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Review

# Nut consumption and risk of cardiovascular disease events and all-cause mortality: A systematic review and dose–response meta-analysis of prospective cohort studies

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ABSTRACT

*Background:* Evidence for the effects of nut consumption on cardiovascular disease (CVD) events and all-cause mortality has been reported inconsistently.
*Aims:* To assess the associations between nut consumption and CVD events and all-cause mortality.
*Methods:* We searched the Web of Science, Embase and PubMed up until 24 October 2023. In order to compute relative risks (RRs) and 95% confidence intervals (CIs), random-effects models were employed. Restricted cubic splines were performed to explore potential linear or non-linear associations. Heterogeneity was assessed (Cochran Q statistic) and quantified ($I^2$-statistic). NutriGrade assessed the certainty of the evidence.
*Results:* Thirty-three publications (63 studies) were included. Comparisons between individuals with the highest versus lowest intake of nuts resulted in RRs (95% CIs) for coronary heart disease (CHD), stroke, CVD, CVD mortality and all-cause mortality of 0.81 (0.75–0.87), 0.91 (0.84–0.99), 0.86 (0.82–0.91), 0.74 (0.70–0.78) and 0.77 (0.73–0.81), respectively. With per 28-g increases in weekly nut intake, the RRs (95% CIs) for CHD, stroke, CVD, CVD mortality and all-cause mortality were 0.96 (0.95–0.97), 0.99 (0.97–1.01), 0.98 (0.97–0.99), 0.90 (0.86–0.94) and 0.92 (0.90–0.94), respectively. Nut intake was linearly associated with incidence of stroke ($P_{non\text{-}linearity} = 0.691$), CVD ($P_{non\text{-}linearity} = 0.101$) and CVD mortality ($P_{non\text{-}linearity} = 0.069$) and non-linearly associated with CHD ($P_{non\text{-}linearity} < 0.05$) and all-cause mortality ($P_{non\text{-}linearity} < 0.001$).
*Conclusions:* This systematic review and meta-analysis revealed an association between nut consumption and reduced risk of CVD and all-cause mortality. It highlighted the importance of nuts as a dietary supplement in the primary prevention of CVD and all-cause mortality.


## 1. Abbreviations

| | |
|---|---|
| BMI | body mass index |
| CHD | coronary heart disease |
| CI | confidence interval |
| CVD | cardiovascular disease |
| GBD | Global Burden of Disease |
| HR | hazard ratio |
| MeSH | Medical Subject Headings |
| NOS | Newcastle-Ottawa scale |
| OR | odds ratio |
| RoB | risk of bias |
| RR | relative risk |

## 2. Background

As reported in the Global Burden of Disease (GBD) study, cases of total cardiovascular disease (CVD) worldwide reached 621 million in 2021, with an age-standardized prevalence reaching 7242 per 100,000 [1]. Further, the number of deaths from CVDs increased to 20.5 million in 2021, with an age-standardized mortality rate of 245 per 100,000, while disability-adjusted life years reached 42.2 million [1]. CVD has become a great threat to public health [2,3]. It is

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therefore essential that the modifiable cardiovascular risk factors for the prevention of CVD and reduction of burden of disease be identified.

The GBD study reported that dietary risks accounted for 6.58 million CVD deaths overall in 2021 [4]. Low nut consumption was one of the major dietary risk factors mentioned by this study, indicating that nuts may be especially protective against CVD because of their bio-active content, including macronutrients, fat-soluble bio-actives, fibres, vitamins, minerals and phenols [5]. In prospective cohort studies, consuming nuts is an effective way to reduce the risks of CVD and all-cause mortality [6–11]. Besides, numerous meta-analyses have assessed the association between nut consumption and the risk of CVD and mortality [12–18]. The most recent meta-analysis was based on randomized controlled trials and was conducted by Houston et al. [12]. It included 139 studies and reported the preventive effects of nuts on blood lipids, one of the risk factors for CVD, but only eight of the 139 studies (6%) had a duration > 1 year [12]. A meta-analysis that included 18 prospective studies, by Chen et al. [15], reported the preventive effect of nut intake on all-cause mortality and CVD mortality. Another meta-analysis, by Becerra-Tomás et al. [14], explored the associations between nut intake and incidence and mortality of CVD. They reported that nut consumption was not associated with stroke incidence. A meta-analysis by Arnesen et al. [18] did not search databases such as PubMed and Web of Science.

There are strict criteria for the selection of subjects included in randomized controlled trials, and follow-up times are relatively short. This limits the applicability of the study results to the general population and the evaluation of long-term effects of exposure on outcomes. Furthermore, since the latest meta-analysis of cohort studies [14], several new cohort studies have been published that provide up-to-date evidence based on larger sample sizes, longer observation periods and more diverse ethnicities, which have reported inconsistent results [8,9,11,19–26].

Taking the above issues into consideration, and based on Web of Science, PubMed and Embase, we conducted a systematic review and meta-analysis of cohort studies to evaluate the associations between nut intake and risks of stroke, coronary heart disease (CHD), CVD, CVD mortality and all-cause mortality and examined the dose–response relationship. We aimed to provide up-to-date scientific evidence and clarify the effect of nut intake on the risk of CVD and all-cause mortality based on a broader population.

## 3. Methods

### 3.1. Search strategy

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Our protocol was registered in the international prospective register of systematic reviews (PROSPERO, CRD42023460353). To find enough relevant studies, we thoroughly examined Web of Science, PubMed and Embase until 24 October 2023. The MeSH terms and key words utilised in this search strategy included: nut, peanut, walnut, almond; cerebrovascular disorders, cardiovascular disease, coronary heart disease, stroke, mortality, death; and prospective, cohort and longitudinal studies. Detailed search strategies are shown in Table A.1. Additional eligible articles were identified by manually searching the literature cited in original and review articles.

### 3.2. Selection criteria

Studies were accepted when they met the following criteria: (1) age of participants ≥ 18 years; (2) prospective cohort design; (3) consumption of almonds, peanuts, walnuts, cashews, pistachios or unspecified 'other' or 'mixed' nuts assessed as exposure; (4) reported all-cause mortality, CVD mortality or incidence (including only non-fatal or a combination of non-fatal and fatal outcomes of a composite of different CVD outcomes) as the outcome; (5) reported odds ratios (ORs), hazard ratios (HRs) or relative risks (RRs) along with 95% confidence intervals (CIs) (or these could be calculated according to the reported data) and (6) described nut intake at ≥ 3 levels (or continuous) in order to be able to conduct dose–response meta-analyses.

Studies were excluded if they were cross-sectional, case-control, randomized controlled trials or animal experiments in design. We also excluded reviews, editorials, non-human studies, conference abstracts, proceedings, guidelines, letters and articles that examined associations with foods other than nuts. Where several articles based on the same cohort showed different outcomes, both papers were included (e.g. CHD in one article [27] and stroke in another [28]). If based on the same cohort and both publications came to the same conclusion, the study with the longer follow-up duration or the larger sample size was included.

### 3.3. Data extraction and quality assessment

Two investigators (M.L. and X.H.) independently extracted the following data: author, publication year, race, region, duration of follow-up, cohort name, category of nut and method used for its assessment, nut intake, outcomes and methods assessment, number of cases and sample size for specific levels of nut consumption, effect estimates (RRs/HRs/ORs and 95% CIs), sex, baseline age and adjusted variables. In order to assess the quality of the original studies, we employed the Newcastle-Ottawa Scale (NOS) [29] in terms of population selection, group comparability and outcome assessment, with scores ranging from 0 to 9. Based on the scores, the quality of studies was assessed as low (0–3), medium (4–6) or high (7–9).

The NutriGrade scoring system was used to rate the overall meta-evidence quality [30]. This system is applicable to the rating of meta-evidence in nutrition research, with a maximum score of 10 points. According to the obtained scores, studies with high, moderate, low and very low meta-evidence quality are scored 8–10, 6–7.99, 4–5.99 and 0–3.99 points, respectively [30]. Risk of bias (RoB) was assessed using the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions version I) [31,32]. Each of the seven domains of the ROBINS-I tool were rated as being at low, moderate, serious or critical RoB, or no information [31]. After completing consensus on the seven domains, the overall RoB for each study was assessed using the criteria in Table A.2. All discrepancies were discussed and resolved with a third author (D.H.).

### 3.4. Data collation and analysis

Due to the differences in the nut exposure units in each study, we uniformly translated nut intake into grams per week (g/week). This conversion was conducted in line with the definitions in the original articles. When portion size was not reported [28,33], recommended conversions (1 serving = 28 g; 1 ounce = 28 g) were adopted. For studies in which the lowest nut intake was not set as reference [34], the effect estimates were re-evaluated with the lowest consumption of nuts as reference. If only HRs were provided, we assumed that the HRs were approximate to RRs [35]. If there were insufficient numbers of cases in each of the exposure groups being reported [36], we evaluated according to the available data. If there were only the aggregate number of participants or person-years reported, we assumed the groups to be the same size [36]. For the free of limitations lowest category [16,37], the lower limit was deemed to be 0. For the free of limitations highest category, the interval width was

considered to be equal to the prior range. When the range of nut intakes was provided [36], its mid-value was regarded as estimates for exposure. When relevant information regarding different sexes or regions was reported in a publication, we considered each as independent studies. We calculated the pooled effect size for total stroke or total CHD for these studies with a fixed-effects model if a study reported separately on the subtype of stroke or CHD. If a study reported total CVD or subtype of CVD incidence (i.e. stroke, CHD, atrial fibrillation), we included it to calculate the pooled RRs for CVD incidence, which were used accordingly in the present meta-analysis. In order to calculate pooled risk estimates [38], a random-effects model was adopted. For the sake of estimation of study-specific RRs and 95% CIs with 28-g/week increments in nut intake, we adopted generalized least squares regression [39], while the random-effects model was employed to count the pooled effect estimates. Studies that provided data on doses for ≥ 3 categories were selected to explore possible non-linear dose–response relationships by restricted cubic splines, with three knot percentiles (25th, 50th and 75th) on nut consumption distribution [40].

In order to evaluate heterogeneity, Cochrane Q and $I^2$ statistics were calculated. Statistically significant means a $P$ value < 0.1 for Q statistics. For the $I^2$, heterogeneity was stratified as high (75%), moderate (50%) or low (25%). When ≥ 10 studies were involved, we conducted subgroup analysis and meta-regression to explore the potential sources of heterogeneity [41]. Subgroups were stratified based on sex, region, years of follow-up, sample size, number of cases and adjustments (alcohol intake, physical activity, energy intake, red or processed meat consumption, fruit and vegetable intake and education). Meta-regression analysis revealed the heterogeneity between subgroups. Sensitivity analyses were performed by excluding one study at a time and re-evaluating the pooled RRs and 95% CIs to test the stability of the results. For the purpose of investigating publication bias, we used funnel plots and Egger's linear regression test in analyses that included ≥ 10 studies [42]. Asymmetry of the funnel plot and $P$ value of the Egger's test revealed publication bias. $P < 0.05$ was statistically significant. When there was publication bias, we employed the trim-and-fill method to adjust the data [43].

Statistical analyses were performed using Stata 17.0 (Stata Corp, College Station, TX). Statistical tests were performed on a two-sided basis, and $P$-values < 0.05 were deemed to be significant, unless otherwise stated.

## 4. Results

### 4.1. Characteristics of the included studies

Overall, 3657 publications were retrieved. After eliminating 987 papers due to duplication, we scanned the type of publications, subject, title or abstract, further excluding 2485 articles, leaving 185 full-text papers that were assessed in more detail (Fig. 1). After screening the full texts of these articles, 152 articles were excluded for various reasons (see Fig. 1). Finally, 33 articles [6–11,19–28,34,44–59] covering 63 prospective cohort studies with 247,322 cases and 2,174,325 participants were included.

Detailed characteristics of the included articles are shown in Table 1. The sample sizes of the selected studies varied from 826 to 566,398 subjects, with follow-up durations ranging from 3.5 to 34 years. Six articles (six studies) [6,9,10,27,46,59] were included for CHD incidence; nine articles (nine studies) [6–10,24,28,34,46] for stroke incidence and 12 articles (14 studies) [6–10,24,27,28,34,46,57,59] for CVD incidence. Seventeen articles (22 studies) [6,9,10,20,21,24,26,44,45,48,50–52,54,55,58,59] were included for CVD mortality and 26 articles (31 studies) [6,9–11,19–26,44,45,47–56,58,59] for all-cause mortality. Among the available articles, 16 were from studies conducted in America [7,9–11,21,25–28,44,47,49,53,57–59], eight in Asia [8,19,20,22–24,48,50], five in Europe [34,46,51,55,56], one in Australia [54], one in America and Canada [45], one in China, Africa and America [52] and one in multiple countries [6]. All studies collected nut consumption data using food-frequency questionnaires. Five articles (15.2%) had low RoB [8,44,46,48,53] and 28 articles (84.8%) had moderate RoB [6,7,9–11,19–28,34,45,47,49–52,54–59]. The quality of meta-evidence for the association between nut consumption and risks of CHD, stroke, CVD, CVD mortality and all-cause mortality was moderate, moderate, high, high, and high, respectively (Table A.3).

### 4.2. Nut consumption and risk of CHD

Six studies [6,9,10,27,46,59] involving 21,298 cases and 420,276 participants were included for CHD. When comparing highest versus lowest nut consumption, the pooled RR was 0.81 (95% CI 0.75–0.87; $I^2 = 11.5\%$; $P_{\text{heterogeneity}} = 0.342$; Fig. 2). Sensitivity analysis showed that the result was stable.

The dose-response meta-analysis included five studies [6,9,10,46,59]. The pooled RR was 0.96 (95% CI 0.95–0.97; $I^2 = 0.3\%$, $P_{\text{heterogeneity}} = 0.405$; Fig. 3) per 28-g/week increase in nut consumption. Evidence of non-linearity was observed ($P_{\text{non-linearity}} < 0.05$; Fig. 4A). Sensitivity analysis showed that the result was stable.

### 4.3. Nut consumption and the risk of stroke incidence

Nine studies [6–10,24,28,34,46] involving 19,846 cases and 586,761 participants were included for stroke. When comparing highest versus lowest nut consumption, the pooled RR was 0.91 (95% CI 0.84–0.99; $I^2 = 34.2\%$; $P_{\text{heterogeneity}} = 0.144$; Fig. 2). Sensitivity analysis indicated that the result was stable.

The dose–response meta-analysis included six studies [6,9,10,28,34,46]. The pooled RR for stroke incidence was 0.99 (95% CI 0.97–1.01; $I^2 = 36.0\%$, $P_{\text{heterogeneity}} = 0.167$; Fig. 3) per 28-g/week increase in nut consumption. There was no evidence indicating non-linearity between nut consumption and stroke incidence ($P_{\text{non-linearity}} = 0.691$; Fig. 4B). Sensitivity analysis indicated that the result remained stable.

### 4.4. Nut consumption and the risk of CVD incidence

Fourteen studies (12 articles) [6–10,24,27,28,34,46,57,59] involving 64,753 cases and 780,826 participants were included for CVD. When comparing highest versus lowest nut consumption, the pooled RR was 0.86 (95% CI 0.82–0.91; $I^2 = 37.0\%$; $P_{\text{heterogeneity}} = 0.081$; Fig. 2). With Egger's test and funnel plot, there was no evidence of publication bias ($P = 0.147$, Fig. A.1). Meta-regression revealed physical activity and consumption of fruit and vegetables may have been the potential sources of heterogeneity ($P_{\text{region}} = 0.002$, $P_{\text{follow-up years}} = 0.001$, $P_{\text{NOS score}} < 0.001$, $P_{\text{BMI}} = 0.041$, Table A.4). Sensitivity analysis suggested that the result remained stable (Fig. A.2).

The dose–response meta-analysis consisted of 11 studies (nine articles) [6,7,9,10,28,34,46,57,59]. The pooled RR for CVD incidence was 0.98 (95% CI 0.97–0.99; $I^2 = 61.1\%$; $P_{\text{heterogeneity}} = 0.004$; Fig. 3) per 28-g/week increase in nut consumption. We also explored the potential linearity or non-linearity between nut consumption and CVD incidence. No evidence of non-linearity observed ($P_{\text{non-linearity}} = 0.101$; Fig. 4C). With Egger's test and funnel plot, there was no evidence of publication bias ($P = 0.635$; Fig. A.3). Meta-regression revealed that sex and fruit and vegetable intake may have been the potential sources of heterogeneity ($P_{\text{sex}} = 0.017$, $P_{\text{fruits}}$

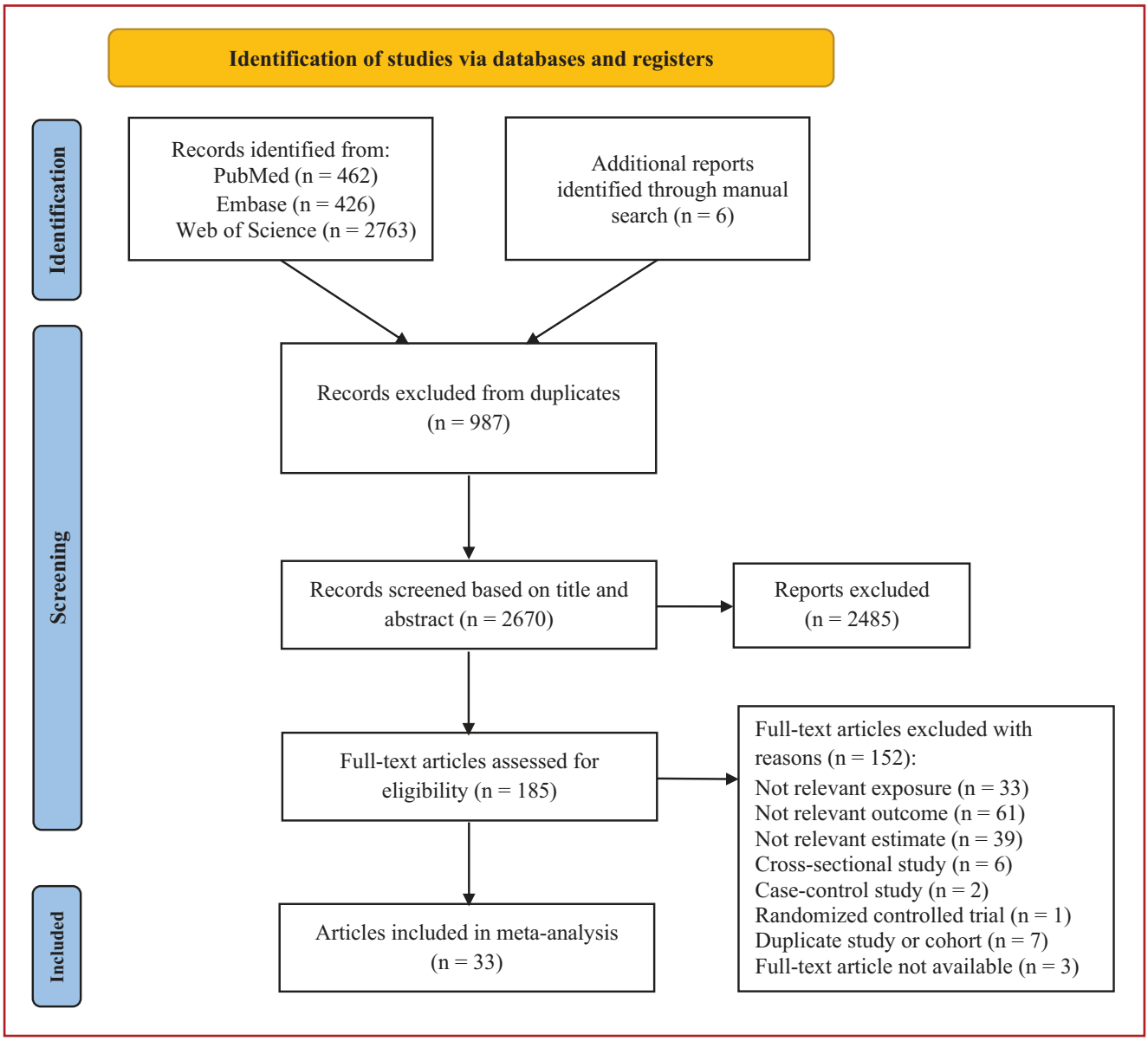



**Fig. 1.** Flowchart of study selection.

and vegetables = 0.028; Table A.5). Sensitivity analysis showed that the result remained stable (Fig. A.4).

### 4.5. Nut consumption and the risk of CVD mortality

For CVD mortality, there were 22 studies (17 articles) [6,9,10,20,21,24,26,44,45,48,50–52,54,55,58,59] covering 38,933 cases and 1,497,610 subjects. Among 21 studies that compared highest versus lowest nut consumption (excluding [50]), the pooled RR for CVD mortality was 0.74 (95% CI 0.70–0.78; $I^2$ = 17.0%; $P_{heterogeneity}$ = 0.239; Fig. 5). With funnel plot and Egger's test, there was no evidence of publication bias ($P$ =0.853; Fig. A.5). Meta-regression did not reveal the source of heterogeneity between subgroups (Table A.6). Sensitivity analysis showed that the result remained stable (Fig. A.6).

The dose–response meta-analysis consisted of 15 studies (12 articles) [6,9,10,26,44,48,50–52,54,58,59]. The pooled RR for CVD mortality was 0.90 (95% CI 0.86–0.94; $I^2$ = 90.8%, $P_{heterogeneity}$ < 0.001; Fig. 6) per 28-g/week increase in nut consumption. We also explored the potential linearity or non-linearity between nut consumption and CVD mortality. No evidence of non-linearity was observed ($P_{non\text{-}linearity}$ = 0.069; Fig. 4D). With Egger's test and funnel plot, there was evidence of publication bias ($P$ < 0.001; Fig. A.7). When trim-and-fill was adopted to adjust the data, the result was consistent (RR 0.90, 95% CI 0.68–0.94). Meta-regression revealed energy intake may have been the source of heterogeneity between subgroups ($P_{energy\ intake}$ = 0.049; Table A.7). Sensitivity analysis showed that the result remained stable (Fig. A.7).

### 4.6. Nut consumption and the risk of all-cause mortality

For all-cause mortality, there were 31 studies (26 articles) [6,9–11,19–26,44,45,47–56,58,59] covering 142,762 cases and 1,697,737 subjects. Among 30 studies that compared highest versus lowest nut consumption (excluding [50]), the pooled RR for all-cause mortality was 0.77 (95% CI 0.73–0.81; $I^2$ = 67.1%; $P_{heterogeneity}$ < 0.001; Fig. 5). With Egger's test and funnel plot, there was evidence of publication bias ($P$ = 0.014; Fig. A.9). When trim-and-fill was adopted to adjust the data, the result was consistent

**Table 1**
Characteristics of included cohort studies.

| Study | Cohort | Country | Duration of follow-up (years) | Age (years) | Sex | Sample size | Outcome | Cases | Adjustment factors | NOS score |
|---|---|---|---|---|---|---|---|---|---|---|
| Zhang et al., 2023 [11] | NHANES | US | 15 | 56–60 | F/M | 5090 | All-cause mortality | 1174 | Age, sex, race/ethnicity, BMI, education level, family income-poverty ratio, drinking status, leisure-time physical activity, smoking status, dietary energy, consumption of red meat, processed meat, vegetables, and fruit, duration of DM, DM medication use, self-reported hypertension, hypercholesterolaemia, CVD, supplement use, haemoglobin A1c | 6 |
| Yang et al., 2022 [19] | Mr. Osteoporosis and Ms. Osteoporosis Study in Hong Kong | China | 13.75 | 65 | F/M | 3995 | Cancer mortality | 469 | Sex, age, dietary energy, BMI, physical activity, systolic BP, medical history (DM, hypertension, stroke, heart attack, angina, congestive heart failure, cancer), smoking habits, alcohol drinking, education level | 6 |
| Wang et al., 2022 [21] | NHANES | US | 11 | 20 | F/M | 6072 | All-cause mortality | 1033 | Age, sex, race/ethnicity, energy, protein, carbohydrate, sugar, fat, smoking, alcohol use, obesity, total cholesterol, triglycerides, high-density lipoprotein cholesterol, hypertension, DM, CHD, congestive heart failure, stroke, cancer, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, dietary phosphorus, dietary sodium, dietary potassium, serum potassium, serum phosphorus | 7 |
| | | | | | | | CVD mortality | [b] | | |
| He et al., 2022 [23] | CLHLS | China | 10 | 75–90 | F/M | 12,202 | All-cause mortality | 9766 | Age, sex, residence, living arrangement, insufficient finical support, activities of daily living, hypertension, DM, physical exercise, smoking, drinking | 6 |
| Wang et al., 2022 [22] | Shanghai Breast Cancer Survival Study | China | 8.27 | 20–75 | F | 2449 | All-cause mortality | 374 | Age at diagnosis, total energy intake, income, education, TNM stage, oestrogen receptor status, progesterone receptor status, menopause age, physical activity, Chinese Food Pagoda 2007 score, soy food intake, BMI, and weight change during first 5-year follow-up | 6 |
| Yamakawa et al., 2022 [20] | Takayama study | Japan | 16 | ≥ 35 | F | 15,724 | CVD mortality | 903 | Age, marital status, years of education, BMI, DM, hypertension, smoking status, alcohol intake, physical activity, use of any vitamin supplement, dietary intake (total energy, vegetables, fruits and red meat) and menopausal status (women only) | 7 |
| Liu et al., 2021 [25] | NHS and HPFS | US | 20 | 60–70 | M | 13,355 | CVD mortality | 775 | Age, sex, race, smoking status, alcohol consumption, physical activity, current multivitamin use, current aspirin use, family history of DM, MI or cancer, menopausal status and hormone use, BMI, presence of DM, hypertension or hypercholesterolaemia, consumption of other nuts, consumption of other foods: fruits, vegetables, sugar-sweetened beverages, meat, dairy products, whole grain and refined grain, total energy intake | 7 |
| | | | | | F/M | 90,340 | All-cause mortality | 30,263 | | |
| Mohammadifard et al., 2021 [24] | Isfahan Cohort Study | Iran | 13 | ≥ 35 | F/M | 6504 | Stroke | 157 | Age, education, residency, smoking status, daily physical activity, family history of CVD, DM, hypertension, hypercholesterolaemia, aspirin use, BMI, dietary factors including red meat, fish, fruits and vegetables, hydrogenated and non-hydrogenated vegetable oils, fast food, cereals, legumes, animal fats, sweets, soft drinks, beverages | 6 |

Table 1 (*Continued*)

| Study | Cohort | Country | Duration of follow-up (years) | Age (years) | Sex | Sample size | Outcome | Cases | Adjustment factors | NOS score |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | CVD | 751 | | |
| | | | | | | | CVD mortality | 179 | | |
| | | | | | | | All-cause mortality | 189 | | |
| Ivey et al., 2021 [9] | MVP | US | 3.5 | 52–76 | F/M | 179,827 | CHD | 9908 | Age, age*age, sex, race, BMI, smoking status, frequency of alcohol intake, level of physical activity, level of education, modified Dietary Approaches to Stop Hypertension (minus nuts) score | 5 |
| | | | | | | | Stroke | 3570 | | |
| | | | | | | | CVD mortality | 1311 | | |
| Imran et al., 2021 [26] | WHS | US | 19 | >=45 | F | 39,167 | CVD mortality | 959 | Age, BMI, alcohol, physical activity, smoking, postmenopausal status, family history of MI in a parent <60 years old, marital status, alternate healthy eating index score excluding nuts | 6 |
| Ikehara et al., 2021 [8] | JPHC | Japan | 15 | 45–74 | F/M | 74,793 | Stroke | 3599 | Public health centre, smoking status, alcohol consumption, physical activity, mental stress, vegetables, fruit, fish, soy and sodium intakes, total energy intake, BMI, history of hypertension, history of DM, and cholesterol-lowering drugs | 7 |
| | | | | | | | CVD | 4448 | | |
| de Souza et al., 2020 [6] | PURE | Multiple countries[a] | 9.5 | 50.5 | F/M | 124,329 | MI | 2559 | Follow-up time plus age, sex, location, and centre; lifestyle factors (education, tobacco use, BMI, waist-to-hip ratio, and physical activity, family history of CVD, DM and cancer); and diet factors (fish, fruits, vegetables, red/processed meat, legumes, and total energy) | 6 |
| | | | | | | | Stroke | 2915 | | |
| | | | | | | | CVD | 5979 | | |
| | | | | | | | CVD mortality | 2039 | | |
| Liu et al., 2019 [10] | NHS/HPFS | US | 34 | 20–55 | F | 16,217 | CHD | 2567 | Follow-up time plus age, sex, location, and centre; lifestyle factors (education, tobacco use, BMI, waist-to-hip ratio, physical activity, family history of CVD, DM and cancer); and diet factors (fish, fruits, vegetables, red/processed meat, legumes and total energy) | 5 |
| | | | 28 | 40–75 | M | | Stroke | 789 | | |
| | | | | | | | CVD | 3336 | | |
| | | | | | | | CVD mortality | 1663 | | |
| Amba et al., 2019 [44] | NIH-AARP Diet and Health Study | US | 15.5 | 50–71 | F/M | 566,398 | CVD mortality | 17,262 | Age, sex, BMI, level of education, race, self-reported health condition, smoking status, total energy consumption, alcohol consumption, vitamin consumption, physical activity, food groups including white meat, red meat, whole grains, vegetables and fruit | 7 |
| | | | | | | | All-cause mortality | 64,464 | | |
| Tharrey et al., 2018 [45] | Adventist Health Study-2 | US, Canada | 9.4 | ≥ 25 | F/M | 81,377 | CVD mortality | 2276 | Sex, race, energy intake, BMI, physical activity, smoking status, alcohol consumption, income, marital status, type of diet in the vegetarian spectrum, polyunsaturated fatty acids, saturated fatty acids, sodium, fibre, vitamins A, C, E, B6, B9 and B12, fat from meat products, fat from nuts | 6 |

Table 1 (*Continued*)

| Study | Cohort | Country | Duration of follow-up (years) | Age (years) | Sex | Sample size | Outcome | Cases | Adjustment factors | NOS score |
|---|---|---|---|---|---|---|---|---|---|---|
| Fadelu et al., 2018 [47] | National Cancer Institute–sponsored Cancer and Leukemia Group B | US | 6.5 | 60 | F/M | 826 | All-cause mortality | 177 | Calorie intake, age, sex, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, treatment group, BMI, physical activity, aspirin use, and glycaemic load | 7 |
| Larsson et al., 2018 [46] | Swedish Men and the Swedish Mammography | Sweden | 16 | 45–83 | F/M | 61,364 | MI | 4983 | Education, family history of MI < 60 years of age, smoking, walking/bicycling, exercise, aspirin use, consumption of alcohol, fruits, vegetables and total energy, BMI, history of DM, history of hypertension, history of hypercholesterolaemia | 8 |
| | | | | | | | Atrial fibrillation | 7550 | | |
| | | | | | | | IS | 3782 | | |
| Guasch-Ferré et al., 2017 [7] | NHSI | US | 21.5 | 20–55 | F | 76,364 | Stroke | 3322 | Age, Caucasian, BMI, physical activity, smoking status, physical examination for screening purposes, current multivitamin use, current aspirin use, family history of DM, family history of MI, family history of cancer, history of DM, history of hypertension, history of hypercholesterolaemia, intake of total energy, intake of alcohol, intake of red or processed meat, intake of fruits, intake of vegetables, menopausal status, hormone use, oral contraceptive use | 7 |
| | | | | | | | CVD | 6727 | | |
| | NHSI | US | 21.5 | 25–42 | F | 92,946 | CVD | 1915 | | |
| | HPFS | US | 22.5 | 40–75 | M | 41,526 | CVD | 5494 | | |
| Eslamparast et al., 2017 [48] | Golestan | Iran | 9 | 40–87 | F | 28,257 | CVD mortality | 911 | Age, sex, BMI, level of education, place of residence, smoking status, opium and alcohol consumption, physical activity, wealth score, DM, hypertension, total energy intake, main food groups (fish, red meat, chicken, fruit, vegetables, dairy products, eggs, total fibre), magnesium, zinc, copper | 7 |
| | | | | | M | 20,855 | CVD mortality | 1105 | | |
| | | | | | F | 28,257 | All-cause mortality | 1732 | | |
| | | | | | M | 20,855 | All-cause mortality | 2249 | | |
| Wang et al., 2016 [50] | Linxian NIT | China | 26 | 40–69 | F/M | 2445 | Heart disease mortality | 355 | Age, sex, commune, smoking, drinking, season, BMI, | 7 |
| | | | | | | | Stroke mortality | 452 | | |
| | | | | | | | All-cause mortality | 1501 | | |
| Di Giuseppe et al., 2015 [34] | EPIC | Germany | 8.3 | F: 49.2<br>M: 52.5 | F/M | 26,285 | Stroke | 288 | Age, sex, BMI, waist circumference, prevalent hypertension, hyperlipidaemia, DM, smoking status, educational attainment, sport activity, alcohol intake, red meat intake, whole-grain breads intake, fruit intake, vegetable intake, fish intake, cakes and cookies intake, confectionary intake, fried potatoes intake, other beverages intake, total energy intake | 8 |

Table 1 (*Continued*)

| Study | Cohort | Country | Duration of follow-up (years) | Age (years) | Sex | Sample size | Outcome | Cases | Adjustment factors | NOS score |
|---|---|---|---|---|---|---|---|---|---|---|
| Wang et al., 2016 [49] | HPFS | US | 21 | 40–75 | M | 47,299 | All-cause mortality | 1285 | PSA screening history, family history of prostate cancer, ethnicity, height, history of DM, current multivitamin use, current supplement use, tomato sauce, coffee intake, Mediterranean diet score, age at diagnosis, time period, time since diagnosis to food frequency questionnaire, energy, BMI, vigorous physical activity, smoking status, Gleason score, clinical T stage, primary treatment, family history of DM, family history of MI, family history of cancer, history of high BP, history of elevated cholesterol | 7 |
| Bonaccio et al., 2015 [55] | Moli-sani study | Italy | 4.3 | > 35 | F/M | 19,386 | CVD mortality | 104 | Age, sex, educational level, smoking, leisure-time physical activity, BMI, energy intake, Mediterranean diet score without nuts, C-reactive protein, platelet count, neutrophil to lymphocyte ratio | 6 |
| Luu et al., 2015 [52] | SCCS | Africa | 5.4 | 40–79 | F/M | 48,345 | All-cause mortality<br>CVD mortality | 334<br>1309 | Age, sex, education, occupation, household income, marital status, smoking pack-years, alcohol consumption, BMI, physical activity, vitamin supplement use, Charlson Comorbidity Index, metabolic conditions, total energy intake, red meat intake, chicken intake, seafood intake, vegetable intake, fruit intake | 8 |
| | | Europe | | | | 23,415 | CVD mortality | 548 | | |
| | SMHS/SWHS | China | 5.4 | 40–79 | F/M | 134,265 | CVD mortality | 2587 | | |
| Hshieh et al., 2015 [53] | PHS | US | 9.6 | 66 | M | 20,742 | All-cause mortality | 2732 | Age, BMI, alcohol consumption, smoking, exercise, calories, saturated fat consumption, fruit/vegetable consumption, red meat consumption, prevalent DM, hypertension, magnesium, fibre | 7 |
| Gopinath et al., 2015 [54] | Blue Mountains Eye Study | Australia | 15 | ≥ 49 | F/M | 2893 | CVD mortality | 546 | Age, sex, qualifications, total diet score, BMI, current smoking status, alcohol consumption, self-rated health, walking disability, presence of hypertension and/or DM, doctor-diagnosed history of cancer, angina, stroke, or acute MI | 7 |
| van den Brandt et al., 2015 [51] | Netherlands Cohort Study | Netherlands | 10 | 55–69 | F/M | 120,852 | All-cause mortality<br>All-cause mortality | 1044<br>8823 | Age at baseline, sex, cigarette smoking, number of cigarettes smoked per day, years of smoking, history of physician-diagnosed hypertension or DM, height, BMI, non-occupational physical activity, highest level of education, intake of alcohol, intake of vegetables, intake of fruit, energy, use of nutritional supplements, postmenopausal hormone replacement therapy | 8 |

Table 1 (*Continued*)

| Study | Cohort | Country | Duration of follow-up (years) | Age (years) | Sex | Sample size | Outcome | Cases | Adjustment factors | NOS score |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | CVD mortality | 2985 | | |
| Fernández-Montero et al., 2014 [56] | Seguimiento Universidad de Navarra | Spanish | 5 | 40 | F/M | 17,184 | All-cause mortality | 119 | Age, sex, total energy intake, BMI, smoking, alcohol, adherence to the Mediterranean diet, use of special diets, marital status, baseline hypercholesterolaemia, hypertension, physical activity, time of television watching, baseline presence of cancer, CVD or DM | 4 |
| Haring et al., 2014 [27] | ARIC study | US | 22 | 45–64 | F/M | 12,066 | CHD | 1147 | Age, sex, race, study centre, total energy intake, smoking, education, systolic BP, use of antihypertensive medication, high-density lipoprotein cholesterol, total cholesterol, use of lipid-lowering medication, BMI, waist-to-hip ratio, alcohol intake, sports-related physical activity, leisure-related physical activity, carbohydrate intake, fibre intake, magnesium intake | 9 |
| Khawaja et al., 2012 [57] | PHS | US | 24 | 40–84 | M | 21,054 | Atrial fibrillation | 3317 | Age, BMI, aspirin, beta-carotene, physical activity, smoking, cereal servings per week, fruit/vegetable servings per week, alcohol consumption, history of hypertension, history of hypercholesterolaemia, history of DM | 7 |
| Djoussé et al., 2010 [28] | PHS | US | 21.1 | 40–84 | M | 21,078 | Stroke | 1424 | Age, aspirin treatment assignment, BMI, alcohol consumption, smoking, fruit and vegetable intake, regular exercise, breakfast cereal, red meat, fish, dairy consumption, prevalent hypertension, DM, atrial fibrillation, CHD | 6 |
| Albert et al., 2002 [58] | PHS | US | 17 | 40–84 | M | 21,454 | CVD mortality | 201 | Age, aspirin treatment assignment, beta carotene treatment assignment, evidence of CVD, BMI, smoking, history of DM, history of hypertension, history of hypercholesterolaemia, alcohol consumption, vigorous exercise, vitamin E use at baseline, vitamin C use at baseline, multivitamin use at baseline, fish consumption, red meat intake, fruit and vegetable intake, dairy intake | 7 |
| Fraser et al., 1992 [59] | Seventh-day Adventists | US | 6 | ≥ 25 | F/M | 26,473 | Non-fatal MI | 134 | Age, sex, smoking, exercise, weight, and high BP | 7 |
| | | | | | | | CHD mortality | 463 | | |

ARIC: Atherosclerosis Risk in Communities Study; BMI: body mass index; BP: blood pressure; CHD: coronary heart disease; CLHLS: Chinese Longitudinal Healthy Longevity Survey; CVD: cardiovascular disease; DM: diabetes mellitus; EPIC: European Prospective Investigation into the Cancer and Nutrition Potsdam Study; F: female; HPFS: Health Professionals Follow-Up Study; JPHC: Japan Public Health Center–Based Prospective Study; M: male; MI: myocardial infarction: MVP: Million Veteran Program; NHANES: National Health and Nutrition Examination Surveys; NHS: Nurses' Health Study; NIH-AARP: National Institutes of Health-American Association of Retired Persons; NIT: Nutrition Intervention Trials; NOS: Newcastle-Ottawa scale; PHS: Physicians Health Study; PSA: prostate-specific antigen; PURE: Prospective Urban and Rural Epidemiology; SCCS: Southern Community Cohort Study; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; TNM: tumour–node–metastasis; US: United States; WHS: Women's Health Study.

[a] Argentina, Bangladesh, Brazil, Canada, China, India, Iran, occupied Palestine territory, Poland, South Africa, Saudi Arabia, Sweden, Tanzania, Turkey, United Arab Emirates, and Zimbabwe.

[b] The original article did not report the number of cases, nor did it provide sufficient data to support indirect estimation.

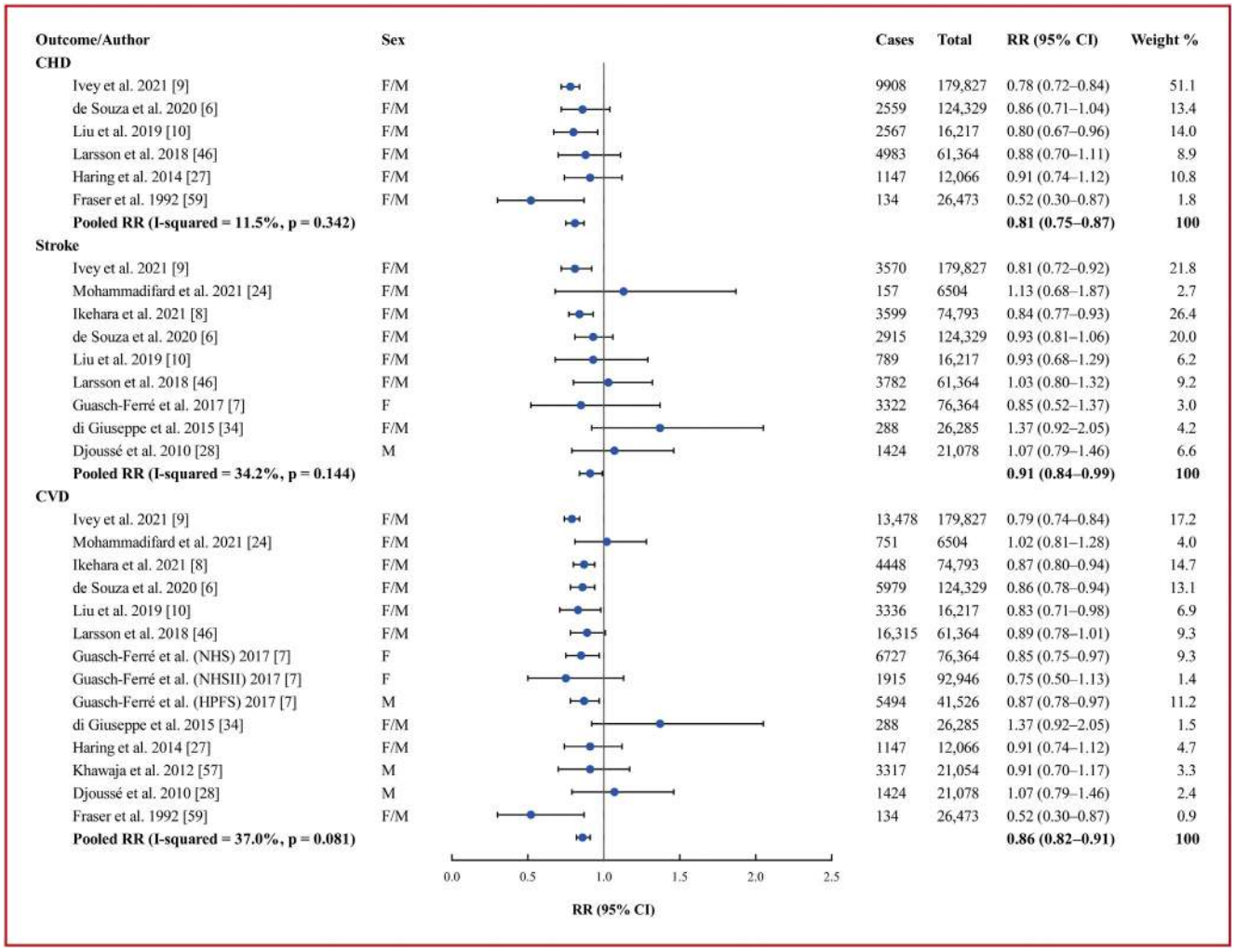



**Fig. 2.** Forest plot of the highest versus lowest total nut intake for the risk of CHD, stroke and CVD. Summary RRs were calculated using a random-effects model. CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; F: female; M: male; RR: relative risk.

(RR 0.77, 95% CI 0.73–0.81). Meta-regression did not reveal the source of heterogeneity between subgroups (Table A.8). Sensitivity analysis showed that the result remained stable (Fig. A.10).

The dose–response meta-analysis included 25 studies (21 articles) [6,9–11,19,20,25,26,44,47–56,58,59]. The pooled RR for all-cause mortality was 0.92 (95% CI 0.90–0.94; $I^2 = 85.4\%$, $P_{\text{heterogeneity}} < 0.001$; Fig. 6) per 28-g/week increase in nut consumption. We also explored the potential linearity or non-linearity between nut consumption and all-cause mortality. Evidence of non-linearity observed ($P_{\text{non-linearity}} < 0.001$; Fig. 4E). Further exploration revealed that when nut intake was lower than 233 g/week, the association between nut intake and all-cause mortality risk was statistically significant. With Egger's test and funnel plot, there was evidence of publication bias ($P < 0.001$; Fig. A.11). When trim-and-fill was adopted to adjust the data, the result was consistent (RR 0.92, 95% CI 0.90–0.94). Meta-regression did not reveal the source of heterogeneity between subgroups (Table A.9). Sensitivity analysis showed that the result remained stable (Fig. A.12).

## 5. Discussion

The current meta-analysis, based on 63 prospective cohort studies, revealed that consumption of nuts was associated with a declining risk of CHD, stroke, CVD, CVD mortality and all-cause mortality. Compared with a lower nut intake, there were 20%, 9%, 14%, 26% and 23% reductions in the risks of CHD, stroke, CVD, CVD mortality and all-cause mortality, respectively, with a higher nut intake. Sensitivity analyses showed the above results were stable.

The dose–response meta-analysis indicated that the risks of CHD, CVD, CVD mortality and all-cause mortality decreased by 4%, 2%, 10% and 8%, respectively, per 28-g/week increase in nut intake. The restricted cubic splines analysis further revealed a linear inverse relationship between nut consumption and risks of CVD and CVD mortality, but a non-linear inverse relationship with the risk of CHD. Although the restricted cubic splines showed an inverse association between nut consumption and risk of all-cause mortality as a whole, the association was significant when nut exposure was below 233 g/week, but was not significant when nut exposure was above 233 g/week due to a large CI. After checking the original articles [11,19,20,49,53,54], we observed that the disparity in exposure levels between adjacent groups in several studies was substantial, and the range of exposure intervals was excessively broad, potentially resulting in an inaccurate estimation of the actual exposure levels, which may be the main reason for the present result. Although the restricted cubic splines suggested that there was a potential negative correlation, there was no significant dose–response relationship between nut intake and stroke. The cohort study from the Nurses' Health Study and the Health Professionals Follow-Up Study also reported the same results [60]. The randomized trail from PREDIMED indicated that supplements of

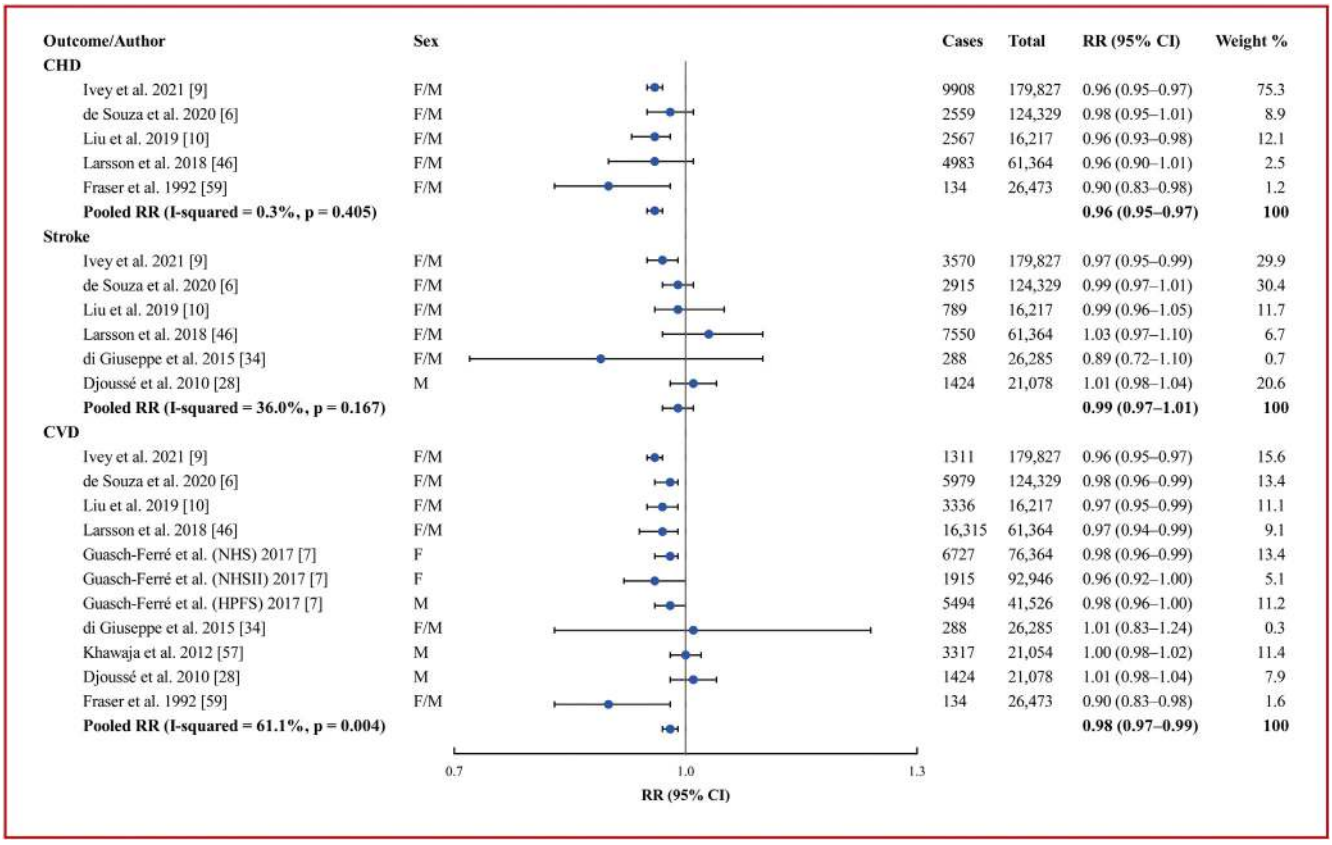



**Fig. 3.** Summary RRs for CHD, stroke and CVD per 28-g/week increase in nut consumption. Summary RRs were calculated using a random-effects model. CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; F: female; M: male; RR: relative risk.

30 g/day of mixed nuts or extra virgin olive oil in the Mediterranean diet can significantly reduce stroke risk [61]. A possible reason for the current results is differences in exposure levels across studies and the number of studies included. Also, the cohort studies by de Souza et al. [6] and di Giuseppe et al. [34] reported relatively low exposure levels. Besides, the accuracy of the measurement for exposure may also obscure the relationship between exposure and outcome.

We evaluated publication bias using funnel plots and Egger's linear regression test. The results showed that there was statistically significant publication bias in the outcomes of CVD mortality and all-cause mortality (Egger's test $P < 0.05$). For CHD and stroke outcomes, formal Egger's tests could not be performed due to the inclusion of < 10 studies. It should be emphasized that meta-analyses with small sample sizes are inherently more sensitive to publication bias. For CHD and stroke (with < 10 included studies), a small number of unpublished studies (especially those with small sample sizes or negative results) may significantly alter the pooled effect size, placing these outcomes in a high-risk category for publication bias. Additionally, it is noteworthy that among the included studies on CHD and stroke, those with larger sample sizes generally reported positive results (showing protective effects) [8–10]. Since large-sample studies typically carry more weight in meta-analyses, the potential absence of small-sample negative studies due to publication bias may further lead to an overestimation of the true protective effects for these two outcomes. More high-quality studies on CHD and stroke are still needed in the future to provide more reliable evidence.

Although Egger's test indicated significant publication bias in the outcomes of CVD mortality and all-cause mortality, we further assessed the impact of such bias on the robustness of the associations using the trim-and-fill method. The pooled effect size and 95% CI after adjustment by the trim-and-fill method were completely consistent with the original results, indicating that the conclusion regarding the protective association has good robustness.

Subgroup analyses were conducted to explore the potential sources of heterogeneity for CVD incidence, CVD mortality and all-cause mortality (Tables A.4–A.9). The results indicated that sex, region, follow-up years, study quality, body mass index (BMI) and intake of fruit and vegetables may influence the risk of CVD. Further, energy intake may influence CVD mortality.

We observed that the health effects of nuts in males and females were different, with a more significant protection among females. Based on a British cohort with over 20,000 participants and a > 25-year follow-up period, Pana et al. [62] revealed that men were more likely to suffer from CVD than females (68.9% vs 57.4%), which supports the present results. However, the number of studies that involved a single sex in the current research is relatively small, which may limit the applicability and stability of these results.

The GBD investigators have reported that the distribution of CVD varies among different countries and regions, with the highest age-standardized prevalence of CVD in Central Asia, Eastern Europe, South Africa and the Middle East and the lowest in Southeast Asia, Central Europe and high-income Asia Pacific in 2021 [1]. The diversity of behaviours, lifestyles and ethnic distribution in different regions may be an important reason for this difference. As is well known, CVD is a chronic non-infectious disease related to the environment and genes, which is characterized by complex aetiology, hidden onset, long course and difficult to cure. A recent cohort study by Wang et al. [63] that included 100,728 Chinese participants concluded that greater fruit and vegetable consumption could help reduce the risk of CVD. A meta-analysis by Zurbau et al. [64] that included 41 cohort studies also revealed the preventive effects of fruit and vegetables on CVD.

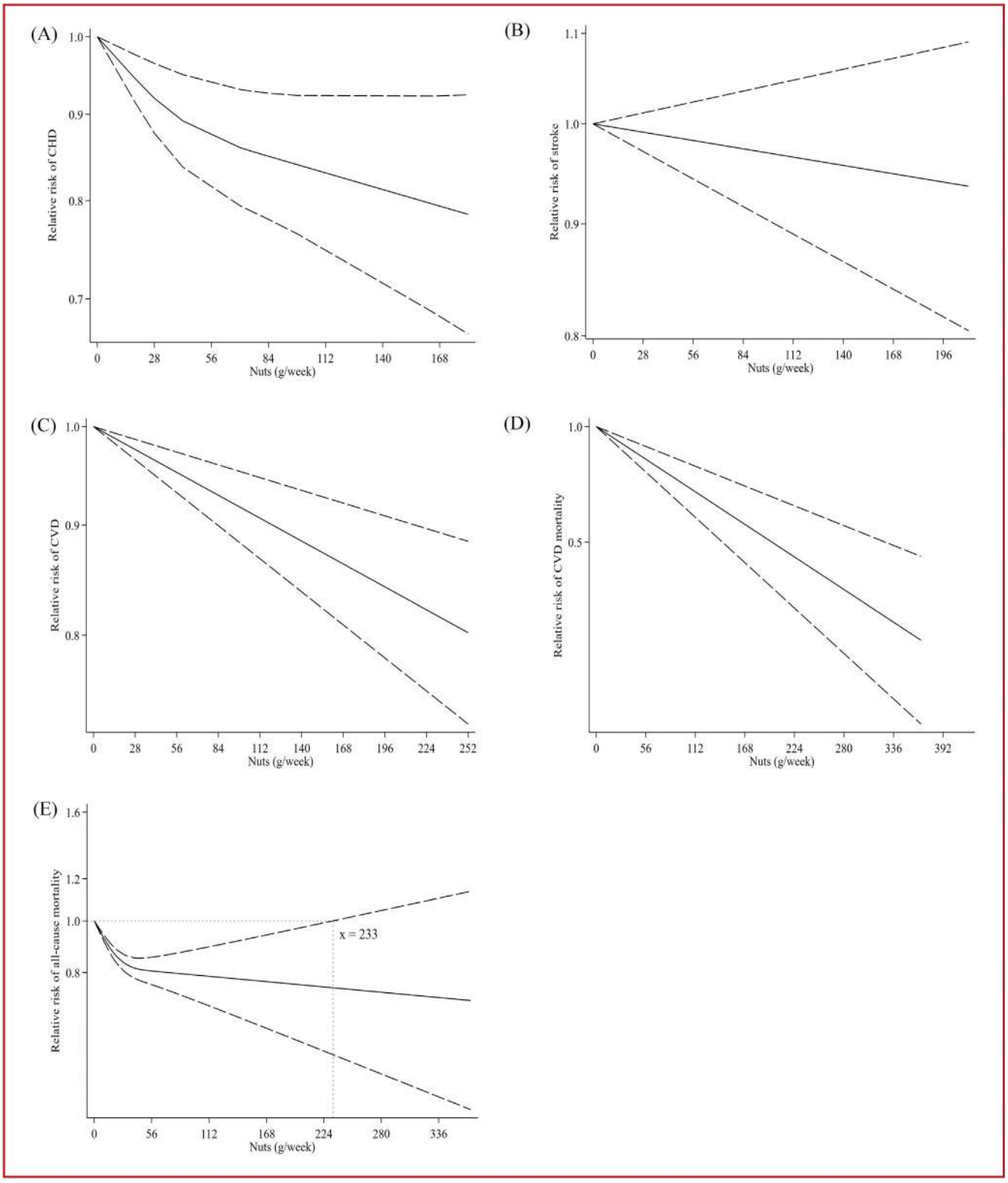



**Fig. 4.** Dose–response associations between nut intake and the risks of (A) CHD, (B) stroke, (C) CVD, (D) CVD mortality and (E) all-cause mortality by restricted cubic splines. Solid lines represent best-fitting cubic lines, dashed lines represent 95% CIs. CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease.

BMI is an important risk factor for many chronic diseases. An umbrella review that included 12 systematic reviews, 53 meta-analyses and 12 Mendelian randomized studies showed that for every 5-kg/m$^2$ increase in BMI, the risks of stroke, CHD, atrial fibrillation, heart failure and hypertension increased by 7%, 17%, 23%, 44% and 49%, respectively [65]. CVD is a leading cause of mortality and diet is one of the most important factors. Carbohydrates, proteins and fats are important sources of energy for humans. The prospective cohort study of UK Biobank reported a non-linear association between carbohydrates and CVD mortality and the negative effects of fat intake on CVD mortality [66]. In another prospective cohort study, higher plant protein intake was associated with lower

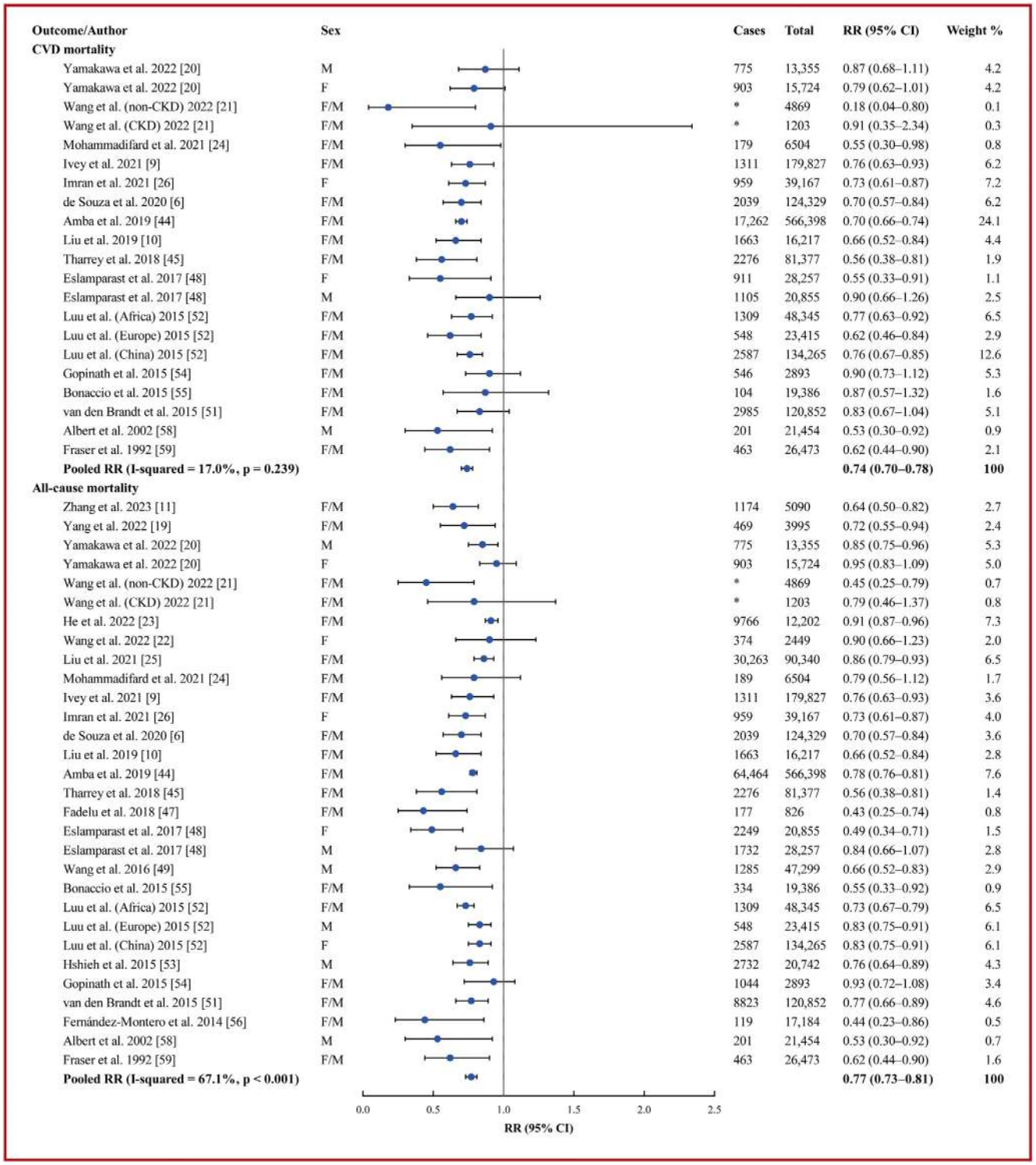



**Fig. 5.** Forest plot of the highest versus lowest total nut intake for the risk of CVD mortality and all-cause mortality. Summary RRs were calculated using a random-effects model. CI: confidence interval; CKD: chronic kidney disease; CVD: cardiovascular disease; F: female; M: male; RR: relative risk. *The original article did not report the number of cases, nor did it provide sufficient data to support indirect estimation.

CVD-related mortality and substituting plant protein for red or processed meat protein was associated with lower overall mortality and CVD-related mortality [67]. Although the Cochrane Q and $I^2$ statistics indicated significant heterogeneity in the meta-analysis of the association between nut consumption and all-cause mortality risk, subgroup analyses and meta-regression did not identify significant sources of heterogeneity. One potential explanations for this finding is that most studies did not adjust for overall dietary patterns (e.g. Mediterranean Diet Score) and nut consumption may be associated with diets high in dietary fibre and low in saturated fat. The uneven distribution of such dietary patterns across studies might indirectly contribute to heterogeneity in effect sizes. Secondly, discrepancies in the definition of 'nut consumption' across studies (e.g. inclusion of peanuts, threshold for daily intake) could have introduced classification bias. Despite our comprehensive efforts to explore potential heterogeneity sources through sub-

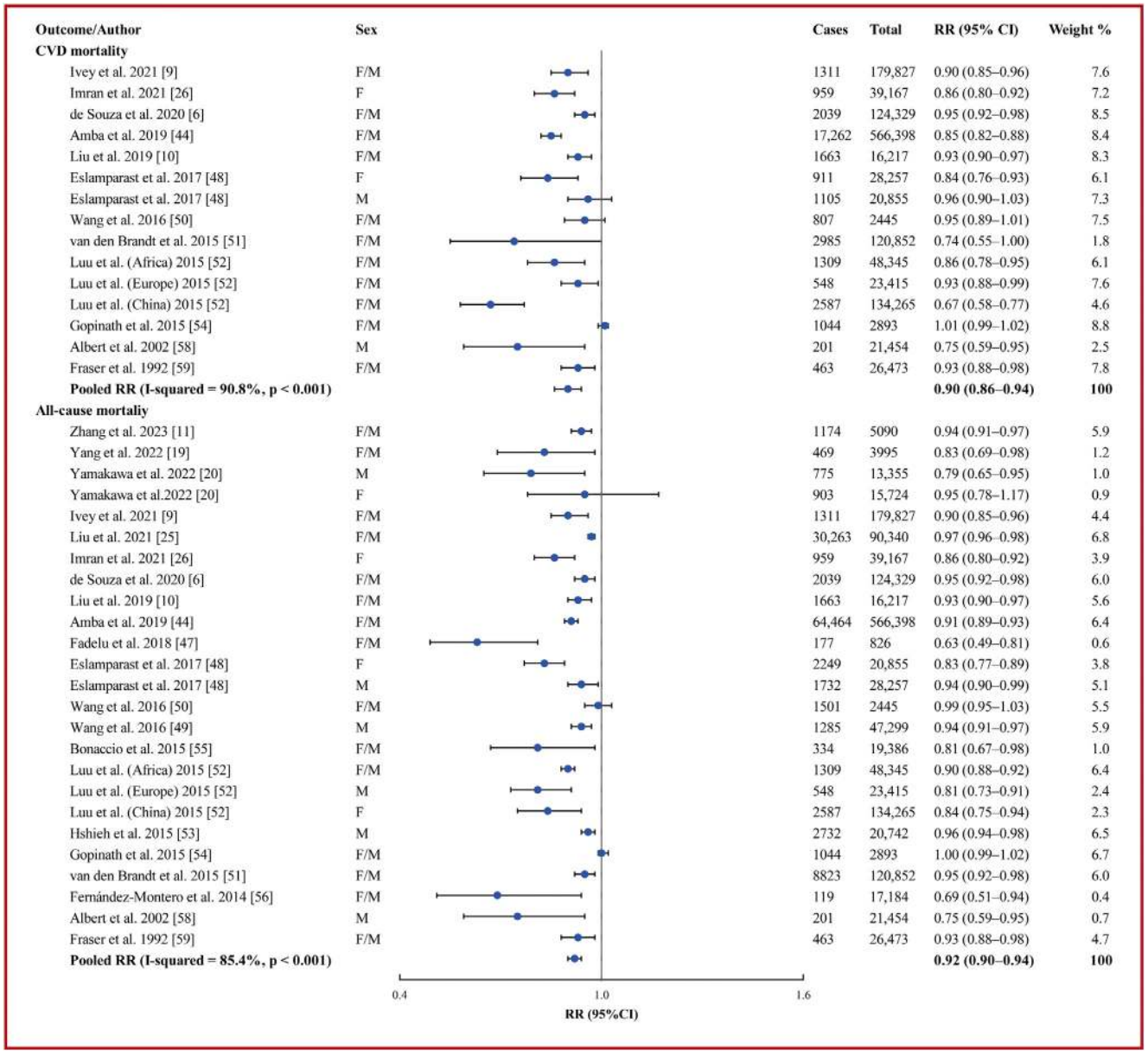



**Fig. 6.** Summary RRs for CVD mortality and all-cause mortality per 28-g/week increase in nut consumption. Summary RRs were calculated using a random-effects model. CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; F: female; M: male; RR: relative risk. *The original article did not report the number of cases, nor did it provide sufficient data to support indirect estimation.

group analyses and meta-regression using information from the original articles, some factors could not be included in the analysis due to missing data. Overall, this provides strong evidence for our findings, reinforcing the authenticity and reliability of this study.

Nuts contain various nutrients including vitamin E, magnesium, dietary fibre, polyunsaturated fats and antioxidants, all of which may decrease CVD risk and mortality by relieving insulin resistance [68], cholesterol concentrations [69], lipid peroxidation [70] and oxidative stress [71]. A meta-analysis [72] of 61 trials with study periods ranging from 3 to 26 weeks reported that nut consumption reduced triglycerides, lipoprotein cholesterol and total cholesterol regardless of the type of nut or background diets. As is well known, fat accumulation in the arterial walls plays a significant role in the progression of atherosclerosis, a significant cause of heart disease and stroke. Oxidative stress participates in the pathogenesis of atherosclerosis [73]. Therefore, dietary antioxidants may contribute to a possible mitigation in atherosclerosis progression. Different nuts (walnuts, pistachios, hazelnuts, macadamias and almonds) showed that their supernatant fractions displayed antioxidant effects after being fermented in vitro [74]. Other possible mechanisms include reducing oxidative stress, reducing circulating levels of inflammatory cytokines (particularly C-reactive protein), improving endothelial function and modulating nitric oxide production [14,75]. As a good source of various nutrients, dietary nuts may be a valuable means of preventing CVD events.

### 5.1. Strengths and limitations

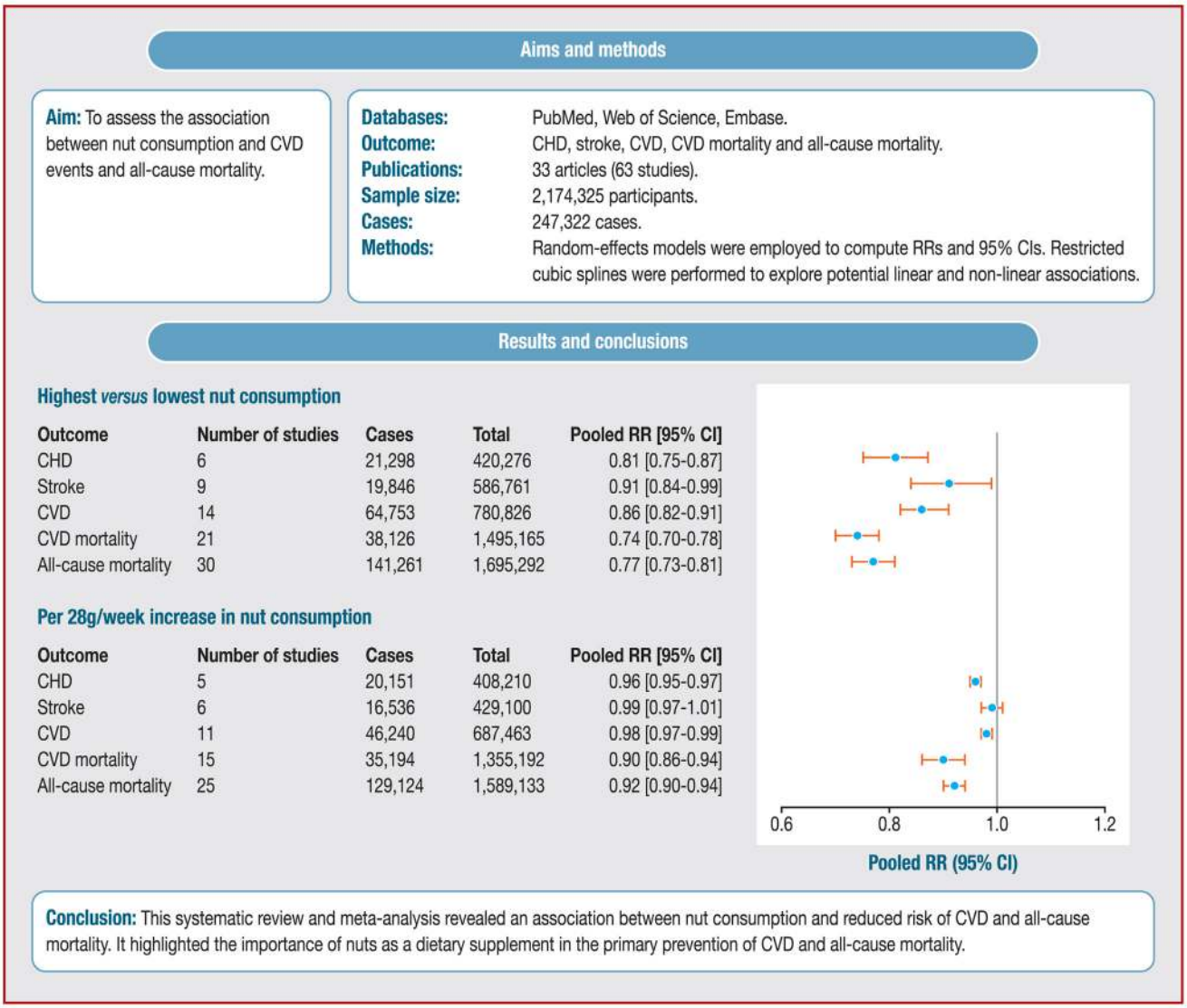
There are some strengths the deserve elucidation in the present analysis. First, prospective cohort studies were identified with a comprehensive search strategy, which effectively controlled recall bias. Sufficient observation periods of a cohort is helpful to obtain accurate incidences. Second, we identified up-to-date evidence

based on larger sample sizes, longer observational periods and more diverse ethnicities. For example, based on the Prospective Urban Rural Epidemiology study, de Souza et al. [6] assessed the association of nuts with mortality and CVD after 9.5 years, which involved 124,329 participants in 16 countries from five continents. Yamakawa et al. [20] and Yang et al. [19] explored the association between nut intake and mortality among non-white, non-Western populations. All of them provided the latest research progress in this field. Finally, dose–response analyses were performed to quantitatively evaluate the association between nut consumption with CHD, stroke, CVD, CVD mortality and all-cause mortality.

However, there remain some shortcomings in the present systematic review and meta-analysis. First, due to an insufficient number of studies, subgroup analyses could not be performed to explore the sources of heterogeneity for stroke and CHD. Furthermore, potential publication bias cannot be ruled out, and the current strength of evidence is relatively weak. Therefore, the estimation of effect sizes requires greater caution. Second, there are some inevitable measurement errors in the evaluation of nut intake because food frequency questionnaires were used for this purpose in all included studies. Third, although we extracted the multivariable-adjusted ORs/RRs/HRs, the effect of residual confounding factors could not be excluded due to insufficient and inconsistent adjustments included in the present study. Fourth, because of the limited articles, we could not further explore the relationships between specific types of nuts and CVD and mortality.

## 6. Conclusions

The present meta-analysis revealed that nut consumption is associated with reduced CVD (stroke and CHD) incidence, CVD mortality and all-cause mortality. Due to the ease of acquisition of nuts and their rich nutrients, including high levels of proteins, unsaturated fats, micronutrients, vitamin E and minerals, adding nuts to the diet may be an effective strategy in the primary prevention of CVDs. In the future, the relationship between specific types of nuts and disease outcomes remains a topic worth exploring.




**Central Illustration**. This meta-analysis indicates that the consumption of nuts may have a protective effect on CVD and mortality. CI: confidence interval; CVD: cardiovascular disease; RR: relative risk.

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## Author contributions

M.L. designed, wrote, performed the literature search and data analysis, and provided the final content. M.L. and X.H. extracted the data. D.H. resolved conflicts regarding data extraction and quality assessment. M.W., M.W., X.F., X.H., Y.Z. and D.H. revised the manuscript. All authors read and approved the final manuscript.

## Disclosure of interest

The authors declare that they have no competing interest.

## Acknowledgements

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## Online supplement. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2025.08.010.

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