Nut consumption in relation to cardiovascular disease risk and type 2 diabetes: a systematic review and meta-analysis of prospective studies1–5

Donghao Zhou, Haibing Yu, Fang He, Kathleen Heather Reilly, Jingling Zhang, Shuangshuang Li, Tao Zhang, Baozhen Wang, Yuanlin Ding, and Bo Xi

ABSTRACT

Background: Many prospective cohort studies have investigated the association between nut consumption and risk of coronary artery disease (CAD), stroke, hypertension, and type 2 diabetes (T2D). However, results have been inconsistent.

Objective: We aimed to investigate the association between nut consumption and risk of CAD, stroke, hypertension, and T2D.

Design: PubMed and EMBASE databases were searched up to October 2013. All prospective cohort studies of nut consumption and risk of CAD, stroke, hypertension, and T2D were included. Summary RRs with 95% CIs were estimated by using a fixed- or random-effects model.

Results: A total of 23 prospective studies (9 studies for CAD, 4 studies for stroke, 4 studies for hypertension, and 6 studies for T2D) from 19 publications were included in the meta-analysis. There were 179,885 participants and 7236 CAD cases, 182,730 participants and 5669 stroke cases, 40,102 participants and 12,814 hypertension cases, and 342,213 participants and 14,400 T2D cases. The consumption of each 1 serving of nuts/d was significantly associated with incident CAD (RR: 0.81; 95% CI: 0.72, 0.91; P < 0.001) and hypertension (RR: 0.66; 95% CI: 0.44, 1.00; P = 0.049). However, there was no association between the consumption of each 1 serving of nuts/d and risk of stroke (RR: 0.90; 95% CI: 0.71, 1.14) or T2D (RR: 0.80; 95% CI: 0.57, 1.14).

Conclusions: A higher consumption of nuts was associated with reduced risk of CAD and hypertension but not stroke or T2D. Large randomized controlled trials are warranted to confirm the observed associations.

INTRODUCTION

Nuts contain a variety of nutrients, including unsaturated fatty acids, fiber, vitamins E and riboflavin, folate, minerals (potassium, copper, selenium, calcium, and magnesium), and other bioactive compounds such as phytosterols and polyphenols (1). Many prospective cohort studies have investigated the association between nut consumption and risk of coronary artery disease (CAD)6 (2–9). In 1992, Fraser et al (2) first reported an inverse relation between nut consumption and risk of CAD in a prospective study of 31,208 non-Hispanic whites. Since then, many cohort studies have attempted to replicate this association. However, results have been inconsistent (3–9). A previous meta-analysis of 4 cohort studies suggested an average risk reduction of CAD death for each weekly serving of nuts (10). However, 2 of the included 4 cohort studies have updated the data with a longer duration of follow-up and more incident cases for each study (6, 7). Furthermore, several additional, large cohort studies have been published on nut consumption and CAD risk (5, 8, 9). Thus, a sufficient statistical power has been achieved to further clarify the association. In addition, a great number of large cohorts have investigated the association of nut consumption with stroke (11–13), hypertension (14–17), and type 2 diabetes (T2D) (18–22). However, these results have also been mixed. Although one recent meta-analysis assessed the association of nut consumption with risk of hypertension and T2D (23), the article was later retracted by the authors, and readers cannot access the full text of the related results again. Thus, it is necessary to further clarify the association.
Therefore, in this study, we performed a systematic review and meta-analysis of prospective cohort studies to clarify the association of nut consumption with risk of CAD, stroke, hypertension, and T2D.

METHODS

Literature and search strategy

Literature databases including PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and EMBASE (http://www.elsevier.com/online-tools/embase) were searched. Search terms were (coronary disease OR myocardial infarction OR stroke OR hypertension OR type 2 diabetes) and (nut OR nuts). Reference lists of retrieved articles were manually searched. The literature search was limited to the English language. If more than one article was published that used the same cohort, only the study with the largest sample size was included. The literature search was updated on 10 October 2013.

Inclusion criteria and data extraction

Studies included in the meta-analysis met all of the following inclusion criteria: 1) evaluated the association between nut consumption and CAD, stroke, hypertension, or T2D; 2) used a prospective cohort design; and 3) provided the amount of nut consumption, distributions of cases and person years, and RRs or HRs with 95% CIs for ≥3 exposure categories. The following information was extracted from each study: 1) name of the first author, 2) year of publication, 3) study name, 4) origin of country, 5) sex of participants, 6) age of the study population at baseline, 7) follow-up period, 8) number of cases and study population, 9) endpoints, 10) the amount of nut consumption for each category, 11) RRs or HRs with 95% CIs for all categories of nut consumption, and 12) covariates used in adjustments. Two authors (BX and SL) independently assessed the articles for compliance with the inclusion and exclusion criteria and resolved disagreements through discussion.

The quality of each study was assessed by using the Newcastle-Ottawa quality scale (24), which is a validated scale for non-randomized studies in a meta-analysis. This scale was used to assign a maximum of 9 points for each study. Three broad perspectives were considered: the selection of the cohorts, comparability of cohorts; and ascertainment of the exposure and outcome of interest.

Statistical analysis

A fixed-effects (25) or random-effects (26) model, on the basis of whether there was heterogeneity, was used to calculate pooled RRs with 95% CIs for highest compared with lowest amounts of nuts consumption and the dose-response analysis. Heterogeneity was assessed by using the Q test and $I^2$ statistic (27). The significance for the Q test was defined as $P < 0.10$. The $I^2$ statistic represents the amount of total variation that could be attributed to heterogeneity. $I^2$ values >25%, >50%, and >75% indicated little, moderate, and significant heterogeneity, respectively.

For the dose-response analysis, the method reported by Greenland et al (28) and Orsini et al (29) was used to calculate study specific slopes (linear trends) on the basis of results across categories of nut consumption. We extracted data on the amount of nut consumption, distributions of cases and person years, and RRs or HRs with 95% CIs for ≥3 exposure categories. The median or mean amount of nut consumption in each category was assigned to the corresponding RR or HR with the 95% CI for each study. When nut consumption was reported by ranges of intakes, the midpoint of the range was used. When the highest category was open ended, we assumed the width of the category to be the same as the adjacent category. When the lowest category was open ended, we set the lower boundary to zero. If a linear dose-response result was already provided by the included study, it was used directly. A potential curvilinear dose-response relation between nut consumption and risk of CAD, stroke, hypertension, or T2D was examined by using restricted cubic splines with 3 knots at percentiles 10%, 50%, and 90% of the distribution (30). A $P$ value for curvilinearity or nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero.

A meta-regression analysis was performed to identify the source of heterogeneity (31). A sensitivity analysis after the exclusion of one study at a time was performed to assess the stability of results. Publication bias was assessed by using Begg’s (32) and Egger’s (33) tests ($P < 0.05$ was considered significant). The statistical analysis was conducted with STATA version 11 software (StataCorp LP).

RESULTS

Characteristics of included prospective studies

After the literature search and selection, a total of 23 prospective studies from 19 publications were included in the meta-analysis of the association between nut consumption and risk of CAD, stroke, hypertension, and T2D (Figure 1). Note that 2 publications (2, 34) were excluded because neither study provided sufficient data for dose-response analyses. The duration of follow-up ranged from 3.8 to 26 y. For CAD, 3 studies were from Europe, and 6 studies were from the United States. For stroke, all 4 studies were from the United States. For hypertension, 3 studies were from the United States and 1 study was from Spain. For T2D, 5 studies were from the United States and 1 study was from China. Included studies have adjusted for most important covariates, but some studies did not adjust for energy intake, BMI, and age.Characteristics of included prospective studies are listed in Table 1 (also see Supplemental Table I under “Supplemental data” in the online issue).

Association between nut consumption and risk of CAD

Highest compared with lowest intakes

Nine cohort studies from 7 publications, including 179,885 participants and 7236 CAD cases, were included. The highest intake of nuts was inversely associated with risk of CAD (RR: 0.83; 95% CI: 0.74, 0.93; see Supplemental Figure 1 under “Supplemental data” in the online issue) compared with the that of the lowest intake with modest evidence of heterogeneity ($I^2 = 59.9\%$, $P = 0.010$). After the sensitivity analysis, RRs (95% CIs) ranged from 0.86 (0.77, 0.96) to 0.81 (0.71, 0.91). There was no evidence of a publication bias (Begg’s test: $P = 0.076$; Egger’s test: $P = 0.142$).

Dose-response analysis

We did not find a curvilinear association between nut consumption and risk of CAD ($P$-nonlinearity $> 0.05$). The summary
We showed no evidence of a curvilinear association between nut consumption and risk of T2D (P-nonlinearity > 0.05). The summary RR for each 1-serving/d intake was 0.66 (95% CI: 0.44, 1.00; P = 0.049; Figure 4) with evidence of heterogeneity (I² = 75.9%, P = 0.006). A sensitivity analysis was performed after the exclusion of one study at a time. Summary RRs (95% CIs) ranged from 0.67 (0.38, 1.17) to 0.55 (0.38, 0.82). No publication bias was detected by using Begg’s (P = 0.734) or Egger’s (P = 0.195) test.

Association between nut consumption and risk of T2D

Highest compared with lowest intakes

Six cohort studies from 5 publications, including 342,213 participants and 14,400 T2D cases, were included. The highest intake of nuts was not associated with risk of T2D (RR: 0.92; 95% CI: 0.78, 1.09; see Supplemental Figure 4 under “Supplemental data” in the online issue) compared with that for the lowest intake with no evidence of heterogeneity (I² = 0.0%, P = 0.927). After the sensitivity analysis, RRs (95% CIs) ranged from 0.67 (0.38, 1.17) to 0.55 (0.38, 0.82). There was no evidence of a publication bias (Begg’s test: P = 0.734; Egger’s test: P = 0.537).

Dose-response analysis

We showed no evidence of a curvilinear association between nut consumption and risk of T2D (P-nonlinearity > 0.05). There was no significant association between higher nut consumption and risk of stroke [RR: 0.90 (95% CI: 0.71, 1.14) for each 1-serving/d consumption, Figure 3] with modest evidence of heterogeneity (I² = 49.6%, P = 0.114). No publication bias was detected by using Begg’s (P = 0.308) or Egger’s (P = 0.273) test. We did not perform additional subgroup analyses by the type of stroke (hemorrhagic compared with ischemic) because there were only a few stroke studies.

Association between nut consumption and risk of hypertension

Highest compared with lowest intakes

Four cohort studies from 4 publications, including 40,102 participants and 12,814 hypertension cases, were included. The highest intake of nuts was inversely associated with risk of hypertension (RR: 0.85; 95% CI: 0.79, 0.92; see Supplemental Figure 3 under “Supplemental data” in the online issue) compared with that for the lowest intake with no evidence of heterogeneity (I² = 0.0%, P = 0.927). After the sensitivity analysis, RRs (95% CIs) ranged from 0.86 (0.79, 0.94) to 0.84 (0.76, 0.93). There was no evidence of a publication bias (Begg’s test: P = 0.734; Egger’s test: P = 0.537).

Dose-response analysis

We showed no evidence of a curvilinear association between nut consumption and risk of hypertension (P-nonlinearity > 0.05). The summary RR for each 1-serving/d intake was 0.66 (95% CI: 0.44, 1.00; P = 0.049; Figure 4) with evidence of heterogeneity (I² = 75.9%, P = 0.006). A sensitivity analysis was performed after the exclusion of one study at a time. Summary RRs (95% CIs) ranged from 0.67 (0.38, 1.17) to 0.55 (0.38, 0.82). No publication bias was detected by using Begg’s (P = 0.734) or Egger’s (P = 0.195) test.

Association between nut consumption and risk of stroke

Highest compared with lowest intakes

Four cohort studies from 3 publications, 182,730 participants, and 5669 stroke cases were included. There was no association between nut intake and risk of stroke (highest compared with lowest categories: RR, 0.87; 95% CI, 0.74, 1.03; see Supplemental Figure 2 under “Supplemental data” in the online issue), with no evidence of heterogeneity (I² = 15.0%, P = 0.317). There was no evidence of a publication bias (Begg’s test: P = 0.734; Egger’s test: P = 0.550).

Dose-response analysis

We showed no evidence of a curvilinear association between nut consumption and risk of stroke (P-nonlinearity > 0.05). There was no significant association between higher nut consumption and risk of stroke [RR: 0.90 (95% CI: 0.71, 1.14) for each 1-serving/d consumption, Figure 3] with modest evidence of heterogeneity (I² = 49.6%, P = 0.114). No publication bias was detected by using Begg’s (P = 0.308) or Egger’s (P = 0.273) test. We did not perform additional subgroup analyses by the type of stroke (hemorrhagic compared with ischemic) because there were only a few stroke studies.
<table>
<thead>
<tr>
<th>First author, publication year (ref)</th>
<th>Study name</th>
<th>Country</th>
<th>Sex</th>
<th>Actual age at baseline</th>
<th>No. of participants</th>
<th>Duration of follow-up</th>
<th>Endpoints</th>
<th>No. of cases</th>
<th>Study quality</th>
</tr>
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<tbody>
<tr>
<td>Key, 1996 (3)</td>
<td>Cohort of vegetarians and other health-conscious people</td>
<td>United Kingdom</td>
<td>M and F</td>
<td>≥16</td>
<td>10,977</td>
<td>17</td>
<td>Ischemic heart disease mortality</td>
<td>350</td>
<td>7</td>
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<tr>
<td>Albert, 2002 (4)</td>
<td>Physicians’ Health Study I</td>
<td>United States</td>
<td>M</td>
<td>40–84</td>
<td>21,454</td>
<td>17</td>
<td>Nonfatal myocardial infarction</td>
<td>1037</td>
<td>7</td>
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<td>Trichopoulou, 2005 (5)</td>
<td>EPIC-Greece Study (CAD)</td>
<td>Greece</td>
<td>M and F</td>
<td>20–86</td>
<td>1302</td>
<td>3.8</td>
<td>Coronary heart disease mortality</td>
<td>566</td>
<td>7</td>
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<td>Blomhoff, 2006 (6)</td>
<td>Iowa Women’s Health Study</td>
<td>United States</td>
<td>F</td>
<td>55–69</td>
<td>31,778</td>
<td>15</td>
<td>Coronary heart disease mortality</td>
<td>85</td>
<td>6</td>
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<td>Li, 2009 (7)</td>
<td>Nurses’ Health Study (Diabetes)</td>
<td>United States</td>
<td>F</td>
<td>57 ± 9</td>
<td>6309</td>
<td>12</td>
<td>Myocardial infarction</td>
<td>452</td>
<td>6</td>
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<td>Bernstein, 2010 (8)</td>
<td>Nurses’ Health Study</td>
<td>United States</td>
<td>F</td>
<td>30–55</td>
<td>84,136</td>
<td>26</td>
<td>Coronary heart disease</td>
<td>3162</td>
<td>7</td>
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<tr>
<td>Dilis, 2012 (9)</td>
<td>EPIC-Greece Study</td>
<td>Greece</td>
<td>M and F</td>
<td>20–86</td>
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<td>10</td>
<td>Coronary heart disease</td>
<td>636</td>
<td>8</td>
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<td>Yochum, 2000 (11)</td>
<td>Nurses’ Health Study</td>
<td>United States</td>
<td>F</td>
<td>55–69</td>
<td>34,492</td>
<td>11</td>
<td>Stroke mortality</td>
<td>215</td>
<td>7</td>
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<tr>
<td>Djousse, 2010 (12)</td>
<td>Physicians’ Health Study I</td>
<td>United States</td>
<td>F</td>
<td>40–84</td>
<td>21,078</td>
<td>12</td>
<td>Stroke</td>
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<td>7</td>
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<td>M</td>
<td>40–75</td>
<td>43,150</td>
<td>22</td>
<td>Stroke</td>
<td>2633</td>
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<td>Steffen, 2006 (14)</td>
<td>CARDIA study</td>
<td>United States</td>
<td>M and F</td>
<td>18–30</td>
<td>4304</td>
<td>15</td>
<td>Hypertension</td>
<td>997</td>
<td>7</td>
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<tr>
<td>Djousse, 2009 (15)</td>
<td>Physicians’ Health Study I</td>
<td>United States</td>
<td>M</td>
<td>40–84</td>
<td>15,966</td>
<td>15</td>
<td>Hypertension</td>
<td>8423</td>
<td>7</td>
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<tr>
<td>Martínez-Lapiscina, 2010 (16)</td>
<td>SUN project</td>
<td>Spain</td>
<td>M and F</td>
<td>36 ± 10</td>
<td>9919</td>
<td>4.3</td>
<td>Hypertension</td>
<td>541</td>
<td>7</td>
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<tr>
<td>Weng, 2013 (17)</td>
<td>ARIC study</td>
<td>United States</td>
<td>M and F</td>
<td>45–64</td>
<td>9913</td>
<td>9</td>
<td>Hypertension</td>
<td>2853</td>
<td>8</td>
</tr>
<tr>
<td>Jiang, 2002 (18)</td>
<td>Nurses’ Health Study</td>
<td>United States</td>
<td>F</td>
<td>34–59</td>
<td>83,818</td>
<td>16</td>
<td>Type 2 diabetes</td>
<td>3206</td>
<td>7</td>
</tr>
<tr>
<td>Park, 2003 (19)</td>
<td>Nurses’ Health Study</td>
<td>United States</td>
<td>F</td>
<td>55–69</td>
<td>35,988</td>
<td>12</td>
<td>Type 2 diabetes</td>
<td>1831</td>
<td>7</td>
</tr>
<tr>
<td>Villegas, 2008 (20)</td>
<td>Shanghai Women’s Health Study</td>
<td>China</td>
<td>F</td>
<td>40–70</td>
<td>64,227</td>
<td>16</td>
<td>Type 2 diabetes</td>
<td>1605</td>
<td>7</td>
</tr>
<tr>
<td>Koch, 2010 (21)</td>
<td>Physicians’ Health Study I</td>
<td>United States</td>
<td>M</td>
<td>41–87</td>
<td>20,224</td>
<td>19.2</td>
<td>Type 2 diabetes</td>
<td>1828</td>
<td>7</td>
</tr>
<tr>
<td>Pan, 2013 (22)</td>
<td>Nurses’ Health Study</td>
<td>United States</td>
<td>F</td>
<td>52–77</td>
<td>58,063</td>
<td>10</td>
<td>Type 2 diabetes</td>
<td>3167</td>
<td>7</td>
</tr>
<tr>
<td>Pan, 2013 (22)</td>
<td>Nurses’ Health Study II</td>
<td>United States</td>
<td>F</td>
<td>35–52</td>
<td>79,893</td>
<td>10</td>
<td>Type 2 diabetes</td>
<td>2764</td>
<td>7</td>
</tr>
</tbody>
</table>

1 ARIC, Atherosclerosis Risk in Communities; CAD, coronary artery disease; CARDIA, Coronary Artery Risk Development in Young Adults; EPIC, European Prospective Investigation into Cancer and Nutrition; ref, reference; SUN, Seguimiento Universidad de Navarra.
2 Assessed by using the Newcastle-Ottawa quality scale (24).
3 Systolic blood pressure/diastolic blood pressure ≥130/85 mm Hg or the use of antihypertensive medications.
4 Systolic blood pressure/diastolic blood pressure ≥140/90 mm Hg or the use of antihypertensive medications.
However, none of these variables were identified as the source of heterogeneity for all 4 outcomes (all \( P > 0.05 \)).

DISCUSSION

The current meta-analysis supported an inverse association between nut consumption and risk of CAD and hypertension, but we did not show any significant association between nut consumption and risk of stroke or T2D.

Comparison with other studies

A previous meta-analysis that consisted of 4 cohort studies suggested that individuals who consume nuts ≥4 times/wk had a 37% reduction in risk of CAD in comparison with individuals who consumed nuts seldom or never with an average reduction of 8.3% for each weekly serving of nuts (10). In the current meta-analysis, we calculated summary RR with 95% CIs for each 1-serving/d increment of nut consumption. Our dose-response meta-analysis suggested a 19% average risk reduction.
of CAD for each 1-serving/d consumption of nuts. In other words, our findings confirmed the beneficial effect of nut consumption on risk of CAD. In addition, the inverse association between nut consumption and hypertension was also observed. Note that the study by Djoussé et al (15) accounted for the largest proportion in weights of all 4 studies (35.15%). However, after the exclusion of the study in the sensitivity analysis, the inverse association remained, which suggested the stability of the result. For stroke, although only 4 cohort studies were identified, the numbers of participants and incident stroke cases were 182,730 and 5669, respectively. Therefore, the null significant association of nut consumption with risk of stroke could not be attributed to the statistical power, and the possible reasons need additional investigation. It was also surprising to us that nut consumption was not shown to be significantly associated with T2D, although an inverse trend was observed. Because there was significant heterogeneity between studies, the pooled negative result should be interpreted with caution.

More recently, 2 large cohort studies (35, 36) showed that an increased frequency of nut consumption was associated with

![Figure 4](https://academic.oup.com/ajcn/article-abstract/100/1/270/4576563)

**FIGURE 4.** Meta-analysis of nut consumption with risk of hypertension (for 1-serving/d increment). Size of the symbol is proportional to inverse of variance of RR; the horizontal line represents 95% CI. ID, identifier.

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steffen, 2006 (14)</td>
<td>0.63 (0.40, 0.99)</td>
<td>24.74</td>
</tr>
<tr>
<td>Djoussé, 2009 (15)</td>
<td>0.90 (0.83, 0.99)</td>
<td>35.15</td>
</tr>
<tr>
<td>Martinez-Lapiscina, 2010 (16)</td>
<td>0.78 (0.38, 1.60)</td>
<td>17.13</td>
</tr>
<tr>
<td>Weng, 2013 (17)</td>
<td>0.39 (0.23, 0.65)</td>
<td>22.97</td>
</tr>
<tr>
<td>Overall (I-squared = 75.9%, p = 0.008)</td>
<td>0.66 (0.44, 1.00)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**NOTE:** Weights are from random-effects analysis

![Figure 5](https://academic.oup.com/ajcn/article-abstract/100/1/270/4576563)

**FIGURE 5.** Meta-analysis of nut consumption with risk of type 2 diabetes (for 1-serving/d increment). Size of the symbol is proportional to inverse of variance of RR; the horizontal line represents 95% CI. ID, identifier.

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiang, 2002 (18)</td>
<td>0.64 (0.53, 0.77)</td>
<td>20.37</td>
</tr>
<tr>
<td>Parker, 2003 (19)</td>
<td>1.54 (1.16, 2.05)</td>
<td>18.98</td>
</tr>
<tr>
<td>Vilegas, 2009 (20)</td>
<td>0.19 (0.05, 0.74)</td>
<td>5.20</td>
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<tr>
<td>Kochar, 2010 (21)</td>
<td>0.87 (0.70, 1.08)</td>
<td>20.08</td>
</tr>
<tr>
<td>Pan, 2013 (walnuts) (22)</td>
<td>0.50 (0.32, 0.76)</td>
<td>16.34</td>
</tr>
<tr>
<td>Pan, 2013 (other nuts) (22)</td>
<td>1.09 (0.83, 1.45)</td>
<td>19.06</td>
</tr>
<tr>
<td>Overall (I-squared = 87.1%, p &lt; 0.001)</td>
<td>0.80 (0.57, 1.14)</td>
<td>100.00</td>
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</table>

**NOTE:** Weights are from random-effects analysis
significantly reduced risk of all-cause mortality, although the significant association did not persist in some cause-specific mortality groups in one study (35). In the Prevención con Dieta Mediterránea (PREDIMED) nutrition intervention trial (median follow-up: 4.8 y), a total of 7216 participants aged 55–80 y were randomly assigned to 1 of 3 interventions (Mediterranean diets supplemented with nuts or olive oil and a control diet). The multivariable-adjusted HR of main cardiovascular events was 0.72 (95% CI: 0.54, 0.96) for the group assigned to a Mediterranean diet with nuts compared with the control group (37). An additional analysis showed that the Mediterranean diet with nuts was only protective against the development of stroke but not myocardial infarction or deaths from CVDs (37). However, our findings in the current meta-analysis suggested that nut intake was not inversely associated with risk of stroke, but it was beneficial to CAD. This difference was not surprising to us because the PREDIMED trial was not powered for individual outcomes of the composite endpoint. The potential explanation was unknown. In the PREDIMED trial cohort, considered as a longitudinal study, individuals who consumed nuts ≥1 times/wk had significantly lower cardiovascular mortality than did individuals who never ate nuts (36). In addition, the Mediterranean diet enriched with nuts showed a beneficial effect on risk of T2D compared with for the control group in the PREDIMED nutrition intervention trial (RR: 0.48; 95% CI: 0.24, 0.96) (38). However, in our current meta-analysis, we did not show the protective effect of nuts on T2D. Additional large-scale randomized controlled trials are necessary to validate the findings of the PREDIMED nutrition intervention trial.

Potential mechanisms

It has been well established that nuts are rich in MUFAs, PUFAs, fiber, minerals, vitamins, and many bioactive compounds. These healthy nutritional components contained in nuts may explain the inverse association with CAD and hypertension. The possible mechanisms include improving the blood lipid profile, decreasing insulin resistance, and modulating inflammation, oxidative stress, and endothelial function. For instance, in a cohort of participants at high risk of CAD, nut consumption was inversely associated with vascular cell adhesion molecule-1, intracellular adhesion molecule-1, C-reactive protein, and IL-6 serum concentrations, although this association was only significant for intracellular adhesion molecule-1 (39). In a clinical trial, a healthy diet supplemented with nuts decreased the insulin response by 22% from the initial value, and the response was significantly different from that of the control group (40). Additional experimental studies and clinical trials are necessary to clarify the mechanisms on protective effect of nut consumption on CAD and hypertension.

Strengths and limitations

The main strength of the current study was that the long duration of follow-up, high follow-up rate, and large number of participants in included studies provided sufficient power to detect the association. However, several limitations should be considered. First, because of the observational nature of the cohort study, the effect of unmeasured or residual confounding on the observed findings could not be ruled out. Second, most included studies did not provide data on types of nuts consumed and their preparation including salted, spiced, roasted, or raw nuts. Thus, we are unable to examine the influence of types of nuts or preparation methods on outcomes. Third, the majority of studies used the nut consumption at baseline as the dietary exposure. However, during the follow-up period, some individuals might have changed their diet habits. Thus, the misclassification of exposure might have biased the results. This possibility may help explain the null association with stroke or T2D but could not explain the significant results for CAD or hypertension because a misclassification is expected to bias the results toward the null. In a previous study, a diet rich in unsaturated fat that is the main component of nuts had a large beneficial effect on blood pressure and serum lipids (41). Fourth, there was evidence of between-study heterogeneity for CAD, stroke, and T2D. Although a meta-regression model was applied to examine the source of heterogeneity for these diseases, none of the introduced variables could explain the heterogeneity, which suggested other unknown factors might have confounded these associations. Fifth, included studies adjusted for important covariates (see Table S1 under “Supplemental data” in the online issue) but not all studies adjusted for all covariates. For example, some but not all studies adjusted for energy intake, BMI, and age. Thus, the combined results should be interpreted with caution.

In conclusion, our meta-analysis suggests a dose-response association between nut consumption and decreased risk of CAD and hypertension. The results do not support any significant association between nut consumption and risk of stroke or T2D. Large random controlled trials are warranted to confirm the observed association.

The authors’ responsibilities were as follows—BX and YD: designed the research and had primary responsibility for the final content of the manuscript; SL, TZ, and JZ: conducted the research; FH, BX, BW, and KHR: analyzed data; DZ, HY, and BX: wrote the manuscript; and all authors: read and approved the final manuscript. None of the authors had a conflict of interest.

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