Nut consumption on all-cause, cardiovascular, and cancer mortality risk: a systematic review and meta-analysis of epidemiologic studies[1–4]

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ABSTRACT

Background: Recent pooled analyses supported a beneficial impact of nut consumption on health, but to our knowledge, whether nuts are associated with overall decreased mortality has not been previously reviewed.

Objectives: We aimed to systematically review prospective studies that explored the effects of nut consumption on all-cause, cardiovascular disease (CVD), and cancer mortality and quantify the size effect through a meta-analysis. We also reviewed confounding factors associated with nut consumption to assess potential clustering with other covariates.

Design: We searched PubMed and EMBASE for studies published up to June 2014. Study characteristics, HRs, and 95% CIs were generated on the basis of quantitative analyses. A dose-response analysis was performed when data were available.

Results: Seven studies for all-cause mortality, 6 studies for CVD mortality, and 2 studies for cancer mortality were included in the meta-analysis with a total of 354,933 participants, 44,636 cumulative incident deaths, and 3,746,534 cumulative person-years. Nut consumption was associated with some baseline characteristics such as lower body mass index and smoking status as well as increased intakes of fruit, vegetables, and alcohol. One-serving of nuts per week and per day resulted in 4% (RR: 0.96; 95% CI: 0.93, 0.98) and 27% (RR: 0.73; 95% CI: 0.60, 0.88) decreased risk of all-cause mortality, respectively, and decreased risk of CVD mortality [RR: 0.93 (95% CI: 0.88, 0.99) and 0.61 (95% CI: 0.42, 0.91), respectively]. Effects were primarily driven by decreased coronary artery disease deaths rather than stroke deaths. Nut consumption was also associated with decreased risk of cancer deaths when highest compared with lowest categories of intake were compared (RR: 0.86; 95% CI: 0.75, 0.98), but no dose-effect was shown.

Conclusion: Nut consumption is associated with lower risk of all-cause, CVD, and cancer mortality, but the presence of confounding factors should be taken into account when considering such findings. *Am J Clin Nutr* 2015;101:783–93.

Keywords: cancer, cardiovascular disease, mortality, nut consumption, prospective studies

INTRODUCTION

Plant-based dietary patterns were shown to have positive and significant impacts on human health over the past century (1). Although most epidemiologic studies have focused on fruit, vegetables, legumes, or cereals and morbidity and mortality from chronic disease, a limited number of cohort studies examined nut consumption and its potential beneficial effects on health outcomes (2). Nuts are a specific kind of fruit characterized by a hard shell and dry seed rich in vitamins, phenolic compounds, fiber, and minerals as well as having a high unsaturated fatty acid content that is relatively unique for fruit (3). Beneficial effects of nut consumption were reported in relation to both cardiovascular disease (CVD) and cancer, although results on the latter are equivocal (2). Possible mechanisms of CVD risk reduction include anti-inflammatory, anti-oxidant, and anti-atherogenic properties of compounds such as tocopherols, folic acids, and phytochemicals that are common in nuts (3). Nut consumption was shown to have beneficial effects on several CVD risk factors, including lowering LDL cholesterol (4), ameliorating endothelial function (5), decreasing visceral adiposity (6), and improving hyperglycemia (7) and insulin resistance (8). Furthermore, nutrients contained in nuts may also modify specific processes related to cancer development such as the regulation of cell differentiation and proliferation, reduction of tumor initiation or promotion, DNA protection, and regulation of immunologic and inflammatory responses (9).

Four recent meta-analyses showed that higher consumption of nuts was associated with reduced risk of coronary artery disease and hypertension (10–13). However, pooled analyses that explored the effects of nut consumption on all-cause, CVD, and cancer mortality are lacking. Therefore, we aimed to systematically

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[3] Supplemental Tables 1 and 2 and Supplemental Figures 1–9 are available from the "Supplemental data" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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review prospective cohort studies that investigated the association between nut consumption and mortality and review confounding factors associated with nut consumption to assess potential clustering with other covariates.

METHODS

Study selection

A comprehensive search on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and EMBASE (http://www.embase.com/) databases of all English language studies on nut consumption and mortality published up to June 2014 was performed. Articles of potential interest were identified by using the search term nut combined with the terms mortality or survival. In the 240 articles retrieved, prospective cohort studies were identified and screened by reading abstracts and, when necessary, full texts. Reference lists of included manuscripts were also examined for any additional study not previously identified. The process of identification and inclusion of studies is summarized in **Figure 1**. Studies were included that met the following inclusion criteria: *1*) evaluated the effects of nut consumption on risk of mortality, *2*) assessed nut consumption by relative intakes (i.e., frequency or quantiles of consumption), and *3*) used a prospective cohort design. Exclusion criteria were as follows: *1*) studies that reported insufficient statistics or results and *2*) studies that assessed nut consumption in combination with other food groups. If more than one article was published that used the same cohort, only the study that included the entire cohort or with the longest follow-up was included.

Data extraction

Data were abstracted from each identified study by using a standardized extraction form. The following information was extracted from each study: *1*) name of the first author; *2*) year of publication; *3*) study cohort; *4*) country; *5*) number of participants; *6*) sex of participants; *7*) age range of the study population at baseline; *8*) follow-up period; *9*) endpoints and cases; *10*) distributions of cases and person-years, HRs, and 95% CIs for all categories of exposure; *11*) covariates used in adjustments; and *12*) background characteristics by categories of exposure. This process was independently performed by GG and SM; and any discordant entries were discussed and resolved by consensus.

The quality of each study was assessed according to the Newcastle-Ottawa Quality Assessment Scale (14), which consists of 3 variables of quality as follows: selection (4 points), comparability (2 points), and outcome (3 points), with a score ≥ 7 reflecting high quality. We also included the following additional criteria: the completeness and accuracy of results (presence of person-years), ascertainment of exposure (nut consumption) with outcomes of interest, number of participants (>5000), duration of follow-up (>5 y), and adjustment for potential confounders (adequate compared with a lack of key confounders), for a total score of 14 points.

Statistical analysis

Outcomes evaluated in analyses included all-cause, CVD, and cancer mortality. In the model in which CVD mortality was evaluated, when a study evaluated specific CVD cause of death [i.e., coronary artery disease (CAD) or stroke], we included the most-specific outcomes to control for possible differences across diseases.

HRs with 95% CIs for all categories of exposure were extracted for the analysis, and random-effects models were used to calculate pooled RRs with 95% CIs for highest compared with lowest categories of exposure and the dose-response analysis. Heterogeneity was assessed by using the Q test and I^2 statistic. The level of significance for the Q test was defined as $P < 0.10$. The I^2 statistic represented the amount of total variation that could be attributed to heterogeneity. I^2 values $\leq 25\%$, $\leq 50\%$, $\leq 75\%$, and $>75\%$ indicated no, little, moderate, and significant heterogeneity, respectively. A sensitivity analysis, in which one study at a time was excluded, was performed to assess the stability of results and potential sources of heterogeneity. A meta-regression analysis was conducted to test the effects on risk estimates as sources of heterogeneity of potential confounding factors considering the year of publication, study quality, duration of follow-up, and amount of nut consumption in the highest category of exposure as moderators. We examined these hypothesized variables by fitting a mixed-effect model that included such variables as moderators. To facilitate the interpretation of the effect of moderators, we obtained predicted average RRs by fitting 4 meta-regression models that included each variable. Pooled effects were estimated via weighted least-squares linear regression with the ln of each study-specific HR as a dependent variable and weights equal to the inverse of the sum of the within-study variance and the residual between-study variance. Publication bias was evaluated by a visual investigation of funnel plots for potential asymmetry.

For dose-response analyses, the method reported by Greenland et al. (15) and Orsini et al. (16) was used to calculate study-specific slopes (corrected 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 HRs with 95% CIs for ≥ 3 exposure categories. The median or mean weekly and daily amount of nut consumption in each category was assigned to the corresponding 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. Because of lack of person-year data in some studies, we further evaluated the dose-response effect by calculating the uncorrected linear trend by performing weighted least-squares regression with HRs and CIs extracted for each intake category.

Background characteristics by category of exposure were graphically plotted to evaluate possible correlations. For each study, linear regression coefficients between nut consumption and alcohol, fruit, vegetable, and red meat intakes as well as BMI and prevalence of smoking were estimated, and subsequently, meta-analyses were performed to pool slope coefficients. All analyses were performed with Review Manager (RevMan) version 5.2 software (The Nordic Cochrane Centre, The Cochrane Collaboration) and R version 3.0.3 software (Development Core Team).

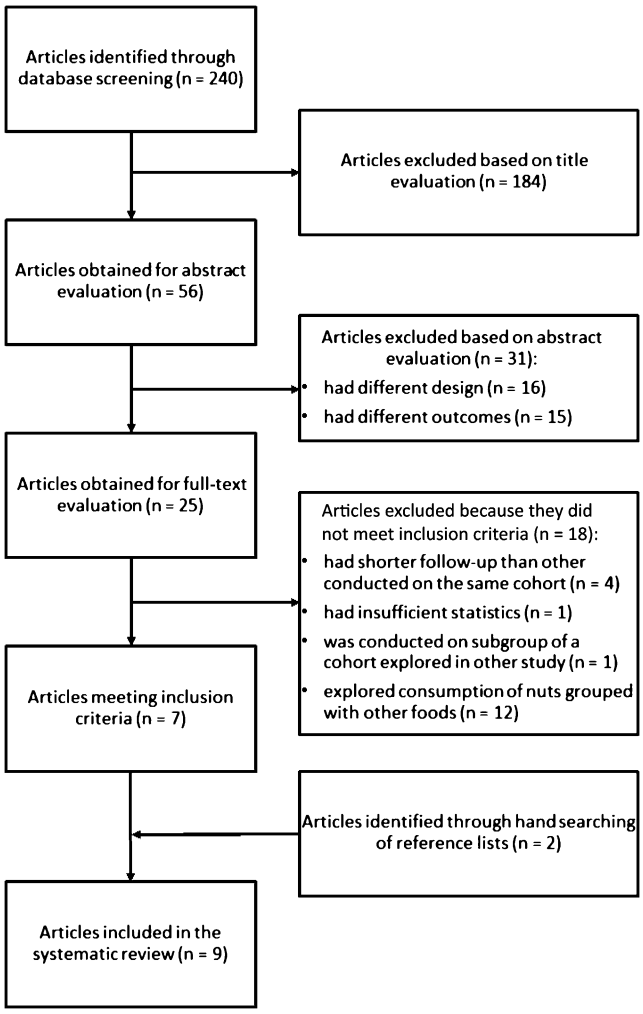

FIGURE 1 Screening and selection process used in this systemic review to include studies that evaluated nut consumption and mortality risk.

RESULTS

Characteristics of included prospective studies

Eighteen of the 25 originally selected studies were excluded after a full-text examination for the following reasons: 1 study reported insufficient statistics, 1 study was conducted in subgroups of a cohort entirely evaluated in another study, 4 studies were conducted in the same cohorts but with shorter follow-up periods, and 12 studies explored the consumption of nuts grouped with other foods. Two additional studies that met the inclusion criteria were identified by hand searching reference lists. This inclusion strategy resulted in the final selection of 9 studies (17–25) (Figure 1) with a total of 354,933 participants, 44,636 cumulative incident deaths, and 3,746,534 cumulative person-years eligible to be included in the systematic review (**Table 1**). Geographically, these studies included 8 cohorts from the United States (17–20, 23, 24), The Netherlands (21), and Spain (22, 25). Most of the studies examined individuals between the ages of 40 and 70 y. All studies included covariates that may have had significant influence on mortality outcomes, such as age, sex (when not analyzed separately), BMI, education, physical activity, and smoking status. Covariates used for adjustments are described in Table 1. In general, study quality was good and comparable in different cohorts, despite one report (24) that presented substantial limitations because it was published in the format of a conference abstract (**Supplemental Table 1**). In addition, only 2 studies (19, 21) were conducted in the general population.

Nut consumption and all-cause mortality

Six studies (18, 19, 22–25) were pooled together to estimate risk of death in individuals with highest compared with lowest intakes of nuts. The analysis revealed an overall inverse association between higher nut consumption and all-cause mortality (RR: 0.77; 95% CI: 0.69, 0.87; **Figure 2**) with moderate evidence of heterogeneity (I^2 = 56%). A sensitivity analysis was performed by the exclusion of one study at a time, and heterogeneity dropped to 49% when we excluded Guasch-Ferré et al. (22), which accounted for the highest weight (9.8%) in included studies. However, no substantial changes in the pooled risk estimate were shown (RR: 0.80; 95% CI: 0.73, 0.89). The funnel plot suggested a publication bias against nonsignificant findings of benefit or harm associated with nuts or, analogously, toward findings with large effect sizes in favor of nuts (**Supplemental Figure 1**A). After the exclusion of these studies from the

TABLE 1
Identified prospective cohort studies evaluating nut consumption and all-cause, stroke, and cardiovascular (including ICD, CAD, and CVD) mortality[1]

Reference	Cohort (country)	Sex	Age range, y	No. of subjects	Outcome	Follow-up, y	Cases, *n*	Person-years	Adjustments	Study quality
Frasier et al., 1992 (17)	Adventists Health Study, non-Hispanic White (US)	Men and women	≥25	26,473	ICD mortality	6	463	158,838	Age, sex, smoking status, physical activity, relative weight, and high blood pressure.	11
Frasier et al., 1997 (18)	Adventists Health Study, black (US)	Men and women	≥25	1668	All-cause mortality	10	153	15,893	Age, smoking status, and physical activity.	10
Ellsworth et al., 2001 (19)	Iowa Women's Health Study (US)	Women	55–69	41,836	All-cause mortality, CAD mortality	10	3726	387,991	Age; energy intake; BMI; waist-to-hip ratio; alcohol consumption; smoking status; history of diabetes, hypertension, and estrogen use; physical activity; education; consumption of cereal fiber, eggs, green leafy vegetables, red meat, and whole-grain foods; and Keys dietary lipid score.	14
Albert et al., 2002 (20)	Physicians' Health Study (US)	Men	40–84	22,071	CAD mortality	17	566	366,751	Age, aspirin, and β-carotene treatment assignment; evidence of CVD before 12-mo questionnaire; BMI; smoking status; history of diabetes, hypertension, and hypercholesterolemia; alcohol consumption; vigorous exercise; vitamin E, vitamin C, and multivitamin use at baseline; fish consumption; and red meat, fruit, vegetable, and dairy intakes at 12 mo of follow-up.	13
van den Brandt, 2011 (21)	Netherlands Cohort Study (The Netherlands)	Men and women	55–69	120,852	All-cause mortality	10	9691	33,872	Age, cigarette smoking status, number of cigarettes smoked per day, years of smoking, BMI, hypertension, highest level of education, and energy intake.	12
Guasch-Ferré et al., 2013 (22)	PREDIMED Study (Spain)	Men and women	55–80	7216	All-cause mortality, CVD mortality, cancer mortality	4.8	323	31,077	Age; sex; intervention group; BMI; smoking status; educational level; leisure-time physical activity; history of diabetes and hypercholesterolemia; use of oral antidiabetic medication, antihypertensive medication, and statins; total energy intake; consumption of vegetables, fruit, red meat, eggs, and fish; alcohol intake; and Mediterranean diet adherence.	13

(Continued)

TABLE 1 (*Continued*)

Reference	Cohort (country)	Sex	Age range, y	No. of subjects	Outcome	Follow-up, y	Cases, *n*	Person-years	Adjustments	Study quality
Bao et al., 2013 (23)	Nurses' Health Study (US)	Women	30–55	76,464	All-cause mortality, CVD mortality, cancer mortality	30	16,200	3,038,853	Age; race; BMI; level of physical activity; status with regard to smoking, whether a physical examination was performed for screening purposes, current multivitamin use, and current aspirin use; status with regard to a family history of diabetes, myocardial infarction, or cancer; status with regard to a history of diabetes, hypertension, or hypercholesterolemia; intakes of total energy, alcohol, red or processed meat, fruit, and vegetables; menopausal status; and hormone use.	13
Bao et al., 2013 (23)	Health Professionals Follow-Up Study (US)	Men	40–75	42,498	All-cause mortality, CVD mortality, cancer mortality	24	11,229		Age; race; BMI; level of physical activity; status with regard to smoking, whether a physical examination was performed for screening purposes, current multivitamin use, and current aspirin use; status with regard to a family history of diabetes, myocardial infarction, or cancer; status with regard to a history of diabetes, hypertension, or hypercholesterolemia; and intakes of total energy, alcohol, red or processed meat, fruit, and vegetables.	13
Djousse et al., 2014 (24)	Physicians' Health Study (US)	Men	40–84	20,742	All-cause mortality, CVD mortality, cancer mortality	9.5	2732		Age; BMI; alcohol use; smoking; exercise; energy, saturated fat, fruit and vegetable, and red meat intakes; and prevalent diabetes and hypertension.	12
Fernández-Montero et al., 2014 (25)	SUN Cohort Study	Men and women	≥18	17,184	All-cause mortality	5	119	80,010	Age; sex; BMI; smoking; alcohol intake; adherence to the Mediterranean diet; use of special diets; marital status; baseline hypercholesterolemia, hypertension, physical activity, and length of television watching; and baseline presence of cancer, cardiovascular disease, or diabetes.	13

[1]CAD, coronary artery disease; CVD, cardiovascular disease; ICD, ischemic coronary disease; PREDIMED, Prevencion con Dieta Mediterranea; SUN, Seguimento University of Navarra.

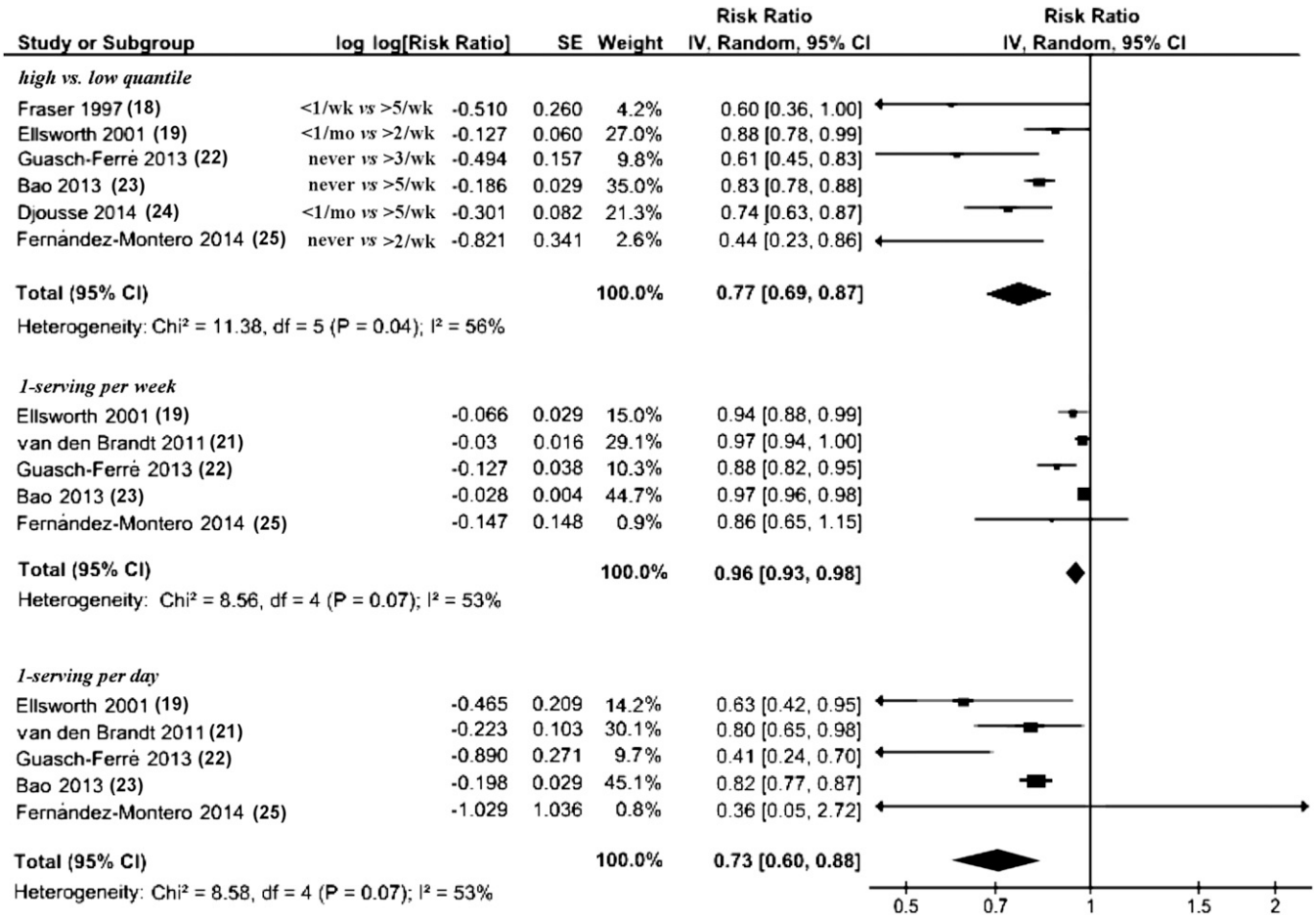

FIGURE 2 Forest plot evaluating pooled risk ratios of all-cause mortality by nut consumption. The size of squares is proportional to the percentage weight of each study; horizontal lines represent 95% CIs; diamonds represent pooled estimates and 95% CIs of risk assessed by considering nut consumption as the category of exposure (highest compared with lowest categories of consumption) or a dose-response analysis (daily and weekly intake of 1 serving, equivalent to 28 g) through corrected linear trends. IV, inverse variance.

analysis, the pooled RR still indicated a 20% decrease in all-cause mortality risk of the highest category of nut consumption (RR: 0.80; 95% CI: 0.73, 0.89). Results of the meta-regression analysis showed none of the moderators examined affected the analysis and, therefore, could potentially explain for the heterogeneity we observed (**Supplemental Table 2**, **Supplemental Figure 2**).

The dose-response analysis that explored the effects of consuming 1-serving nuts/wk and per day was examined in 5 studies (19, 21–23, 25). We excluded studies that did not report detailed information on person-years (18, 24) and included van den Brandt et al. (21), which reported HRs for nut-consumption frequency by treating it as a continuous variable. One serving per week and per day resulted in 4% (RR: 0.96; 95% CI: 0.93, 0.98) and 27% (RR: 0.73; 95% CI: 0.60, 0.88) decreased risk of all-cause mortality, respectively (Figure 2). We observed moderate heterogeneity (I^2 = 53%) and evidence of publication bias with the funnel plot especially for 1-serving/wk (Supplemental Figure 1B, C). Heterogeneity and publication bias were due to the same aforementioned studies, and their exclusion led to comparable but more-consistent results (I^2 = 0%) with no significant change in the final results [RR: 0.97 (95% CI: 0.96, 0.98) for 1-serving/wk; RR: 0.81 (95% CI: 0.77, 0.86) for 1-serving/d). However, although the absolute difference in RR estimates seemed negligible, the exclusion of 2 of 5 studies caused a significant attenuation in RR results of ~25% for weekly consumption and ~30% for daily consumption. An additional dose-response analysis that included all studies strengthened the effect size for both weekly (RR: 0.93; 95% CI: 0.90, 0.96) and daily (RR: 0.59; 95% CI: 0.48, 0.74) consumption of nuts on risk of all-cause mortality (**Supplemental Figure 3**).

Nut consumption and CVD mortality

The association between nut consumption and CVD mortality was evaluated by pooling data from 6 studies (17, 19, 20, 22–24), which accounted for 7775 deaths from CVD. High consumption of nuts was inversely associated with CVD mortality risk compared with for those with the lowest category of intake (RR: 0.71; 95% CI: 0.62, 0.81; **Figure 3**). We observed no significant evidence of heterogeneity (I^2 = 25%) or publication bias (**Supplemental Figure 4**A). After a sensitivity analysis, no significant change of results was shown. However, the meta-regression analysis revealed a significant association with the duration of follow-up as a potential source of heterogeneity

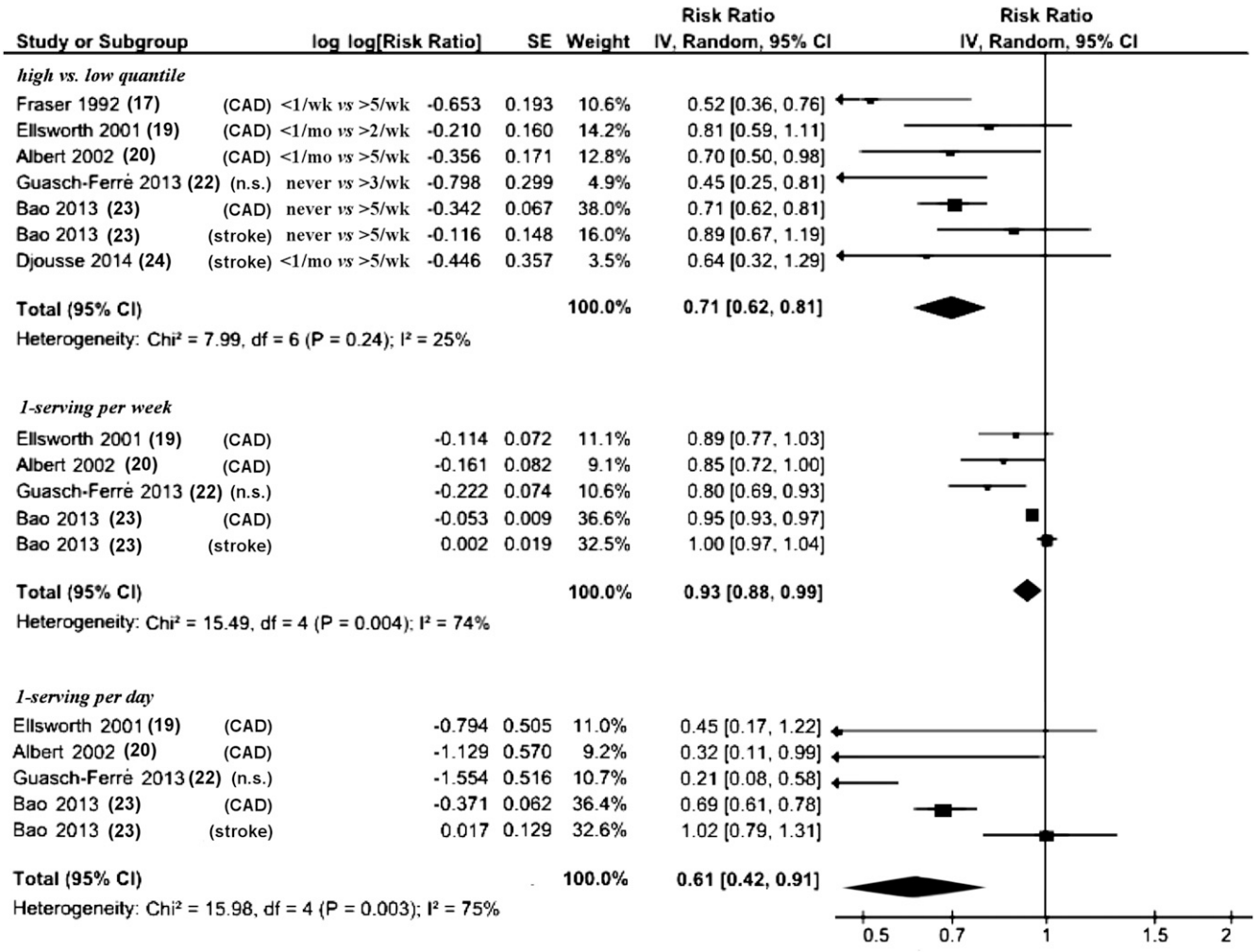

FIGURE 3 Forest plot evaluating pooled risk ratios of cardiovascular mortality (including coronary heart disease and stroke mortality) by nut consumption. The size of squares is proportional to the percentage weight of each study; horizontal lines represents 95% CIs; diamonds represent pooled estimates and 95% CIs of risk assessed by considering nut consumption as the category of exposure (highest compared with lowest categories of consumption) or a dose-response analysis (daily and weekly intake of 1 serving, equivalent to 28 g) through corrected linear trends. CAD, coronary artery disease; IV, inverse variance; n.s., not specified.

(Supplemental Table 2, **Supplemental Figure 5**) because a longer follow-up duration was associated with increased risk toward a null effect.

Pooled RR to estimate HRs for 1-serving nuts/wk and per day was applied to 4 studies (19, 20, 22, 23) and resulted in decreased risks of CVD mortality (RR: 0.93 (95% CI: 0.88, 0.99) and 0.61 (95% CI: 0.42, 0.91), respectively; Figure 3) with evidence of heterogeneity (I^2 = 74% and 75%, respectively) and publication bias on the funnel plot (Supplemental Figure 4B, C). Evidence of publication bias may have been attributed to studies that explored the association between nut consumption and death by stroke (23, 24). When excluded, the analysis resulted in decreased heterogeneity (I^2 = 48%) and stabled pooled risk. The subgroup analysis of studies that evaluated mortality by specific CVD outcomes revealed that nut consumption was associated with significantly decreased risk of CAD death (RR: 0.70; 95% CI: 0.62, 0.79; I^2 = 13%) and a nonsignificant decrease in stroke mortality (RR: 0.84; 95% CI: 0.64, 1.09; I^2 = 0%). The additional dose-response analysis, which included all studies, again strengthened the effect size for both weekly (RR: 0.90; 95% CI: 0.87, 0.92) and daily (RR: 0.48; 95% CI: 0.37, 0.63) consumption of nuts on CVD mortality risk (**Supplemental Figure 6**).

Nut consumption and cancer mortality

Three studies (22–24) that accounted for 10,423 deaths from cancer were included. There was a significant reduction of cancer mortality risk by nut consumption (RR for highest compared with lowest categories of exposure: 0.86; 95% CI: 0.75, 0.98; **Figure 4**) with neither evidence of heterogeneity (I^2 = 16%) nor publication bias (Supplemental Table 2, **Supplemental Figures 7** and **8**). A dose-response analysis was estimated by pooling HRs of 2 studies (22–24) without significant results for both 1-serving nuts/wk and per day (Figure 4, **Supplemental Figure 9**).

Background characteristics associated with nut consumption

Detailed information on subjects' background characteristics by nut consumption was reported in 5 studies (19, 20, 22, 23,

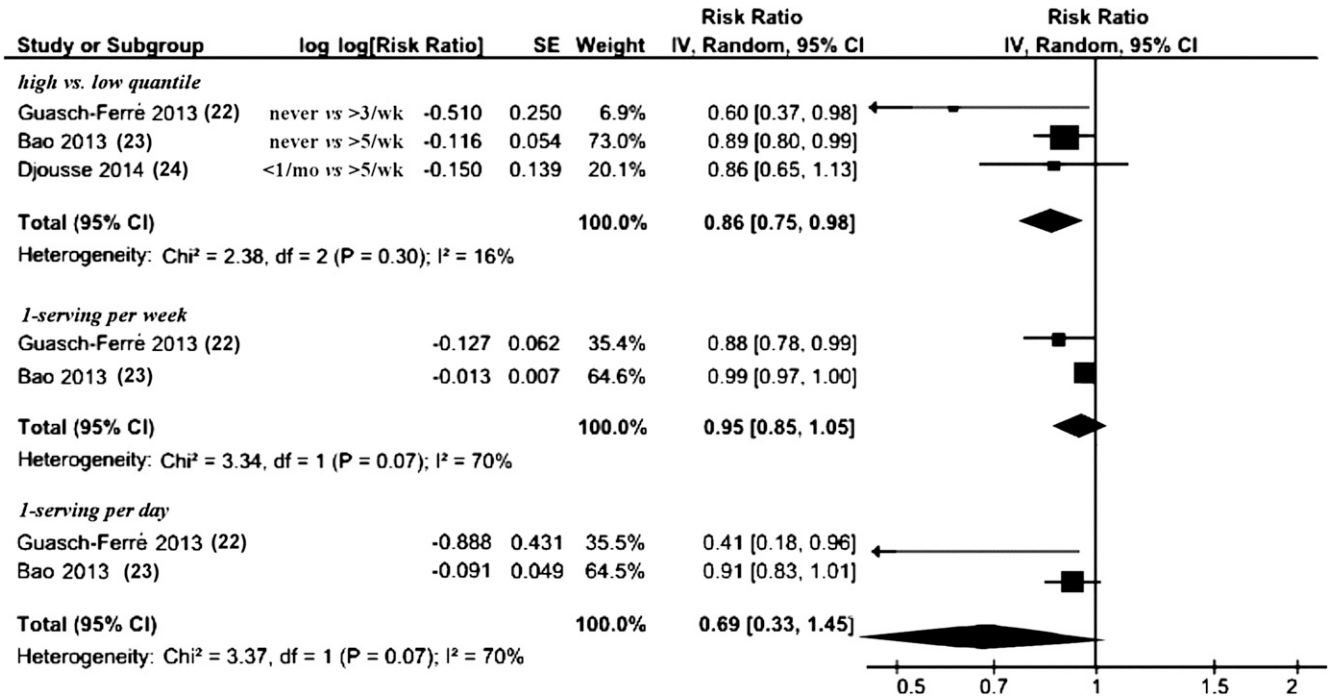

FIGURE 4 Forest plot evaluating pooled risk ratios of cancer mortality by nut consumption. The size of squares is proportional to the percentage weight of each study; horizontal lines represents 95% CIs; diamonds represent pooled estimates and 95% CIs of risk assessed by considering nut consumption as the category of exposure (highest compared with lowest categories of consumption) or a dose-response analysis (daily and weekly intake of 1 serving, equivalent to 28 g) through corrected linear trends. IV, inverse variance.

25). Pooled results of the slope coefficient for a meta-analysis of the linear association between nut consumption and background characteristics revealed that each additional serving per week of nuts was associated with increased alcohol intake of ~1 g/d (slope coefficient: 0.99; SE: 0.79, 1.20), increased fruit intake of ~10 g/d (slope coefficient: 9.82; SE: 4.5, 15.14), and increased vegetable intake of ~13 g/d (slope coefficient: 13.28; SE: 6.09, 20.46), whereas BMI and smoking prevalence decreased by 0.15 (slope coefficient: −0.15; SE: −0.24, −0.06) and 0.59% (slope coefficient: −0.59; SE −0.99, −0.20), respectively (**Figure 5**). No association of nut consumption with red meat was shown.

DISCUSSION

This meta-analysis showed consistent results in prospective cohort studies that supported decreased risks of mortality in individuals with higher nut intake. To the best of our knowledge, this is the first meta-analysis to evaluated the effect of nut consumption on all-cause, CVD, and cancer mortality.

Although nut consumption and CVD-morbidity outcomes have been thoroughly researched in the past, mortality risk is a relatively recent discussion among researchers. Indeed, the first publications that showed potential benefits of nut consumption on CVD mortality were conducted in the early 1990s, such as the Adventist Health Study (17), the Iowa Women Health Study (19), and the Physicians Health Study (20). It was only during the past few years that results from larger cohorts with more-detailed information were published. The association was consistent for all-cause and CVD mortality, whereas the result was marginal for cancer mortality because only 3 studies examined this outcome (22–24). Although our results did not show a significant dose-response effect of nut consumption on cancer mortality, there were very limited studies available to analyze (2), which limited any conclusion.

Overall, the results from this analysis were convincing because a general agreement across studies included was observed in the pooled analysis. Recently published pooled analyses of prospective studies on nut consumption mostly focused on CVD-related morbidities and reported decreased risk of overall CVD, CAD, and hypertension (10–13). On the contrary, nut consumption was not observed to significantly decrease stroke incidence (10), which was in line with our results on the association of stroke mortality.

Nuts are considered one of the most-nutritional foods because they contain high amounts of vegetable protein and unsaturated fatty acids. Nuts have a wide variety of nutrients including dietary fiber, vitamins (folic acid, niacin, tocopherols, and vitamin B-6), minerals (calcium, magnesium, and potassium), and many-other bioactive constituents such as phytosterols and phenolic compounds (26). The unique fat composition of nuts is characterized by a low SFA content (4–16%) and high MUFA content, such as oleic acid, as well as a variable amount of PUFAs, such as α-linolenic acid (the plant omega-3 fatty acid), which is especially abundant in walnuts (27). In other compounds that may exert a certain protection against CVD, nuts have a high content of L-arginine, the precursor of the endogenous vasodilator nitric oxide, which may contribute to vascular reactivity (28). Phytosterols may exert a cholesterol-lowering effect by reducing its absorption (29). Despite their high content of energy, both epidemiologic and experimental studies reported that regular nut consumption does not contribute to obesity (30) nor does it increase risk of developing metabolic syndrome (31). The unique fatty acid composition of nuts is considered one of the key

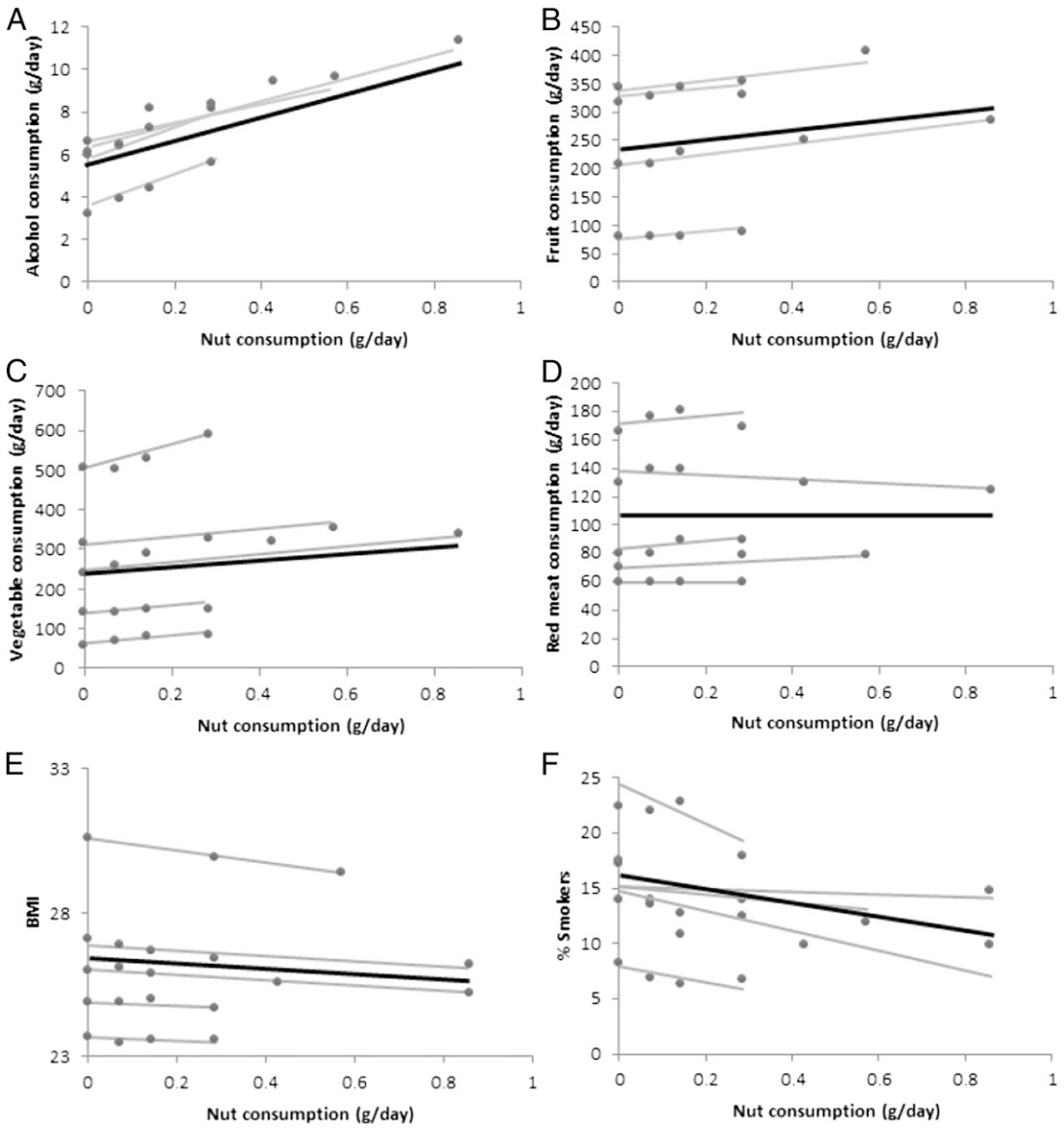

FIGURE 5 Scatter plot for associations between nut consumption and background characteristics including alcohol intake (A), fruit intake (B), vegetable intake (C), red meat intake (D), BMI (E), and the percentage of smokers (F). Light lines represent linear regression coefficients of individual studies; bold lines represent the pooled estimate average increase of each variable per increase of nut intake.

features responsible for the health benefits of nuts, for instance in relation to their lipid-lowering and glucose metabolism ameliorating effects (4, 32). In metabolic syndrome criteria, a meta-analysis of randomized controlled trials with a dietary intervention on the basis of nut administration showed a lowering in triglycerides and fasting plasma glucose compared with the use of control diet interventions (33). There was no effect on waist circumference, HDL cholesterol, or blood pressure, but the direction of effect that favored tree nuts for waist circumference was established (33). In addition, another meta-analysis showed that nuts improved glycemic control in individuals with type 2 diabetes, which further supported the inclusion of nuts in a healthy diet (34).

A number of studies reported that nut consumption was associated with decreased incidences of pancreatic cancer (35) and colorectal cancer (36, 37), whereas some case-control studies reported a decreased association with endometrial cancer (38) and prostate cancer (39), which suggested a logical substrate for the marginally significant decreased risk of cancer mortality observed in this study. It has been hypothesized that nuts provide beneficial protection against cancer through their anti-oxidant and anti-inflammatory properties, for instance, by reducing lipid peroxidation or oxidative DNA damage (40). Fiber and folate in nuts may also play a role in cancer mortality prevention. Fiber decreases intestinal mucosa's exposure to carcinogens by increasing anaerobic fermentation and reducing the intestinal transit duration (31). Folate, which is a B vitamin necessary for normal cellular function, DNA synthesis, and metabolism, may reduce DNA damage or induce repair and is thought to play an important role in detoxifying homocysteine (41). Although experimental studies suggested that nuts may have a chemopreventive action, especially on colorectal and prostate cancer (40), no sufficient evidence confirming their anticancer properties is currently available. Further research is needed to better

understand the potential mechanisms through which nuts may decrease cancer risks.

Potential limitations of studies included in this meta-analysis included possible residual confounding effect by variables not equally distributed in categories of exposure. To further evaluate findings, it is important to consider adjustments for potential confounders. Five studies (19, 20, 22, 23, 25) included in this meta-analysis reported a distribution of baseline characteristics of participants studied. After pooling together data for characteristics that potentially play a role in mortality, we reported that nut consumption was associated with lower BMI and decreased smoking status. In Bao et al. (23), a specific analysis for each potential confounding factor was performed to show that inverse association between nut consumption and mortality persisted across subgroups, but no additional analyses could be retrieved from other studies. Similarly, all investigations agreed that nut consumption was correlated with fruit, vegetable, and alcohol intakes. Although we had limited information on participants' background characteristics from other cohorts, our analyses on studies with sufficient data indicated that higher nut consumption was positively correlated with healthier background characteristics. It is unclear if the protective effects we observed were mediated by nut consumption or through the clustering of healthy food preferences. Nonetheless, nut consumption may reflect overall healthier lifestyle choices that eventually lead to decreased mortality risk.

Our study also has some specific limitations. First, cancer mortality was assessed in only 3 of the 9 cohorts investigated. Besides the lower statistical power than in other analyses, it was also possible that results from other cohorts on nut consumption and cancer mortality were not significant and unpublished. Second, our analysis indicated an association between nut consumption and mortality, but whether or not the relation is independent of other dietary or lifestyle factors remains unknown. Thus, as previously suggested, higher nut consumption may be part of better nutrition and lifestyle habits that all contribute to decreased mortality. Third, questions about specific consumption over time, duration, and type of nuts in relation with mortality remain to be elucidated. Forth, most of the studies included were conducted in specific group of individuals with social [i.e., health care workers (20, 23) and postgraduate students (25)] or health-related [i.e., individuals at high CVD risk (22)] characteristics that differed them from general population. Thus, findings from such cohorts may not be universally generalizable.

In conclusion, nut consumption is inversely associated with all-cause, CVD, and cancer mortality. Future research should emphasize the exploration of more-detailed background characteristics of study population to better isolate the independent effects of nut consumption from overall dietary patterns, lifestyle habits, and mortality. Moreover, more information on the specific types of nuts consumed would be of interest to better identify specific constituents responsible for their health benefits.

The authors' responsibilities were as follows—GG: designed the research; GG and SM: conducted the research; GG, SM, and AM: analyzed data; GG, JY, and SNK: wrote the manuscript; and GG, FG, and SNK: had primary responsibility for the final content of the manuscript. None of the authors reported a conflict of interest related to the study.

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