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A systematic review and meta-analysis of nut consumption and incident risk of CVD and all-cause mortality

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Abstract

Dietary patterns containing nuts are associated with a lower risk of CVD mortality, and increased nut consumption has been shown to have beneficial effects on CVD risk factors including serum lipid levels. Recent studies have reported on the relationship between nut intake and CVD outcomes and mortality. Our objective was to systematically review the literature and quantify associations between nut consumption and CVD outcomes and all-cause mortality. Five electronic databases (through July 2015), previous reviews and bibliographies of qualifying articles were searched. In the twenty included prospective cohort studies (*n* 467 389), nut consumption was significantly associated with a lower risk of all-cause mortality (ten studies; risk ratio (RR) 0·81; 95 % CI 0·77, 0·85 for highest *v.* lowest quantile of intake, $P_{het}=0{\cdot}04$, $I^2=43\,\%$), CVD mortality (five studies; RR 0·73; 95 % CI 0·68, 0·78; $P_{het}=0{\cdot}31$, $I^2=16\,\%$), all CHD (three studies; RR 0·66; 95 % CI 0·48, 0·91; $P_{het}=0{\cdot}0002$, $I^2=88\,\%$) and CHD mortality (seven studies; RR 0·70; 95 % CI 0·64, 0·76; $P_{het}=0{\cdot}65$, $I^2=0\,\%$), as well as a statistically non-significant reduction in the risk of non-fatal CHD (three studies; RR 0·71; 95 % CI 0·49, 1·03; $P_{het}=0{\cdot}03$, $I^2=72\,\%$) and stroke mortality (three studies; RR 0·83; 95 % CI 0·69, 1·00; $P_{het}=0{\cdot}54$, $I^2=0\,\%$). No evidence of association was found for total stroke (two studies; RR 1·05; 95 % CI 0·69, 1·61; $P_{het}=0{\cdot}04$, $I^2=77\,\%$). Data on total CVD and sudden cardiac death were available from one cohort study, and they were significantly inversely associated with nut consumption. In conclusion, we found that higher nut consumption is associated with a lower risk of all-cause mortality, total CVD, CVD mortality, total CHD, CHD mortality and sudden cardiac death.

Key words: **Nuts: Mortality: CVD: CHD**

CVD is the leading cause of death globally, accounting for 30 % of all deaths worldwide[1]. The CVD burden is projected to increase in the next two decades. Although pharmacological treatments (e.g. statins) have contributed significantly to reduced CVD morbidity and mortality globally[2], recent reviews of the evidence suggest that statins may increase the risk of type 2 diabetes[3], as well as be medically contraindicated for some persons. Thus, lifestyle modification, including healthy eating, remains a cornerstone of CVD prevention.

In recent years, a substantial amount of data have shown that fat quality is associated with CVD surrogate outcomes and events[4–6]. A readily available source of unsaturated fat is nuts, which include tree nuts (e.g. almonds, hazelnuts, walnuts and pistachios) and peanuts (technically a legume but with a similar nutrient composition to tree nuts)[7]. Randomised controlled trials (RCT) have shown that dietary patterns containing nuts such as the 'Mediterranean diet' reduce CVD mortality in healthy[8] and high-risk populations[9]. There are also many clinical trials investigating the effect of nuts on risk factors of CVD such as serum lipid levels and lipoproteins[10]. However, to date, there is a paucity of data from clinical trials assessing the independent impact of nut consumption on CVD events. Meanwhile in recent years, additional data from prospective cohort studies with a substantial number of mortality outcomes including CVD and individual events such as myocardial infarction and stroke have been published[11–14]. Since January 2013, there have been six meta-analyses related to CVD and nut consumption[15–20]. However, the most recently updated literature search was conducted in June 2014 and limited outcomes to all-cause mortality, CVD mortality and cancer mortality[15]. Since that time, three large prospective cohort studies of nut consumption and CVD outcomes with initial or expanded analyses have been published[21–23]. Our study also offers the advantage of being specific to nuts, whereas other previous meta-analyses have included studies that group nut consumption with other food groups including seeds or fruit, which may introduce imprecision into the results.

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NOS, Newcastle–Ottawa Scale; RR, risk ratio.

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In this study, we systematically reviewed the updated literature on nut intake and CVD events and investigated associations with additional cardiovascular outcomes such as stroke mortality and sudden cardiac death. Further, we used GRADE (Grading of Recommendations Assessment, Development, and Evaluation), to assess the quality of the evidence for each outcome of interest and to help facilitate incorporation of our findings into nutrition policy and guidelines development.

Methods

This review was conducted in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (online Supplementary Appendix S1)[24]. Ethics approval was not required for this research.

Search strategy and study selection

An electronic search strategy was developed to identify observational human studies (prospective cohort, retrospective, nested case–control or case-cohort design) and randomised trials investigating nut consumption and mortality and CVD outcomes. We searched MEDLINE (1946 through 8 July 2015); EMBASE (1974 through 8 July 2015); Cochrane Central Registry of Controlled Trials (1996 through 8 July 2015); Evidence Based Medicine Reviews Health Technology Assessment (1996 through 8 July 2015); and Evidence Based Medicine NHS Economic Evaluation Database (1996 through 8 July 2015). The bibliographies of retrieved articles were reviewed for additional studies. Studies were limited to original English language articles that included the terms mortality, CVD, myocardial infarction, CHD, stroke, brain ischaemia, cerebrovascular accident, sudden cardiac death, CHD or CVD mortality as the outcomes of interest and nuts, walnut, almond, pecan, macadamia, hazelnut, peanut, pistachio or peanut butter as the exposure variables being explored. The full search strategy is presented in online Supplementary Appendix S2. One reviewer (A. J. M.) assessed titles and abstracts of all studies identified through electronic searches. Potentially eligible studies were reviewed independently by a second reviewer (R. J. d. S.) with discrepancies resolved by discussion. A third author (A. M.) was consulted to reach consensus when necessary.

Data extraction

Two authors (A. J. M. and R. J. d. S.) independently extracted details of the study design, country of conduct, assessment of exposures and outcomes, participant characteristics and statistical analyses including degree of adjustment for potential confounders using pre-tested instruments. Discrepancies were resolved by discussion. In cases in which two or more manuscripts provided the same estimates of association from the same cohort, we chose the one with the longest follow-up time. For each study, the most-adjusted multivariable risk ratio (RR) and corresponding 95 % CI for each outcome were extracted, including data on different types of nuts when provided. For studies with more than one multivariable adjusted model, we selected the most-adjusted model that adjusted for potential confounders including other dietary factors associated with nut consumption (such as fruit and vegetables or alcohol) but without the inclusion of variables on the putative causal pathway (e.g. blood cholesterol and blood pressure), where possible.

Study risk of bias

The Newcastle–Ottawa Scale (NOS)[25] was used to assess the risk of bias of the included studies on the basis of selection of study groups, comparability of groups and ascertainment of the exposure or outcome of interest. The following elements were adapted for nutritional studies. Ascertainment of exposure: one star was given if a validated instrument (e.g. semi-quantitative FFQ) was used; however, as there is no accepted 'gold' standard of dietary measurement, one star was given if other instruments were used (e.g. multiple 24-h dietary recall or 7-d food records), and data were provided on (i) completion rate (≥90 %) or (ii) information on reliability from repeat administration, or it was explicitly stated that (iii) participants trained to complete records, or (iv) ambiguous or incomplete records were subsequently clarified. Comparability: each study began with two stars for 'comparability' and lost one star for each one of these five variables that was not controlled or matched for age, smoking, total energy and family history. For length of follow-up for outcome ascertainment, one star was given for follow-up of at least 5 years, chosen because a previous systematic review of >200 cohort studies relating dietary factors to CHD risk found that approximately 80 % had a follow-up of ≥5 years.

Grading of Recommendations Assessment, Development and Evaluation

The GRADE approach was used to assess the confidence in the effect estimates derived from the body of evidence (quality of evidence) by outcome and to produce evidence profiles[26–28]. Evidence summaries and GRADE assessments were discussed and reviewed by all investigators. Confidence in the estimate of each association was categorised into four levels, from very low (⊕⊕◯◯) to high (⊕⊕⊕⊕). Outcomes were downgraded for inconsistency if the I^2 value for the summary relative risk estimate was >50 %. If nut consumption was estimated using a non-validated method or if the outcome was self-reported, the outcome was downgraded for indirectness. To determine the presence of imprecision, we first considered the optimal information size (the number of cases included in the review compared with the number required by a conventional sample size calculation for a single adequately powered trial. On the basis of a 5 % event rate in the control group and a 25 % relative risk reduction, we calculated the optional information size to be 400 cases[29]. If the optimal information size criterion was not met, the evidence was downgraded for imprecision. The outcome was also downgraded for imprecision if the optimal information size criterion was met but the 95 % CI included 1·00[30].

Statistical analysis

The principal effect measures were adjusted RR between extreme levels of intake (highest *v.* lowest quantile) for prospective studies

and the OR for retrospective studies. The principal effect measures were the RR between extreme levels of intake (highest *v.* lowest quantile). In cases in which at least two studies provided combinable data, a DerSimonian and Laird's random effects meta-analysis was performed, which yields conservative CI around the relative risks in the presence of heterogeneity[31].

Heterogeneity was detected using Cochran's Q test (significant at $P<0{\cdot}10$) and quantified using the I^2 statistic (ranging from 0 to 100 %), which informed the rating of the GRADE confidence in the estimates. Subgroup analyses were conducted to explore heterogeneity by sex (women, men, both sexes), geographic location and type of nut. Sensitivity analyses were conducted by removing studies with NOS scores <7 and re-calculating the pooled effect for each outcome. Outcomes that are potentially sensitive to quality include all-cause mortality and CHD mortality.

Dose–response meta-analyses were conducted using the method reported by Greenland & Longnecker[32] and Orsini *et al.*[33]. Study-specific slopes based on the results across quantiles of nut consumption were calculated using generalised least squares for trend estimation. The study-specific estimates were then combined using the restricted maximum likelihood method. The fully adjusted RR, 95 % CI, dose and number of cases and person-years were extracted for each study and outcome. The amount of nuts consumed was converted to servings per week (serving size of 28 g or 1 ounce) using the median or mean intake level for each quantile. Summary estimates for the slope of the association between nut intake and outcomes were computed for an increment of 4-weekly servings, which is consistent with the Dietary Approach to Stop Hypertension (DASH) eating plan[34]. For the highest dose category, the servings per week were estimated as the minimum for that quantile plus one half of the median/mean of the previous quantile to minimise potential for underestimation.

Publication bias was investigated by visual inspection of funnel plots and quantitatively assessed using Egger's and Begg's tests where a P value <0·10 was considered evidence of small study effects[35,36]. The trim and fill method was used to estimate the number of potentially missing studies in the meta-analyses and the effect these studies may have had on the outcome[37].

We used commercially available statistical software, Review Manager[38], to conduct the meta-analysis and Stata, version 14[39] to conduct dose–response analyses and the assessment of publication bias.

Results

Literature flow

Of the 1490 potentially eligible articles that were identified, seventy-five remained after screening the titles and abstracts for applicability and twenty-six remained after full-text review. From these articles, twenty prospective cohort studies, which contributed at least one data point to the quantitative synthesis, were identified (Fig. 1). One case–control study was identified, which is discussed individually. No relevant RCT were found. Fig. 2 provides the pooled multivariable risk estimates for all outcomes.

Table 1 summarises the characteristics and results of the twenty prospective cohort studies (NOS scores in online Supplementary Appendix S3). The articles were based on data from twelve different cohorts, seven of which are from the USA (Nurses' Health Study[13,40–43], Physician's Health Study[11,13,40,44], California Seventh-Day Adventist Study[14,45,46], Iowa Women's Health Study[47], Women's Health Initiative[48,49], Atherosclerosis Risk in Communities Study[50], Southern Community Cohort Study[21], PREDIMED study and the Seguimiento University of Navarra (SUN) Project in Spain[51,52], Netherlands Cohort Study[53], European Prospective Investigation into Cancer and Nutrition (EPIC) study in Germany[23] and a sample of community dwelling people in the UK)[54]. Two RCT (Women's Health Initiative and PREDIMED)[48,51] provided prospective associations according to reported nut consumption independent of randomisation assignment, and thus they were included as cohort studies. In total, 467 389 participants were included in the analysis with a median follow-up time of 11·8 years (range, 4·6–30 years), a mean age of 60·4 years and 68·0 % of participants being women. All studies used FFQ to assess nut consumption. The GRADE estimates of the quality of evidence are summarised in online Supplementary Appendix S4.

Prospective cohort studies

All-cause mortality. Ten prospective studies examined the association between dietary nut consumption and mortality from any cause[21,40,45–48,51–54]. The summary multivariable RR for a meta-analysis of these ten studies with fifteen subgroups involving 277 432 participants (182 272 women) with 49 232 events over 4·6–30 years of follow-up was 0·81 (95 % CI 0·77, 0·85; $P_{het}=0{\cdot}04$, $I^2=43$ %) (least adjusted RR 0·78; 95 % CI 0·73, 0·82). The effect was similar in studies conducted exclusively in women (0·84; 95 % CI 0·81, 0·88; $P_{het}=0{\cdot}40$, $I^2=3$ %) and in studies conducted exclusively in men (0·78; 95 % CI 0·69, 0·88; $P_{het}=0{\cdot}02$, $I^2=67$ %) (Fig. 3). After removal of studies that scored <7 on the NOS, six studies with ten subgroups remained[21,40,46,51–53] and provided a relative risk estimate of 0·79 (95 % CI 0·74, 0·84; $P_{het}=0{\cdot}02$, $I^2=56$ %). The GRADE estimate for quality of evidence was moderate (⊕⊕⊕⊕○).

Total CVD. One study[41] involving 6309 women with diabetes accrued 634 CVD events during the 8·7-year follow-up and showed a relative risk of 0·56 (95 % CI 0·36, 0·88) (least adjusted RR 0·43; 95 % CI 0·30, 0·61). The GRADE estimate for the quality of evidence was moderate (⊕⊕⊕○). The study was at a low risk for bias with a NOS score of 9.

CVD mortality. In a meta-analysis of five prospective cohort studies[21,22,40,47,51] with seven subgroups involving 243 795 participants experiencing 13 726 events after 4·8–30 years of follow-up, the summary multivariable RR was 0·73 (95 % CI 0·68, 0·78; $P_{het}=0{\cdot}31$, $I^2=16$ %) (least adjusted RR 0·73; 95 % CI 0·73, 0·80). When analysed separately, women and men had a similar risk estimate (0·76; 95 % CI 0·66, 0·88 *v.* 0·74; 95 % CI 0·64, 0·83, respectively; $P_{het}=0{\cdot}61$, $I^2=0$ %). Three studies[21,22,51] in both men and women provided a relative risk estimate of 0·72 (95 % CI 0·64, 0·81; $P_{het}=0{\cdot}13$, $I^2=47$ %) (Fig. 4).

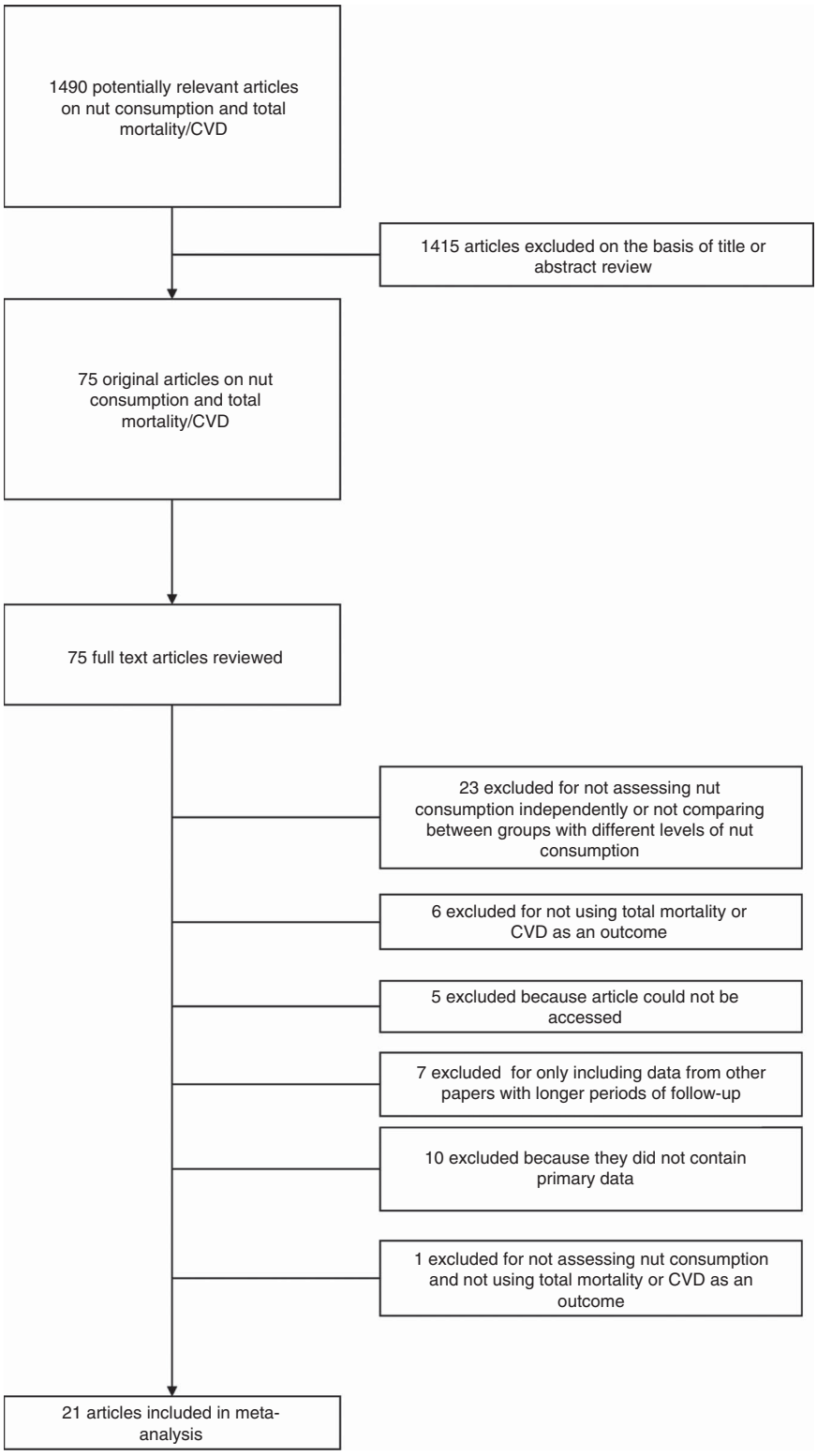

Fig. 1. Flow diagram of systematic literature search.

Removing the single study with a NOS below 7 does not materially alter the estimated relative risk (0·74; 95 % CI 0·69, 0·79; $P_{het} = 0·17$, $I^2 = 21$ %). The GRADE estimate for quality of evidence was low (⊕⊕◯◯).

Total CHD. For total CHD, the summary multivariable RR for nut consumption in three studies[42,50,55] (three subgroups), including 123 971 participants (87 869 women) followed up for 6–26 years, accruing a combined 4757 events, was 0·66 (95 % CI

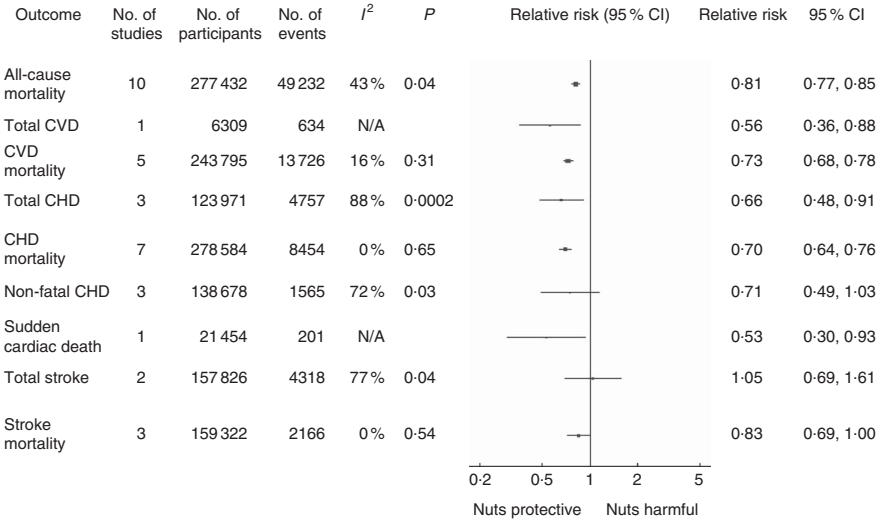

Fig. 2. Summary meta-analysis of the association between nut consumption and all-cause mortality and cardiovascular outcomes.

0·48, 0·91; $P_{het}=0·0002$, $I^2=88\,\%$) (least adjusted RR 0·57; 95 % CI 0·45, 0·72) (Fig. 5). After removing studies with an NOS score of <7, only one study remained with a relative risk estimate of 0·68 (95 % CI 0·60, 0·77)[42]. The GRADE estimate for quality of evidence was very low (⊕○○○).

CHD mortality. For CHD death, the summary multivariable RR for nut consumption in seven studies[14,21,22,40,45,47,54] (ten subgroups), including 278 584 participants (180 734 women) followed up for 5·4–30 years, experiencing a combined 8454 events, was 0·70 (95 % CI 0·64, 0·76; $P_{het}=0·65$, $I^2=0\,\%$) (least adjusted RR 0·62; 95 % CI 0·55, 0·70). The estimates were similar in women and men (0·69; 95 % CI 0·59, 0·82 *v.* 0·71; 95 % CI 0·61, 0·82, respectively, $P_{het}=0·96$, $I^2=0\,\%$) (Fig. 6). After removing studies with NOS scores below 7, four studies[14,21,22,40] remained and showed a risk estimate of 0·70 (95 % CI 0·62, 0·78; $P_{het}=0·32$, $I=15\,\%$). The GRADE estimate for quality of evidence was moderate (⊕⊕⊕○).

Non-fatal CHD. In three prospective cohort studies[11,14,43] involving 138 678 participants experiencing 1565 non-fatal myocardial infarction events after 6–17 years of follow-up, the summary multivariable RR was 0·71 (95 % CI 0·49, 1·03; $P_{het}=0·03$, $I^2=72\,\%$) (least adjusted RR 0·65; 95 % CI 0·43, 0·98), with sex explaining much of the heterogeneity. The RR in men was 1·04 (95 % CI 0·82, 1·32) and in women it was 0·71 (95 % CI 0·47, 1·07; $P_{het}=0·12$, $I^2=59\,\%$) (Fig. 7). In a mixed population of men and women, the RR was 0·49 (95 % CI 0·28, 0·85). No studies had NOS scores below 7. The GRADE estimate for quality of evidence was very low (⊕○○○).

Sudden cardiac death. One study[11] investigated the relationship between nut consumption and sudden cardiac death in 21 454 men (201 events) over 17 years. The multivariable RR for sudden cardiac deaths was 0·53 (95 % CI 0·30, 0·93) (least adjusted RR 0·64; 95 % CI 0·40, 1·02). The GRADE estimate for the quality of evidence was very low (⊕○○○). The study is at a low risk for bias with a NOS score of 8.

Total stroke. In two studies[13,23] of 157 826 participants and 4381 events accrued after 8·3–26 years of follow-up, the summary multivariable RR is 1·05 (95 % CI 0·69, 1·61; $P_{het}=0·04$, $I^2=77\,\%$) (least adjusted RR 1·01; 95 % CI 0·71, 1·44). One study compared the risk of stroke in women and in men (0·86; 95 % CI 0·75, 0·98 *v.* 0·92; 95 % CI 0·77, 1·09, respectively; $P_{het}=0·55$, $I^2=0\,\%$). The summary multivariable RR in three studies[13,23,49] with 240 508 participants and 3496 events investigating ischaemic stroke is 1·06 (95 % CI 0·81, 1·38), whereas in one study[13] investigating haemorrhagic stroke in 127 160 people with 693 events the RR is 0·83 (95 % CI 0·59, 1·16) (Fig. 8). No studies had NOS scores below 7. The GRADE estimate for quality of evidence was very low (⊕○○○).

Stroke mortality. Three studies[22,23,40] with four subgroups included 159 322 participants and 2166 deaths after 8.3–30 years of follow-up. The summary multivariable RR was 0·83 (95 % CI 0·69, 1·00; $P_{het}=0·54$, $I^2=0\,\%$) (least adjusted RR 0·70; 95 % CI 0·58, 0·84). One study[40] investigated men and women separately, and a non-significant trend for benefit was found in men (0·78; 95 % CI 0·58, 1·05), whereas no evidence of association was found in women (1·05; 95 % CI 0·73, 1·52). Another study[21] compared the risk of haemorrhagic stroke *v.* ischaemic stroke (1·21; 95 % CI 0·63, 2·33 *v.* 0·78; 95 % CI 0·43, 1·43, respectively, $P_{het}=0·50$, $I^2=0\,\%$) (Fig. 9). No studies had NOS scores below 7. The GRADE estimate for quality of evidence was very low (⊕○○○).

Dose–response. Seven of the outcomes (all-cause mortality, total CVD, CVD mortality, CHD mortality, non-fatal CHD, sudden cardiac death and stroke mortality) had sufficient data to use generalised least squares for trend estimation analysis. Studies that did not provide the number of cases and number of

Table 1. Study characteristics and results
(Numbers; medians; risk ratios (RR) and 95 % confidence intervals)

CVD outcomes	References	Country	*n*	Age	Sex	Dietary measure	Comparison groups	Follow-up (median)	Risk of bias	Result (RR and 95 % CI)
All-cause mortality	Bao *et al.*[40]	USA	118 962	Unreported	Men and women	FFQ	Never and >5 servings/ week (5 groups)	24 years men, 30 years women	Low	0·86 (0·82, 0·89), P_{trend} = <0·001
	Blomhoff *et al.*[47]	USA	31 778	55–69	Women	FFQ	Never and >5 servings/ week (4 groups)	15 years	Moderate	0·89 (0·81, 0·99), P_{trend} = 0·26
	Fernández-Montero *et al.*[52]	Spain	17 184	Mean age: 38·8 years	Men and women	FFQ	Highest *v.* lowest quintile	5 years	Low	0·56 (0·30, 1·06), P_{trend} = 0·058
	Fraser *et al.*[45]	USA	1668	Mean age about 50 years	Men and women	FFQ	<1 to >5 servings/ week (3 categories)	11 years	Moderate	0·82 (0·70, 0·96)
	Fraser & Shavlik[46]	USA	603	Mean age: 88·3 years	Men and women	FFQ	<1 to >5 servings/ week (3 categories)	12 years	Moderate	0·60 (0·30, 1·0)
	Guasch-Ferré *et al.*[51]	Spain	7216	Mean age: 66·6 years	Men and women	FFQ	Never to >3 servings/ week (3 categories)	4·8 years	Moderate	0·61 (0·45, 0·83), P_{trend} = 0·012
	Levitan *et al.*[48]	USA	3215	Mean age: 72·7 years	Women	FFQ	Highest *v.* lowest quartile	4·6 years	Moderate	0·86 (0·74, 0·96), P_{trend} = 0·049
	Luu *et al.*[21]	USA	71 764	Mean age: 52·4 years	Men and women	FFQ	Highest *v.* lowest quintile	5·4 years	Low	0·79 (0·73, 0·86), P_{trend} = <0·001
	Mann *et al.*[54]	UK	10 802	16–79 years	Men and women	FFQ	<Once to >5 times/ week (3 categories)	13·3 years	High	0·77 (0·58, 1·01), P_{trend} = not significant
	van den Brandt & Schouten[22]	The Netherlands	14 075	55–69 years of age at baseline	Men and women	FFQ	Never and >10 g of nuts daily	10 years	Low	Pooled RR is 0·77 (0·66, 0·89), RR for men is 0·76 (0·63, 0·92) and RR for women is 0·70 (0·57, 0·86). P_{trend} = 0·003, 0·001 and <0·001, respectively
All CVD	Li *et al.*[41]	USA	6309	Mean age: 57·1 years	Women	FFQ	Almost never to >5 servings/week (4 groups)	8·7 years	Low	0·56 (0·36, 0·89), P_{trend} = 0·85
All CVD morality	Bao *et al.*[40]	USA	118 962	Unreported	Men and women	FFQ	Never and >5 servings/ week (5 groups)	24 years men, 30 years women	Low	Pooled RR is 0·75 (0·62, 0·84), RR for men is 0·73 (0·64, 0·83) and 0·82 (0·66, 1·01) for women. P_{trend} = <0·001, <0·001 and 0·04, respectively
	Blomhoff *et al.*[47]	USA	31 778	55–69	Women	FFQ	Never and >5 servings/ week (4 groups)	15 years	Moderate	0·72 (0·59, 0·87), P_{trend} = 0·0008
	Guasch-Ferré *et al.*[51]	Spain	7216	Mean age: 66·6 years	Men and women	FFQ	Never to >3 servings/ week (3 categories)	4·8 years	Moderate	0·45 (0·25, 0·81), P_{trend} = 0·091
	Luu *et al.*[21]	USA	71 764	Mean age: 52·4 years	Men and women	FFQ	Highest *v.* lowest quintile	5·4 years	Low	0·77 (0·63, 0·92), P_{trend} = 0·03
	van den Brandt & Schouten[22]	The Netherlands	14 075	55–69 years of age at baseline	Men and women	FFQ	Never and >10 g of nuts daily	10 years	Low	0·83 (0·69, 1·00), P_{trend} = 0·013
All CHD	Bernstein *et al.*[42]	USA	84 136	Mean age: 58 years	Women	FFQ	Highest *v.* lowest quintile	26 years	Low	0·68 (0·60, 0·77), P_{trend} = <0·0001
	Fraser *et al.*[55]	USA	27 769	Not reported	Men and women	FFQ	Low *v.* high	6 years	Moderate	0·45 (0·35, 0·59), P_{trend} was not evaluated
	Haring *et al.*[50]	USA	12 066	Mean age: 53·8 years	Men and women	FFQ	Highest *v.* lowest quintile	22 years	Moderate	0·91 (0·74, 1·12), P_{trend} = 0·67
CHD mortality	Bao *et al.*[40]	USA	118 962	Unreported	Men and women	FFQ	Never and >5 servings/ week (5 groups)	24 years men, 30 years women	Low	Pooled RR is 0·74 (0·68, 0·81), RR for men is 0·71 (0·61, 0·83) and 0·72 (0·55, 0·94) for women. P_{trend} = <0·001, <0·001 and 0·003, respectively
	Blomhoff *et al.*[47]	USA	31 778	55–69	Women	FFQ	Never and >5 servings/ week (4 groups)	15 years	Moderate	0·52 (0·36, 0·76), P_{trend} = 0·02
	Fraser *et al.*[14]	USA	31 208	> 25 years	Men and women	FFQ	<1 to >5 servings/ week (3 categories)	6 years	Moderate	0·62 (0·44, 0·90), P_{trend} = <0·01

Table 1. *Continued*

CVD outcomes	References	Country	*n*	Age	Sex	Dietary measure	Comparison groups	Follow-up (median)	Risk of bias	Result (RR and 95 % CI)
	Fraser *et al.*[45]	USA	603	> 84 years	Men and women	FFQ	<1 to >5 servings/ week (3 categories)	12 years	Moderate	Pooled RR is 0·61 (0·45, 0·83), for men it is 0·66 (0·38, 1·14) and for women it is 0·61 (0·42, 0·88)
	Luu *et al.*[21]	USA	71 764	Mean age: 52·4 years	Men and women	FFQ	Highest *v.* lowest quintile	5·4 years	Low	0·62 (0·45, 0·85), $P_{trend} = 0·01$
	Mann *et al.*[54]	UK	10 802	16–79 years	Men and women	FFQ	<Once to >5 times/ week (3 categories)	13·3 years	High	0·87 (0·45, 1·68), P_{trend} is non-significant
	van den Brandt & Schouten[22]	The Netherlands	14 075	55–69 years of age at baseline	Men and women	FFQ	Never and >10 g of nuts daily	10 years	Low	0·83 (0·67, 1·04), $P_{trend} = 0·026$
Non-fatal CHD	Albert *et al.*[11]	USA	21 454	40–84 years	Men	FFQ	<1/month to >2/week (4 categories)	17 years	Low	1·04 (0·82, 1·33), $P_{trend} = 0·87$
	Fraser *et al.*[14]	USA	31 208	>25 years	Men and women	FFQ	<1 to >5 servings/ week (3 categories)	6 years	Moderate	0·52 (0·30, 0·87), $P_{trend} = <0·01$
	Hu *et al.*[43]	USA	86 016	34–59 years	Women	FFQ	Almost never to >5 times/week (4 categories)	14 years	Low	0·71 (0·47, 1·07), $P_{trend} = 0·19$
Sudden cardiac death	Albert *et al.*[11]	USA	21 454	40–84 years	Men	FFQ	<1/month to >2/week (4 categories)	17 years	Low	0·53 (0·30, 0·92), $P_{trend} = 0·01$
Total stroke	Bernstein *et al.*[13]	USA	127 160	Women 30–55 years, men 40–75 years	Men and women	FFQ	Highest *v.* lowest quintile	22 years for PHS and 26 years for NHS	Low	Pooled RR is 0·88 (0·79, 0·98), for men the RR is 0·89 (0·68-1·16) and for women the RR is 0·71 (0·51, 1·00). For ischaemic stroke the RR is 0·97 (0·84, 1·12) and for haemorrhagic stroke the RR is 0·83 (0·59, 1·16)
	di Giuseppe *et al.*[23]	Germany	26 285	29·2 years men and 52·5 years women	Men and women	FFQ	1/2 *v.* >1 portion/week	8·3 years	Low	1·37 (0·92, 2·05) for total stroke and 1·62 (1·05, 2·49) for ischaemic stroke
	Yaemsiri *et al.*[49]	USA	87 025	Mean age: 63·5 years	Women	FFQ	1 medium serving/d *v.* no nuts	Average of 8 years	Low	0·89 (0·66, 1·20)
Stroke mortality	Bao *et al.*[40]	USA	118 962	Unreported	Men and women	FFQ	Never and >5 servings/ week (5 groups)	24 years men, 30 years women	Low	Pooled RR is 0·96 (0·81, 1·15), RR for men is 0·78 (0·58, 1·06) and RR for women is 1·05 (0·73, 1·52). $P_{trend} = 0·91$, 0·39 and 0·43, respectively
	di Giuseppe *et al.*[23]	Germany	26 285	29·2 years men and 52·5 years women	Men and women	FFQ	1/2 *v.* >1 portion/week	8·3 years	Low	0·67 (0·15, 2·97)
	Luu *et al.*[21]	USA	71 764	Mean age: 52·4 years	Men and women	FFQ	Highest *v.* lowest quintile	5·4 years	Low	1·37 (0·67, 2·80), $P_{trend} = 0·02$ for haemorrhagic stroke. 0·89 (0·45, 1·74), $P_{trend} = 0·35$ for ischaemic stroke
	van den Brandt & Schouten[22]	The Netherlands	14 075	55–69 years of age at baseline	Men and women	FFQ	Never and >10 g of nuts daily	10 years	Low	0·76 (0·56, 1·02), $P_{trend} = 0·029$

PHS, Physicians' Health Study; NHS, Nurses' Health Study.

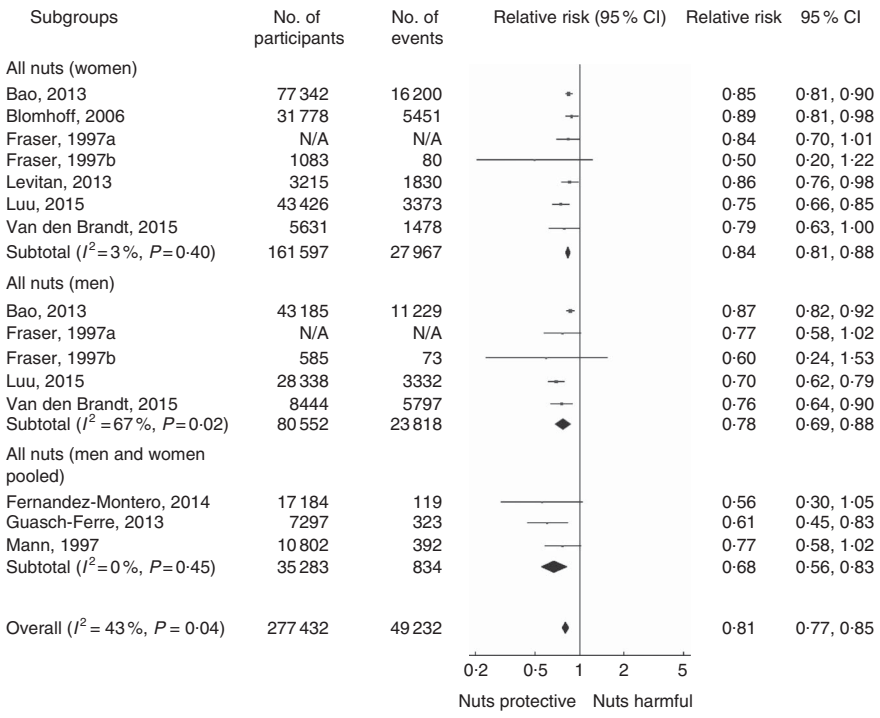

Fig. 3. Meta-analysis of the association between nut consumption and all-cause mortality.

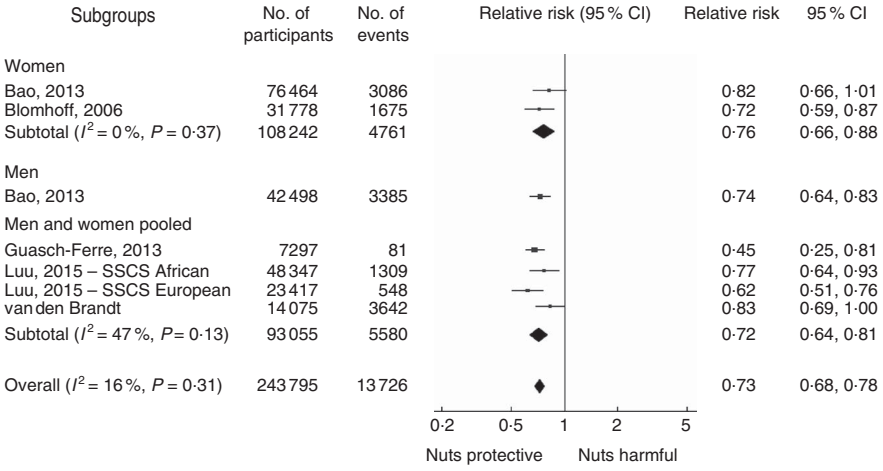

Fig. 4. Meta-analysis of the association between nut consumption and CVD mortality.

person-years of follow-up were excluded. Significant reductions in risk per 4 weekly servings were seen for all-cause mortality (0·81; 95 % CI 0·75, 0·92), total CVD (0·72; 95 % CI 0·55, 0·96), non-fatal CHD (0·81; 95 % CI 0·72, 0·96) and sudden cardiac death (0·71; 95 % CI 0·55, 0·93). A statistically non-significant reduction in risk of CVD mortality (0·78; 95 % CI 0·63, 1·00), CHD mortality (0·78; 95 % CI 0·57, 1·08) and stroke mortality (0·85; 95 % CI 0·55, 1·31) was found.

Types of nuts. Five studies reported on different types of nut consumption[21,22,40,43,51]. Guasch-Ferré *et al.*[51] reported on walnut consumption *v.* CVD death and all-cause mortality. Hu *et al.*[43] reported on peanut consumption *v.* total CHD. Bao *et al.*[40] reported peanut intake *v.* all-cause mortality, CHD mortality and stroke mortality. Van den Brandt & Schouten reported on the same outcomes, as well as CVD mortality for peanut consumption, and Luu *et al.* reported on the same outcomes using data from the Shanghai Men's and Women's Health Studies[21,22]. Peanut consumption was associated with a significantly reduced risk of all-cause mortality (0·86; 95 % CI 0·82, 0·90), CVD mortality (0·77; 95 % CI 0·70, 0·85), total CHD (0·66; 95 % CI 0·46, 0·94) and CHD mortality (0·76; 95 % CI 0·69, 0·83),

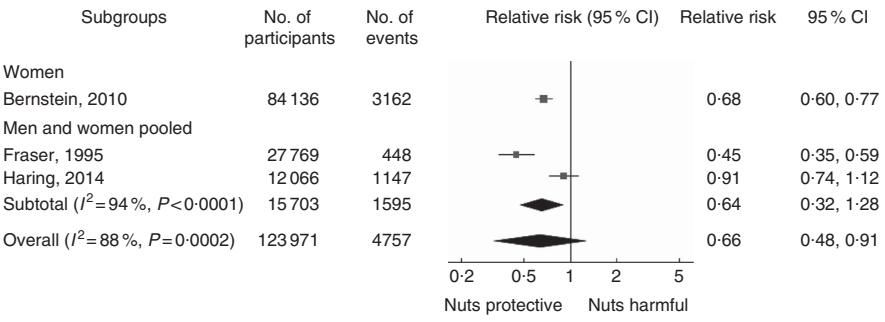

Fig. 5. Meta-analysis of the association between nut consumption and total CHD.

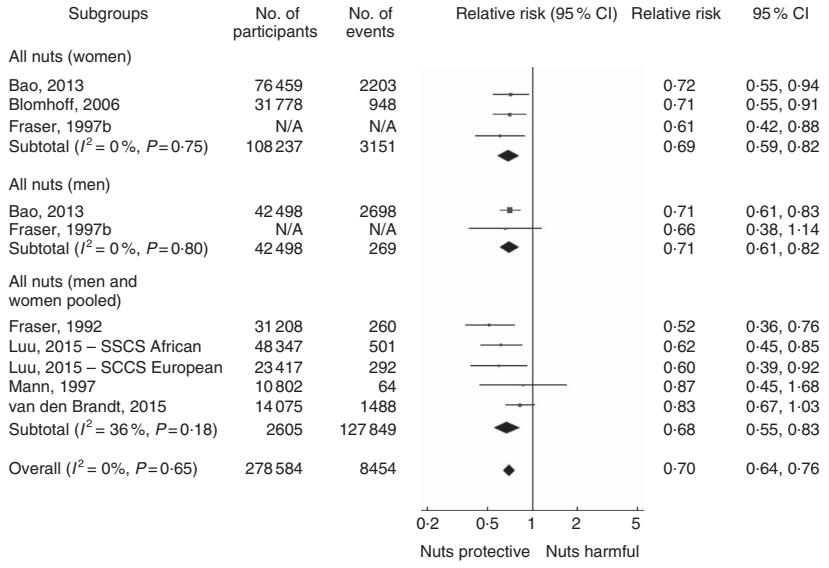

Fig. 6. Meta-analysis of the association between nut consumption and CHD mortality.

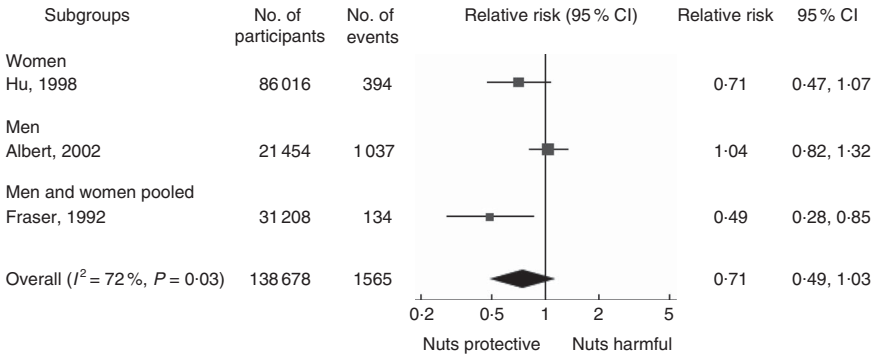

Fig. 7. Meta-analysis of the association between nut consumption and non-fatal CHD.

and a non-significant trend was found for stroke mortality (0·81; 95 % CI 0·60, 1·10). Walnut consumption was associated with a significantly reduced risk of all-cause mortality (0·55; 95 % CI 0·40, 0·76) and CVD mortality (0·53; 95 % CI 0·29, 0·97) (online Supplementary Appendix S5).

Geographic location. Three outcomes had two or more studies conducted in both the USA and Europe. No studies were conducted on other continents. We explored heterogeneity by continent. For all-cause mortality, the summary multivariable RR was 0·83 (95 % CI 0·77, 0·89; P_{het} = 0·01, I^2 = 67 %) in the USA and 0·73 (95 % CI 0·65, 0·83; P_{het} = 0·45, I^2 = 0 %) in Europe. For CVD mortality, the RR was 0·73 (95 % CI 0·67, 0·81; P_{het} = 0·67, I^2 = 0 %) in the USA and 0·65 (95 % CI 0·36, 1·17; P_{het} = 0·05, I^2 = 74 %) in Europe. For CHD mortality, the relative risk was 0·69 (95 % CI 0·62, 0·76; P_{het} = 0·33, I^2 = 18 %) in the USA and 0·83 (95 % CI 0·68, 1·02; P_{het} = 0·89, I^2 = 0 %) in Europe (online Supplementary Appendix S6).

Publication bias. Because of the small number of studies for each outcome, the risk of publication bias could only be assessed for

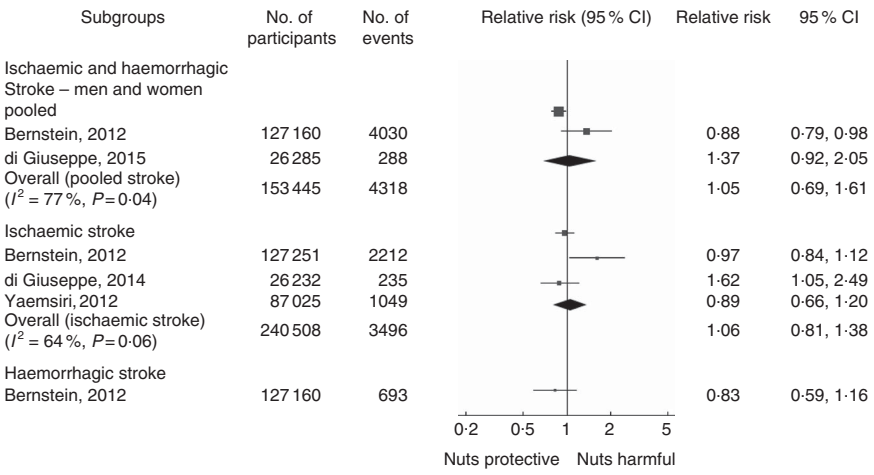

Fig. 8. Meta-analysis of the association between nut consumption and total stroke.

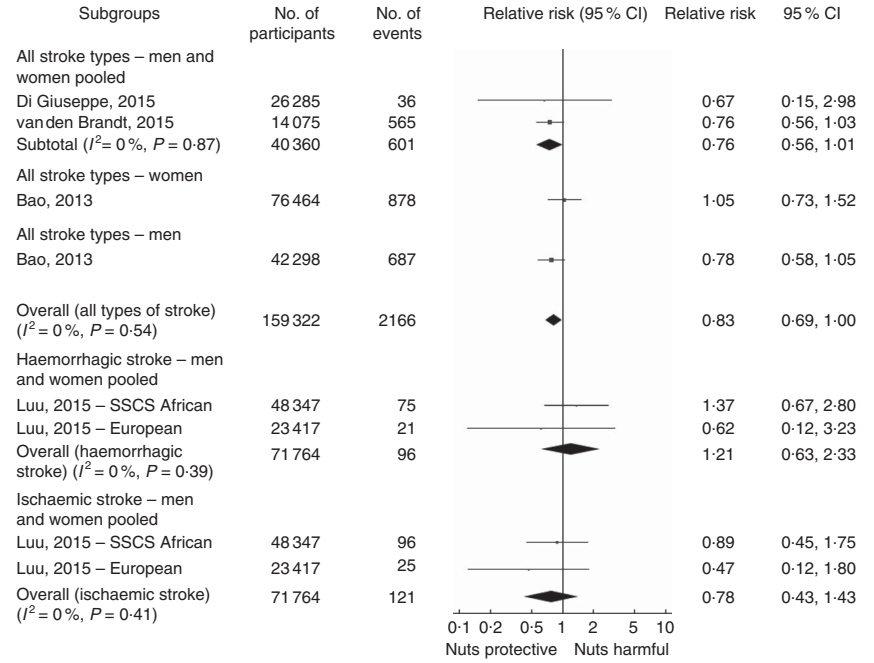

Fig. 9. Meta-analysis of the association between nut consumption and stroke mortality.

all-cause mortality[56]. Visual inspection of the funnel plot suggested asymmetry with the tendency for the publication of small and/or imprecise studies to favour nuts (online Supplementary Appendix S7). Both Egger's and Begg's tests suggested publication bias (Egger's P = 0·006; Begg's P = 0·067). However, the trim and fill method did not remove any studies or indicate that there were any studies missing.

Retrospective studies

One study from India[57] compared the odds of consuming nuts in hospitalised myocardial infarction patients in comparison with community controls. Of the 500 participants (407 men and ninety-three women), 205 of the men and forty-five of the women were cases. The fully adjusted OR was not provided for men, and it was 10·9 (95 % CI 2·49, 48·2) for women. The least adjusted OR was 2·02 (95 % CI 1·24, 3·30) in men and 9·11 (95 % CI 2·22, 43·28) in women. The study is at a high risk for bias with an NOS score of 5.

Discussion

In this systematic review of twenty prospective cohort studies involving 467 389 participants and 13 226 CVD outcomes including 10 120 deaths from CVD, comparing highest with lowest nut consumers, we found that nut consumption was associated with a 19 % lower risk of all-cause mortality, a 44 % lower risk of total CVD, a 27 % lower risk of death from any type of CVD, a 34 %

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lower risk of all CHD, a 30 % lower risk of CHD mortality and a 47 % lower risk of sudden cardiac death, as well as a statistically non-significant reduction in risk of non-fatal CHD by 29 % and stroke mortality by 17 %. Further, a 4-weekly servings increment in nut intake, an amount consistent with the DASH diet[34], was associated with a 19 % lower risk of all-cause mortality, a 28 % lower risk of total CVD, a 19 % lower risk of non-fatal CHD, a 75 % lower risk of sudden cardiac death and a statistically non-significant reduction in CVD mortality by 22 %, CHD mortality by 22 % and stroke mortality by 15 %. No evidence of association between nut intake and total stroke was found, but the quality of evidence was very low for this outcome. The estimates across studies were homogeneous for each outcome, except for total CHD, non-fatal CHD and total stroke. Of the statistically significant outcomes, all-cause mortality, total CVD and CHD mortality had a moderate quality of evidence. Taken together, our findings are compatible with findings of previous systematic reviews that similarly found evidence of an inverse association of nut consumption with all-cause mortality[15,19], total CVD[16,19], CVD mortality[15], total CHD[19,20], CHD mortality[18] and non-fatal CHD[18] and no evidence of association for total stroke[18–20].

The role of nuts as part of a healthy diet is not well emphasised in most guidelines. For example, the World Health Organization[58] states that the evidence supporting unsalted nuts for decreasing CVD risk is 'probable', but the quality of the evidence underlying this statement was not evaluated using GRADE criteria. The American Heart Association's dietary guidelines simply refer to nuts as part of the DASH diet[59]. The Canada Food Guide states that 60 ml of nuts makes up a serving of 'meat and alternatives' with no other information provided[60]. The 2010 *Dietary Guidelines for Americans* provide the most detail on the possible benefits of nuts, stating that they are a nutrient-dense, high-fibre food and a good source of protein, and provide a recommended intake of 4 ounces of nuts (and seeds/soya products)/week for a 8368 kJ (2000-kcal) diet[61]. Nonetheless, these 2010 guidelines state that 'moderate' evidence exists on nut consumption and reduced CVD risk factors, indicating a need to consider the most updated evidence on nut consumption and CVD outcomes, which if warranted may prompt organisations to place greater emphasis on nut consumption. In some regions of the world where contamination with aflatoxins is common, it may not be appropriate to recommend increased nut consumption for populations[62].

Our findings of an inverse association between nut consumption and CVD outcomes are consistent with meta-analyses of observational studies[15–20,63–67] and RCT[9,68–70] showing that following a Mediterranean diet that includes nuts is related to a lower risk of CVD. However, there are currently no clinical trials that independently assess nut consumption and CVD outcomes. In the absence of randomised trials, we focused on the available epidemiologic data. Although nut consumption is inversely associated with several outcomes (total CVD, CVD mortality, CHD mortality, sudden cardiac death), the strongest association is found for total CVD and CHD mortality. The main data sources on nut intake and CVD events come from five cohorts: the Adventist Health Study[14,45,46], the Nurses' Health Study[13,40–43], Physicians' Health Study[11,13,40,44], the Iowa Women's Health Study[28] and the Southern Community Cohort Study[21]. These cohorts have a prolonged follow-up (4–30 years), large sample size (31 208–86 016 participants) and assessed populations living in the USA. Of these studies, the Adventist Health Study is unique in that it focused on a population that largely abstains from alcohol and tobacco and frequently follows a lacto-vegetarian diet, whereas the Southern Community Cohort Study recruited participants at an elevated risk of cancer including individuals with low incomes, African-Americans and people from rural settings. Nevertheless, each found a significant inverse association between nut intake and CVD outcomes, with a pooled relative risk of 0·73 (95 % CI 0·68, 0·78) for nut consumption and CVD mortality. There are also numerous clinical trials investigating the effect of nuts on CVD surrogate measures[10]. Collectively, these showed beneficial effects on LDL-cholesterol, ratio of LDL:HDL-cholesterol, total cholesterol and TAG[71,72]. Taken together, the evidence from observational studies of health outcomes and clinical trials of surrogate measures indicates a consistent role of nuts in a heart-healthy diet.

There are a number of dietary constituents in nuts that may explain their observed beneficial associations with multiple causes of mortality. Despite almost 80 % of energy coming from fat[73], nuts are low in SFA (4–16 %) and high in both monounsaturated and polyunsaturated fat, which have beneficial effects on inflammation, lipid markers, blood pressure and are inversely associated with CVD outcomes[7,74–77]. Nuts also are a good source of many micronutrients that are individually associated with decreases in CVD risk including folate, antioxidant vitamins and compounds, plant sterols, Ca, Mg and K[7]. In addition, increased nut consumption may displace intake of less healthy foods such as highly refined sugars and starches, reducing glycaemic load and risk of CVD, other chronic diseases including cancer and all-cause mortality[78]. Therefore, the finding of benefit with nut intake that is nonspecific to a single outcome is in keeping with its impact on a wide range of aetiologies and physiologic pathways.

We found limited data on the effects of different types of nuts (e.g. peanuts and tree nuts including almonds, hazelnuts, walnuts and pistachios) on mortality and CVD risk, which precluded an assessment of their association with most CVD outcomes. Three studies[21,22,40] showed an association of peanut consumption with a lower risk of all-cause mortality and CHD mortality. Two of those studies[21,22] also showed an inverse association of peanut consumption with CVD mortality, whereas one study[43] found an inverse association with total CHD. Two studies providing data on stroke mortality[22,40] did not find evidence of an association. The relative risk estimates for peanut consumption and these outcomes were similar to those found in the meta-analysis for all nuts. Walnuts were also associated with a lower risk of all-cause mortality and CVD mortality[51], although the relative risk estimates were markedly lower than the summary relative risk estimates for all nuts. However, the relative risk estimates for all-cause mortality and CVD mortality for all types of nuts excluding walnuts within the same study were similarly lower compared with the summary relative risk estimates for all other studies. This indicates that the lower relative risk estimates for walnuts may be reflective of study differences rather than the effect of walnuts. We also found a minimal impact of sex or study quality on the relative risk estimates for all outcomes. Owing to the small number of available studies, our analyses of the effect of nuts on different types of stroke (haemorrhagic *v.* ischaemic stroke) were

inconclusive. Larger studies providing data on the associations between different types of nuts and total and stroke subtypes are needed.

In our analyses by geographic region, the estimates for the association between nut intake and outcomes were not materially different in North America compared with Europe. This assessment is limited by the small number of studies for each geographic region (two to five), as well as the small number of outcomes with sufficient data to analyse. In addition, these findings may not be generalisable to geographic regions outside of North America and Europe, particularly to low- and middle-income countries where there are different types of nuts available and varying dietary patterns. Further work is needed in these regions.

This study has several strengths. First, a thorough systematic search of the literature was conducted, with each study evaluated for the risk of bias. Second, retrospective observational designs (e.g. case–control studies) were excluded, given their limitations in assessing dietary effects on long-term clinical outcomes. Third, the quality of the evidence was evaluated using the GRADE approach to help facilitate translation of our findings into guidelines. Last, the quantitative synthesis was focused on studies measuring comparable outcomes using similar designs, reducing methodological heterogeneity.

This study also has some limitations. Measurement error in assessing dietary intake may dilute associations towards the null, resulting in attenuated associations between nut consumption and CVD outcomes. Second, because of a modest number of cohorts, dose–response relationships or differences between key subgroups (based on age, sex, geographic region, measurement tools) could not be robustly quantified. Third, data on two outcomes (total CVD and sudden cardiac death) were available only from an individual cohort study for each, which precludes performing meta-analyses for these outcomes. Fourth, the lack of available data did not allow us to adequately assess the association of individual types of nuts (e.g. peanuts *v.* tree nuts) with CVD outcomes or the effect of salted *v.* unsalted nuts. Fifth, because of the small number of studies identified, we could not statistically assess the potential for publication bias for any outcome but all-cause mortality. Given that only eleven large prospective cohorts are represented, it is possible that unpublished data may exist, or that an important literature published in non-English language journals was missed by our search strategy. A visual inspection of the funnel plot and Egger's and Begg's tests suggested possible publication bias. However, the trim and fill method did not detect any missing studies, which suggests that publication bias may be present but that our findings are minimally affected by publication bias. Last, our analysis used the most-adjusted multivariable models to compute summary estimates of association. We attempted to assess the potential impact of over-adjustment; however, only four studies included 'intermediately adjusted models' – that is those that adjusted for the most-relevant confounders (smoking, age, sex and total energy), but not potential causal intermediates (blood pressure or anti-hypertensive medications, serum lipids or lipid-lowering medications). Models adjusted for both potential confounders and intermediate variables are more likely to provide a conservative estimate of association because of possible over-adjustment for the effect of causal intermediates[79,80].

Conclusions

This systematic review and meta-analysis of large, generally well-designed prospective cohort studies showed that nut consumption is inversely associated with all-cause mortality, total CVD, CVD mortality, total CHD, CHD mortality and sudden cardiac death, and a statistically non-significant reduction in risk of non-fatal CHD and stroke mortality. No evidence of an association between nut intake and total stroke was found, but the quality of evidence for this outcome was very low. We judged the quality of evidence as moderate for all-cause mortality, CVD mortality and CHD mortality, as low for total CVD and sudden cardiac death and as very low for total CHD, non-fatal CHD, total stroke and stroke mortality. Our study supports the statement that higher nut consumption is associated with a decreased risk of CVD events and all-cause mortality. More data are needed on the effects of individual types of nuts on CVD outcomes and mortality, and in populations outside North America and Europe.

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A. J. M., A. M. and R. J. d. S. designed the research question. A. J. M. and R. J. d. S. conducted the research. A. J. M. and R. J. d. S. analysed the data and performed the statistical analysis. A. J. M., R. J. d. S., S. S. A., D. M. and A. M. wrote the paper. A. M. had primary responsibility for the final content. All authors read and approved the final manuscript.

The authors declare that there are no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit http://dx.doi.org/doi:10.1017/S0007114515004316

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