) and the risk of stroke

Figure S16 Association between peanut consumption (highest vs lowest categories) and the risk of stroke

Figure S17 Association between tree nut consumption (highest vs lowest categories) and the risk of stroke

Figure S18 Association between walnut consumption (highest vs lowest categories) and the risk of stroke

Figure S19 Association between peanut butter consumption (highest vs lowest categories) and the risk of stroke

Figure S20 Association between nut consumption (highest vs lowest categories) and the risk of stroke mortality

Figure S21 Association between peanut consumption (highest vs lowest categories) and the risk of stroke death

Figure S22 Association between tree nut consumption (highest vs lowest categories) and the risk of stroke mortality

Figure S23 Association between nut consumption (highest vs lowest categories) and the risk of hemorrhagic stroke

Figure S24 Association between nut consumption (highest vs lowest categories) and the risk of ischemic stroke

Figure S25 Association between nut consumption (highest vs lowest categories) and the risk of atrial fibrillation

Figure S26 Association between nut consumption (highest vs lowest categories) and the risk of heart failure

Figure S27 Linear and non-linear dose-response relation between increasing total nut intake by 28-g increments and the risk of cardiovascular disease incidence

Figure S28 Linear and non-linear dose-response relation between increasing total nut intake by 28-g increments and the risk of cardiovascular disease mortality

Figure S29 Linear and non-linear dose-response relation between increasing total nut intake by 28-g increments and the risk of coronary disease incidence

Figure S30 Linear and non-linear dose-response relation between increasing total nut intake by 28-g increments and the risk of coronary disease mortality

Figure S31 Linear and non-linear dose-response relation between increasing total nut intake by 28-g increments and the risk of stroke incidence

Figure S32 Linear and non-linear dose-response relation between increasing total nut intake by 28-g increments and the risk of stroke mortality

Figure S33 Linear and non-linear dose-response relation between increasing total nut intake by 28-g increments and the risk of hemorrhagic stroke

Figure S34 Linear and non-linear dose-response relation between increasing total nut intake by 28-g increments and the risk of ischemic stroke

Figure S35 Subgroup analyses of total nut consumption and the risk of cardiovascular disease mortality

Figure S36 Risk of bias (Newcastle-Ottawa Scale [NOS]) subgroup analysis of total nut consumption and the risk of cardiovascular disease mortality

Figure S37 Subgroup analyses of total nut consumption and the risk of coronary heart disease mortality

Figure S38 Risk of bias (Newcastle-Ottawa Scale [NOS]) subgroup analysis of total nut consumption and the risk of coronary heart disease mortality

Figure S39 Subgroup analyses of total nut consumption and the risk of stroke mortality

Figure S40 Risk of bias (Newcastle-Ottawa Scale [NOS]) subgroup analysis of total nut consumption and the risk of stroke mortality

Figure S41 Funnel plot of the natural logarithm risk ratio for cardiovascular disease mortality

Figure S42 Funnel plot of the natural logarithm risk ratio for coronary heart disease mortality

Figure S43 Funnel plot of the natural logarithm risk ratio for stroke mortality

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