Nut consumption and risk of mortality in the Physicians' Health Study[1–4]

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ABSTRACT

Background: Previous studies have suggested that nut consumption is associated with beneficial cardiovascular outcomes. However, limited data are available on the association between nut intake and all-cause mortality.

Objective: Our aim was to test the hypothesis that nut consumption is inversely associated with the risk of all-cause mortality.

Design: In this prospective cohort study in 20,742 male physicians, we assessed nut intake between 1999 and 2002 via a food-frequency questionnaire and ascertained deaths through an endpoint committee. We used Cox regression to estimate multivariable-adjusted HRs for death according to nut consumption. In secondary analyses, we evaluated associations of nut consumption with cause-specific mortality.

Results: During a mean follow-up of 9.6 y, there were 2732 deaths. The mean (±SD) age at baseline was 66.6 ± 9.3 y. Median nut consumption was 1 serving/wk. Multivariable-adjusted HRs (95% CIs) were 1.0 (reference), 0.92 (0.83, 1.01), 0.85 (0.76, 0.96), 0.86 (0.75, 0.98), and 0.74 (0.63, 0.87) for nut consumption of never or <1 serving/mo, 1–3 servings/mo, 1 serving/wk, 2–4 servings/wk, and ≥5 servings/wk, respectively (*P*-linear trend < 0.0001), after adjustment for age, body mass index, alcohol use, smoking, exercise, prevalent diabetes and hypertension, and intakes of energy, saturated fat, fruit and vegetables, and red meat. In a secondary analysis, results were consistent for cardiovascular disease mortality but only suggestive and non–statistically significant for coronary artery disease and cancer mortality.

Conclusion: Our data are consistent with an inverse association between nut consumption and the risk of all-cause and cardiovascular disease mortality in US male physicians. *Am J Clin Nutr* 2015;101:407–12.

Keywords cardiovascular disease, coronary artery disease, mortality, nut consumption, nuts

INTRODUCTION

Nuts (peanuts and tree nuts) are rich in a variety of nutrients, including folate, niacin, vitamin E, and vitamin B-6 (1, 2). They are also rich in a number of macronutrients, such as unsaturated fatty acids, dietary fiber, phytoestrogens, phytochemicals, and micronutrients such as essential minerals, including copper, magnesium, potassium, and zinc (3).

Because nuts are important dietary sources of vitamin E and unsaturated fatty acids, it has been speculated that their antioxidant and anti-inflammatory properties may have a beneficial impact on overall health (4–10). Observational studies and small clinical trials have shown that nut consumption reduces the risk of cardiovascular disease (CVD)[5] and type 2 diabetes (11–13). The pathophysiologic mechanisms remain unclear but may be due to the beneficial effects nuts have on blood cholesterol, inflammatory markers, and endothelial function (14–17). A Mediterranean diet supplemented with 30 g of mixed nuts/d lowers blood pressure compared with the typically recommended low-fat diet (18, 19). Nut consumption was also found to be protective against cancer (17, 20, 21). The micronutrients within nuts may combat free radicals and inflammation commonly implicated in increasing cancer risk.

Few studies have examined the relation between nuts and mortality (22–26). Some of these studies were conducted in European populations in whom nut consumption is more frequent than in US populations. It would be important to elucidate the role of nut consumption on the risk of overall mortality in large population settings. Hence, we sought to determine whether nut consumption is associated with the risk of death in a large prospective cohort of US male physicians.

SUBJECTS AND METHODS

Study population

The Physicians' Health Study (PHS) I trial was a large, randomized, double-blind placebo-controlled trial designed to assess the effects of aspirin and β-carotene on CVD and cancer in 22,071 male physicians. The PHS II was also a randomized trial designed to assess the effects of vitamins on CVD and cancer in

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[5] Abbreviations used: CAD, coronary artery disease; CVD, cardiovascular disease; FFQ, food-frequency questionnaire; PHS, Physicians' Health Study.

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7000 newly recruited male physicians and 7641 participants from PHS I. A detailed description of the PHS I and PHS II was previously published (27–31). Subsequently, we will refer to subjects who provided information on nut consumption (1997–2001) as PHS participants. All PHS participants provided written informed consent and the Institutional Review Board at Brigham and Women's Hospital approved the study. Of the total 29,071 PHS participants, 21,075 completed food-frequency questionnaires (FFQs) and were alive at baseline (between 1999 and 2002). Of these, we excluded 333 subjects due to missing data on nut consumption. Thus, a final sample of 20,742 male participants was used for the current analyses.

Assessment of nut consumption

Nut consumption information was self-reported by using a self-administered FFQ between 1999 and 2002. Participants were asked, "Please fill in your average use, during the year, of each specified food: Nuts [small packet or 1 ounce (~28.4 g)]." Possible response categories included "never or less than once per month," "1–3 servings/mo," "1 serving/wk," "2–4 servings/wk," "5–6 servings/wk," "1 serving/d, "2–3 servings/d, "4–5 servings/d," and ≥6 servings/d." Approximately 3% of participants indicated consumption of ≥1 serving/d, so these responses were combined with 5–6 servings/wk for stable estimation. Participants were asked about nuts without specifically excluding peanuts. Hence, "nuts" in the current article could include peanuts. We did, however, ask subjects to report information on peanut butter intake: "Please fill in your average use, during the year, of each specified food: Peanut butter (1 tablespoon)." Although the FFQ was not validated in the PHS, it has been validated in several other cohorts (32, 33).

Ascertainment of deaths

A questionnaire was mailed to participants every 6 mo during the first year and annually thereafter to collect data on intervention compliance and new medical diagnoses, including death. Participants who did not return the questionnaires within 5–6 wk were sent a follow-up questionnaire. Up to 4 questionnaires were sent to nonrespondents. Last, subjects were called if they were still nonrespondents. A letter with a return postcard was also mailed to participants at the 6-mo time point between annual mailings, which was to be completed if any major medical problems (e.g., death) occurred. An endpoints committee confirmed death after review of the medical records. The deaths were categorized by type as due to CVD, coronary artery disease (CAD), stroke, or cancer and based on review of autopsy reports, death certificates, medical records, or family/next of kin report (27, 30, 31, 34, 35). Details on endpoint validation in the PHS have been published.

Other variables

Demographic data including BMI were collected at baseline. Data on exercise, smoking, alcohol consumption, and nonsteroidal anti-inflammatory use were obtained through self-report at baseline on enrollment. Information on comorbidity was gathered through annual follow-up questionnaires. Other dietary variables were obtained from the FFQ as were energy and nutrient intakes.

Statistical analyses

We computed person-time of follow-up from exposure assessment (at the date the FFQ was received) until the first occurrence of either death or date of last available participant information. For each category of nut consumption, the incidence rate was initially computed by dividing the number of cases by corresponding person-time of follow-up. We used Cox regression proportional hazards models to compute multivariable-adjusted HRs with corresponding 95% CIs using <1 serving of nuts/mo as the reference group. In secondary analyses, we evaluated associations of nut consumption with cause-specific mortality (CAD, CVD, stroke, or cancer deaths). Our adjusted model controlled for age, BMI (continuous), smoking (never, former, or current), alcohol consumption in the past year (<1, 1–4, 5–7, or ≥8 drinks/wk), exercise (none, 1–2 d/wk, 3–4 d/wk, or 5–7 d/wk), prevalent diabetes, prevalent hypertension, and intakes of red meat (tertiles), fruit and vegetables (tertiles), saturated fat (tertiles), and energy (tertiles). We were unable to distinguish "never" from "former" drinkers. We also examined a fully adjusted model that controlled for these factors plus magnesium and fiber intakes. For categorical variables, indicator variables were created for missing responses. We performed additional post hoc analyses stratified by other risk factors, namely BMI and prevalent type 2 diabetes. To test the assumptions for proportional hazard models, we evaluated plots of Schoenfeld residuals and person-time, and no significant violations were found. All analyses were performed by using SAS, version 9.3 (SAS Institute). The significance level was set at $\alpha = 0.05$, with 2-tailed P values.

RESULTS

Baseline characteristics of the 20,742 subjects included in this study are summarized in **Table 1**. The mean (±SD) age was 66.6 ± 9.3 y. Participants who consumed nuts more frequently had a lower BMI ($P < 0.0001$), were less likely to be former smokers ($P = 0.02$), were more likely to exercise frequently ($P < 0.0001$ for both 3–4 d/wk and <1 d/wk), consumed more fruit and vegetables ($P < 0.0001$), and had a higher energy intake ($P < 0.0001$). There was a tendency toward a nonlinear, U-shaped association between exercise frequency and nut consumption. In testing for nonlinear trend, we found that the association between frequent activity/exercise and nut consumption frequency of 3–4 servings/wk was $P = 0.0589$ but for ≥5 d/wk was $P = 0.0007$. Participants were also more likely to consume magnesium, fiber, and polyunsaturated and monounsaturated fats overall ($P < 0.0001$ for all). Participants who consumed nuts more frequently were also less likely to have prevalent heart failure ($P = 0.01$), hypertension ($P \leq 0.0001$), or myocardial infarction ($P < 0.001$).

During the mean follow-up of 9.6 y, there were 2732 deaths, including 760 (27.8%) deaths due to CVD, 868 (31.8%) cancer deaths, 405 (14.8%) CAD deaths, and 142 (5.2%) stroke deaths. Multivariable-adjusted HRs (95% CIs) for total deaths after adjustment for age, BMI, alcohol use, smoking, exercise, prevalent diabetes, hypertension, and intakes of energy, saturated fat, fruit and vegetables, and red meat were 1.0 (reference), 0.92 (0.83, 1.01), 0.85 (0.76, 0.96), 0.86 (0.75, 0.98), and 0.74 (0.63, 0.87) for nut consumption of rarely/<1 serving/mo,

TABLE 1
Baseline characteristics of PHS participants according to frequency of nut consumption[1]

	<1 serving/mo (*n* = 5439)	1–3 servings/mo (*n* = 7128)	1 serving/wk (*n* = 3947)	2–4 servings/wk (*n* = 2582)	≥5 servings/wk (*n* = 1646)	*P*-trend
Age, y	67.4 ± 9.5[2]	66.1 ± 9.2	66.2 ± 9.1	66.6 ± 9.2	67.2 ± 8.9	0.75
BMI, kg/m^2	25.7 ± 3.4	25.9 ± 3.4	25.9 ± 3.3	25.7 ± 3.2	25.3 ± 3.3	<0.0001
Smoking, %						
Never	51.7	54.7	55.0	54.9	54.5	0.01
Past	44.5	42.0	41.8	41.9	41.9	0.02
Current	3.7	3.3	3.1	3.1	3.6	0.30
Exercise, %						
<1 d/wk	40.0	37.0	37.0	34.4	34.8	<0.0001
1–2 d/wk	14.5	17.2	16.8	15.8	16.2	0.15
3–4 d/wk	27.1	29.1	29.8	33.7	30.2	<0.0001
5–7 d/wk	16.5	15.0	14.9	14.8	17.4	0.65
Alcohol consumption in past year, %						
Never or <1/mo	18.2	16.8	15.7	15.8	22.3	0.37
Monthly	8.9	7.8	6.7	6.1	7.1	<0.0001
Weekly	38.4	38.9	38.7	37.1	32.3	0.0002
Daily	34.1	35.9	38.2	40.5	38.0	<0.0001
Prevalent heart failure, %	2.7	2.0	2.3	1.7	1.8	0.01
Prevalent hypertension, %	48.9	45.7	46.1	45.3	43.1	<0.0001
Prevalent diabetes, %	8.6	7.0	7.0	7.1	9.0	0.43
Prevalent MI, %	4.7	4.5	4.3	2.9	3.7	0.001
Daily intake, kcal	1526.5 ± 466.9	1631.0 ± 478.4	1738.8 ± 517.0	1846.6 ± 535.2	2022.5 ± 592.2	<0.0001
Fruit and vegetables, servings/d	4.5 ± 2.6	4.7 ± 2.4	5.0 ± 2.8	5.3 ± 2.8	5.9 ± 3.4	<0.0001
Red meat, servings/d	0.6 ± 0.5	0.7 ± 0.6	0.8 ± 0.6	0.8 ± 0.7	0.8 ± 0.9	<0.0001
Saturated fat,[3] g/d	16.4 ± 7.5	18.4 ± 5.4	18.9 ± 5.1	18.8 ± 5.4	18.6 ± 5.8	<0.0001
Sodium intake,[3] kcal	1502.8 ± 348.4	1497.6 ± 326.0	1500.4 ± 301.2	1472.2 ± 289.6	1423.0 ± 311.1	<0.0001
Magnesium,[3] mg/d	303.2 ± 261.0	303.1 ± 264.8	302.1 ± 263.9	314.5 ± 276.1	338.3 ± 294.2	
Fiber,[3] g/d	18.0 ± 14.2	18.0 ± 14.5	17.9 ± 14.5	18.7 ± 15.0	19.6 ± 15.9	<0.0001
Potassium,[3] mg/d	3039.0 ± 2672.4	2994.5 ± 2671.3	2975.6 ± 2658.2	2963.0 ± 2660.6	2956.9 ± 2605.1	<0.0001
Dietary polyunsaturated fat,[3] g/d	7.1 ± 6.1	7.8 ± 6.7	8.3 ± 7.3	9.5 ± 8.4	11.7 ± 10.2	<0.0001
Dietary mono-unsaturated fat,[3] g/d	17.6 ± 13.8	18.4 ± 15.0	19.5 ± 16.1	20.8 ± 17.4	23.3 ± 19.2	<0.0001
NSAID use >180 d/y, %	7.0	7.2	7.2	6.9	7.3	0.8209

[1]Mantel-Haenszel chi-square test was used for categorical variables; ANOVA was used for continuous variables to determine the significance of the associations between nut consumption frequency and various baseline characteristic categories. Daily, ≥1 drink/d; MI, myocardial infarction; Monthly, 1–3 drinks/mo; NSAID, nonsteroidal anti-inflammatory drug; PHS, Physicians' Health Study; Weekly, 1–6 drinks/wk.

[2]Mean ± SD (all such values).

[3]Calorie adjusted.

1–3 servings/mo, 1 serving/wk, 2–4 servings/wk, and ≥5 servings/wk, respectively (*P*-linear trend < 0.001; **Table 2**). Additional adjustment for magnesium and fiber intake had little effect on the results [corresponding HRs (95% CIs): 1.0 (reference), 0.92 (0.83, 1.01), 0.84 (0.75, 0.95), 0.86 (0.75, 0.95), and 0.76 (0.64, 0.89), respectively (*P*-linear trend < 0.001; Table 2)].

In a secondary analysis, the inverse association between nut consumption and mortality was consistent among participants who succumbed to CVD. Corresponding multivariable-adjusted HRs (95% CIs) were 1.0 (reference), 0.98 (0.82, 1.17), 0.89 (0.72, 1.11), 0.80 (0.62, 1.03), and 0.74 (0.55, 1.02) across consecutive categories of nut consumption, respectively (*P*-trend = 0.015).

TABLE 2
HRs (95% CIs) of all-cause mortality according to categories of nut consumption[1]

	Frequency of nut consumption in the Physicians' Health Study					
All-cause mortality	<1 serving/mo	1–3 servings/mo	1 serving/wk	2–4 servings/wk	≥5 servings/wk	*P*-trend
Cases/total, *n*	863/5439	894/7128	475/3947	317/2582	183/1646	
Age-adjusted HRs	1.00 (reference)	0.88 (0.80, 0.96)	0.82 (0.74, 0.92)	0.82 (0.72, 0.93)	0.71 (0.60, 0.83)	<0.001
Fully adjusted HRs[2]	1.00 (reference)	0.92 (0.83, 1.01)	0.85 (0.76, 0.96)	0.86 (0.75, 0.98)	0.74 (0.63, 0.87)	<0.001
Fully adjusted HRs + magnesium and fiber	1.00 (reference)	0.92 (0.83, 1.01)	0.84 (0.75, 0.95)	0.86 (0.75, 0.95)	0.76 (0.64, 0.89)	0.001

[1]Cox regression proportional hazards models were used to compute multivariable-adjusted HRs with corresponding 95% CIs with <1 serving of nuts/mo as the reference group.

[2]Fully adjusted for age, BMI, alcohol consumption, smoking, exercise, calories, saturated fat consumption, fruit/vegetable consumption, red meat consumption, prevalent diabetes, and hypertension.

TABLE 3
HRs (95% CIs) of cause-specific mortality according to categories of nut consumption[1]

	Frequency of nut consumption in the Physicians' Health Study					
	<1 serving/mo	1–3 servings/mo	1 serving/mo	2–4 servings/wk	≥5 servings/wk	*P*-trend
CVD deaths						
Cases/total *n*	235/5439	256/7128	135/3947	83/2582	51/1646	
Age-adjusted HRs	1.00 (reference)	0.94 (0.78, 1.12)	0.87 (0.71, 1.08)	0.80 (0.62, 1.02)	0.74 (0.55, 1.00)	0.013
Fully adjusted HRs[2]	1.00 (reference)	0.98 (0.82, 1.17)	0.89 (0.72, 1.11)	0.80 (0.62, 1.03)	0.74 (0.55, 1.02)	0.015
CAD deaths						
Cases/total *n*	129/5439	140/7128	69/3947	38/2582	29/1646	
Age-adjusted HRs	1.00 (reference)	0.94 (0.74, 1.19)	0.81 (0.61, 1.09)	0.67 (0.46, 0.96)	0.77 (0.51, 1.15)	0.019
Fully adjusted HRs[2]	1.00 (reference)	1.02 (0.80, 1.30)	0.88 (0.66, 1.19)	0.72 (0.50, 1.04)	0.85 (0.56, 1.28)	0.083
Cancer deaths						
Cases/total *n*	262/5439	284/7128	155/3947	101/2582	66/1646	
Age-adjusted HRs	1.00 (reference)	0.89 (0.75, 1.05)	0.87 (0.71, 1.06)	0.84 (0.67, 1.06)	0.83 (0.63, 1.08)	0.071
Fully adjusted HRs[2]	1.00 (reference)	0.91 (0.77, 1.08)	0.88 (0.72, 1.07)	0.87 (0.68, 1.09)	0.87 (0.66, 1.15)	0.161
Stroke deaths						
Cases/total *n*	43/5439	46/7128	25/3947	19/2563	10/1646	
Age-adjusted HRs	1.00 (reference)	0.93 (0.61, 1.41)	0.89 (0.54, 1.45)	1.00 (0.58, 1.71)	0.80 (0.40, 1.59)	0.637
Fully adjusted HRs[2]	1.00 (reference)	0.91 (0.60, 1.39)	0.82 (0.50, 1.36)	0.84 (0.48, 1.47)	0.64 (0.32, 1.30)	0.205

[1]Cox regression proportional hazards models were used to compute multivariable-adjusted HRs with corresponding 95% CIs with <1 serving of nuts/mo as the reference group. CAD, coronary artery disease; CVD, cardiovascular disease.

[2]Fully adjusted for age, BMI, alcohol consumption, smoking, exercise, calories, saturated fat consumption, fruit/vegetable consumption, red meat consumption, prevalent diabetes, and hypertension.

Furthermore, the relation of nut consumption with death due to CAD ($P = 0.083$), cancer ($P = 0.161$), and stroke ($P = 0.205$) was not significant (**Table 3**). Collapsing the last 2 higher frequencies of nut consumption did not alter the conclusion. In our post hoc analyses, we stratified by BMI and diabetes because people may avoid nuts once they develop diabetes or become overweight/obese as a means to lose weight. However, neither BMI nor diabetes modified the association of nut consumption with mortality (**Table 4**).

DISCUSSION

We found a significant and inverse association between frequency of nut consumption and all-cause mortality in a large prospective cohort of US male physicians, after adjustment for confounding factors. Neither BMI nor diabetes modified this association. As expected, diets higher in magnesium, fiber, and poly- and monounsaturated fats were more common among participants who consumed nuts frequently. There was also a significant inverse relation between nut consumption and CVD mortality but not deaths due to cancer, stroke, or CAD.

Our results are comparable to the findings of Bao et al. (26) who reported a 20% lower mortality rate for nut consumption of ≥7 servings/wk compared with none in the Nurses' Health Study and the Health Professionals Follow-Up Study. Smaller previous observational studies, including the Adventist Health Study (36–38), the Iowa Women's Health Study (23), the Netherlands Cohort Study (39), and a United Kingdom cohort (40) also showed similar inverse associations between nut consumption and mortality among whites, African Americans, and older persons (22, 23, 36–40). Estruch et al. (18, 19) demonstrated

TABLE 4
HRs (95% CIs) of total mortality according to nut consumption, stratified by BMI and prevalent diabetes[1]

	Frequency of nut consumption in the Physicians' Health Study					
	<1 serving/mo	1–3 servings/mo	1 serving/wk	2–4 servings/wk	≥5 servings/wk	*P*-interaction
BMI[2] (kg/m^2)						0.40
<25	1.00 (reference)	0.91 (0.80, 1.05)	0.79 (0.67, 0.94)	0.88 (0.73, 1.06)	0.61 (0.48, 0.78)	
25 to <30	1.00 (reference)	0.94 (0.82, 1.09)	0.89 (0.75, 1.06)	0.85 (0.69, 1.04)	0.91 (0.72, 1.15)	
≥30	1.00 (reference)	0.83 (0.61, 1.15)	1.02 (0.71, 1.46)	0.95 (0.62, 1.44)	0.81 (0.45, 1.47)	
Prevalent diabetes[3]						0.97
No	1.00 (reference)	0.91 (0.83, 1.02)	0.85 (0.75, 0.97)	0.87 (0.76, 1.01)	0.73 (0.61, 0.88)	
Yes	1.00 (reference)	0.91 (0.70, 1.18)	0.89 (0.66, 1.19)	0.78 (0.54, 1.21)	0.72 (0.48, 1.09)	

[1]Cox regression proportional hazards models were used to compute multivariable-adjusted HRs with corresponding 95% CIs with <1 serving of nuts/mo as the reference group.

[2]Fully adjusted for age, alcohol consumption, smoking, exercise, calories, saturated fat consumption, fruit/vegetable consumption, red meat consumption, prevalent diabetes, and hypertension.

[3]Adjusted for age, BMI, alcohol consumption, smoking, exercise, calories, saturated fat consumption, fruit/vegetable consumption, red meat consumption, and hypertension.

in their multicenter randomized trial that an intervention with a Mediterranean diet supplemented with 30 g of mixed nuts/d was associated with a 28% lower risk of cardiovascular events (myocardial infarction, stroke, and death from other cardiovascular causes) when compared with a control diet.

Many previous studies have shown beneficial effects of nut consumption on various risk factors and disease-specific biomarkers (11–19), although the underlying pathophysiologic pathways remain to be clearly elucidated. Nuts are rich in both magnesium and fiber, but arguably, healthy eaters may also consume these nutrients from other dietary sources. We found that additional adjustment for magnesium and fiber did not alter the inverse relation between nut consumption and mortality, suggesting that the beneficial effects of nuts on mortality may be mediated via pathways that do not involve fiber or magnesium. Nut consumption has been shown to lower blood pressure, improve lipid profiles (41–45), decrease inflammation (46–48), and increase insulin sensitivity (10, 49). Nuts may decrease blood pressure by virtue of their low sodium and high magnesium content (50). Dietary magnesium was shown to decrease blood pressure by acting as a calcium channel blocker and vasodilator via prostacyclin production and nitrous oxide synthesis (51–53). Nut intake improves lipid profiles, perhaps through their high fiber content, omega-3 fatty acids, and antioxidants. Nut consumption can also decrease inflammatory markers including C-reactive peptide, IL-6, and fibrinogen, thus preventing atherosclerosis (9, 47). Despite inconsistent data available in the literature, there is some evidence that, at higher concentrations, ω-3 fatty acids in nuts (primarily α-linolenic acid, 18:3n−3) can inhibit platelet activation and aggregation, which has a preventative role in cerebrovascular events and myocardial ischemia (54, 55). Finally, nut consumption may lower the risk of type 2 diabetes through a decrease in insulin resistance and hyperglycemia (15, 56–58). There are also sufficient data from other observational studies and interventional trials suggesting that unsaturated fatty acids, high fiber content, healthy proteins, minerals, phytochemicals, and antioxidants in nuts might be beneficial for human health when consumed frequently (18, 19, 24–26).

Our prospective cohort study in the PHS participants has a number of strengths, including the long duration of follow-up of nearly a decade, a large sample size, and a relatively large number of confirmed deaths. Finally, ascertainment of mortality and cause of death was thorough, with a careful review of the medical records by an endpoint committee. The wealth of demographic, medical, and lifestyle data on this particular population allowed us to minimize confounding by measured factors.

In contrast, the observational nature of our study prevents us from establishing causality between nut consumption and mortality. Other limitations of our study include limited generalizability of our results because only male physicians who were relatively healthy at baseline were recruited and these male physicians are more likely to be different in their behaviors and lifestyles than the general US population. Nut consumption was only assessed once and although the questionnaire asked about peanut butter use, the types of nuts (tree nuts and peanuts) and their preparations (roasted, salted, spiced, or raw) were not ascertained. We had limited statistical power to detect small effect sizes in the higher nut consumption categories (2–4 servings/wk and ≥5 servings/wk), given the small sample sizes and fewer numbers of deaths in these groups. To explore this, we collapsed the last 2 consumption categories to increase sample size and statistical power. Ultimately, the associations remained the same for cause-specific mortality.

Participants could have changed their dietary habits during the 10 y of follow-up, with a subsequent impact on their risk of death. The resulting misclassification, however, would likely bias the results toward the null, producing a more conservative estimate of the true effect of nuts on mortality. Finally, there is a potential for reverse causality, in that people with chronic diseases and poor health (including poor dentition, severe food allergies, and dietary restrictions such as puréed foods) may abstain from nut consumption.

In conclusion, our study suggests an inverse association between nut consumption and all-cause mortality in male physicians. These promising prospective results underscore the need for future research designed to establish whether the observed nut-mortality relation is causal. The type of nuts, method of preparation, and portion sizes necessary for maximal health benefits should also be explored in further studies.

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REFERENCES

1. Ye X, Scott T, Gao X, Maras JE, Bakun PJ, Tucker KL. Mediterranean diet, Healthy Eating Index 2005, and cognitive function in middle-aged and older Puerto Rican adults. J Acad Nutr Diet 2013;113:276–81, e271–3.
2. Nurk E, Refsum H, Drevon CA, Tell GS, Nygaard HA, Engedal K, Smith AD. Cognitive performance among the elderly in relation to the intake of plant foods: the Hordaland Health Study. Br J Nutr 2010;104:1190–201.
3. Kesse-Guyot E, Andreeva VA, Lassale C, Ferry M, Jeandel C, Hercberg S, Galan P; Supplementation with Vitamins and Mineral Antioxidants (SU.VI.MAX) Research Group. Mediterranean diet and cognitive function: a French study. Am J Clin Nutr 2013;97:369–76.
4. Cunnane S. Good fats, bad fats, polyunsaturated fatty acids, and cognition in the elderly. Ann Neurol 2013;73:438.
5. Cunnane SC, Chouinard-Watkins R, Castellano CA, Barberger-Gateau P. Docosahexaenoic acid homeostasis, brain aging and Alzheimer's disease: can we reconcile the evidence? Prostaglandins Leukot Essent Fatty Acids 2013;88:61–70.
6. Cunnane SC, Schneider JA, Tangney C, Tremblay-Mercier J, Fortier M, Bennett DA, Morris MC. Plasma and brain fatty acid profiles in mild cognitive impairment and Alzheimer's disease. J Alzheimers Dis 2012;29:691–7.
7. Gopinath B, Buyken AE, Flood VM, Empson M, Rochtchina E, Mitchell P. Consumption of polyunsaturated fatty acids, fish, and nuts and risk of inflammatory disease mortality. Am J Clin Nutr 2011;93:1073–9.
8. Torabian S, Haddad E, Rajaram S, Banta J, Sabate J. Acute effect of nut consumption on plasma total polyphenols, antioxidant capacity and lipid peroxidation. J Hum Nutr Diet 2009;22:64–71.
9. Jiang R, Jacobs DR Jr., Mayer-Davis E, Szklo M, Herrington D, Jenny NS, Kronmal R, Barr RG. Nut and seed consumption and inflammatory markers in the multi-ethnic study of atherosclerosis. Am J Epidemiol 2006;163:222–31.
10. Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. Nut and peanut butter consumption and risk of type 2 diabetes in women. JAMA 2002;288:2554–60.
11. Féart C, Samieri C, Rondeau V, Amieva H, Portet F, Dartigues JF, Scarmeas N, Barberger-Gateau P. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. JAMA 2009;302:638–48.

12. O'Neil CE, Keast DR, Nicklas TA, Fulgoni VL III. Nut consumption is associated with decreased health risk factors for cardiovascular disease and metabolic syndrome in U.S. adults: NHANES 1999-2004. J Am Coll Nutr 2011;30:502–10.
13. Grant WB. Diet and risk of dementia: does fat matter? The Rotterdam Study. Neurology 2003;60:2020–1.
14. Casas-Agustench P, Bullo M, Ros E, Basora J, Salas-Salvado J, Nureta-PREDIMED investigators. Cross-sectional association of nut intake with adiposity in a Mediterranean population. Nutr Metab Cardiovasc Dis 2011;21:518–25.
15. Casas-Agustench P, Lopez-Uriarte P, Bullo M, Ros E, Cabre-Vila JJ, Salas-Salvado J. Effects of one serving of mixed nuts on serum lipids, insulin resistance and inflammatory markers in patients with the metabolic syndrome. Nutr Metab Cardiovasc Dis 2011;21:126–35.
16. Sabaté J, Oda K, Ros E. Nut consumption and blood lipid levels: a pooled analysis of 25 intervention trials. Arch Intern Med 2010;170:821–7.
17. Jenkins DJ, Kendall CW, Nguyen TH, Teitel J, Marchie A, Chiu M, Taha AY, Faulkner DA, Kemp T, Wong JM, et al. Effect on hematologic risk factors for coronary heart disease of a cholesterol reducing diet. Eur J Clin Nutr 2007;61:483–92.
18. Estruch R, Ros E, Martinez-Gonzalez MA. Mediterranean diet for primary prevention of cardiovascular disease. N Engl J Med 2013;369:676–7.
19. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368:1279–90.
20. González CA, Salas-Salvado J. The potential of nuts in the prevention of cancer. Br J Nutr 2006;96(Suppl 2):S87–94.
21. Singh PN, Fraser GE. Dietary risk factors for colon cancer in a low-risk population. Am J Epidemiol 1998;148:761–74.
22. Goldstein MR. Nuts, nuts good for your heart...? Arch Intern Med 1992;152:2507.
23. Ellsworth JL, Kushi LH, Folsom AR. Frequent nut intake and risk of death from coronary heart disease and all causes in postmenopausal women: the Iowa Women's Health Study. Nutr Metab Cardiovasc Dis 2001;11:372–7.
24. Guasch-Ferré M, Bullo M, Babio N, Martinez-Gonzalez MA, Estruch R, Covas MI, Warnberg J, Aros F, Lapetra J, Serra-Majem L, et al. Mediterranean diet and risk of hyperuricemia in elderly participants at high cardiovascular risk. J Gerontol A Biol Sci Med Sci 2013;68:1263–70.
25. Guasch-Ferré M, Bullo M, Martinez-Gonzalez MA, Ros E, Corella D, Estruch R, Fito M, Aros F, Warnberg J, Fiol M, et al. Frequency of nut consumption and mortality risk in the PREDIMED nutrition intervention trial. BMC Med 2013;11:164.
26. Bao Y, Rosner BA, Fuchs CS. Nut consumption and mortality. N Engl J Med 2014;370:882.
27. Djoussé L, Gaziano JM. Egg consumption in relation to cardiovascular disease and mortality: the Physicians' Health Study. Am J Clin Nutr 2008;87:964–9.
28. Djoussé L, Rudich T, Gaziano JM. Nut consumption and risk of heart failure in the Physicians' Health Study I. Am J Clin Nutr 2008;88:930–3.
29. Christen WG, Gaziano JM, Hennekens CH. Design of Physicians' Health Study II—a randomized trial of beta-carotene, vitamins E and C, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of results of completed trials. Ann Epidemiol 2000;10:125–34.
30. Kurth T, Gaziano JM, Berger K, Kase CS, Rexrode KM, Cook NR, Buring JE, Manson JE. Body mass index and the risk of stroke in men. Arch Intern Med 2002;162:2557–62.
31. Muntwyler J, Hennekens CH, Manson JE, Buring JE, Gaziano JM. Vitamin supplement use in a low-risk population of US male physicians and subsequent cardiovascular mortality. Arch Intern Med 2002;162:1472–6.
32. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–26; discussion 1127–36.
33. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.
34. Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, Ma J. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. N Engl J Med 2002;346:1113–8.
35. Bowman TS, Gaziano JM, Kase CS, Sesso HD, Kurth T. Blood pressure measures and risk of total, ischemic, and hemorrhagic stroke in men. Neurology 2006;67:820–3.
36. Fraser GE, Shavlik D. Risk factors, lifetime risk, and age at onset of breast cancer. Ann Epidemiol 1997;7:375–82.
37. Fraser GE, Shavlik DJ. Risk factors for all-cause and coronary heart disease mortality in the oldest-old: the Adventist Health Study. Arch Intern Med 1997;157:2249–58.
38. Fraser GE, Sumbureru D, Pribis P, Neil RL, Frankson MA. Association among health habits, risk factors, and all-cause mortality in a black California population. Epidemiology 1997;8:168–74.
39. van den Brandt PA. The impact of a Mediterranean diet and healthy lifestyle on premature mortality in men and women. Am J Clin Nutr 2011;94:913–20.
40. Mann JI, Appleby PN, Key TJ, Thorogood M. Dietary determinants of ischaemic heart disease in health conscious individuals. Heart 1997;78:450–5.
41. Sabaté J, Fraser GE, Burke K, Knutsen SF, Bennett H, Lindsted KD. Effects of walnuts on serum lipid levels and blood pressure in normal men. N Engl J Med 1993;328:603–7.
42. Lovejoy JC, Most MM, Lefevre M, Greenway FL, Rood JC. Effect of diets enriched in almonds on insulin action and serum lipids in adults with normal glucose tolerance or type 2 diabetes. Am J Clin Nutr 2002;76:1000–6.
43. Almario RU, Vonghavaravat V, Wong R, Kasim-Karakas SE. Effects of walnut consumption on plasma fatty acids and lipoproteins in combined hyperlipidemia. Am J Clin Nutr 2001;74:72–9.
44. Kris-Etherton PM, Yu-Poth S, Sabate J, Ratcliffe HE, Zhao G, Etherton TD. Nuts and their bioactive constituents: effects on serum lipids and other factors that affect disease risk. Am J Clin Nutr 1999;70(Suppl):504S–11S.
45. Griel AE, Kris-Etherton PM. Tree nuts and the lipid profile: a review of clinical studies. Br J Nutr 2006;96(Suppl 2):S68–78.
46. Kris-Etherton PM, Hu FB, Ros E, Sabate J. The role of tree nuts and peanuts in the prevention of coronary heart disease: multiple potential mechanisms. J Nutr 2008;138(Suppl):1746S–51S.
47. Jenkins DJ, Kendall CW, Marchie A, Faulkner DA, Josse AR, Wong JM, de Souza R, Emam A, Parker TL, Li TJ, et al. Direct comparison of dietary portfolio vs statin on C-reactive protein. Eur J Clin Nutr 2005;59:851–60.
48. Estruch R, Martinez-Gonzalez MA, Corella D, Salas-Salvado J, Ruiz-Gutierrez V, Covas MI, Fiol M, Gomez-Gracia E, Lopez-Sabater MC, Vinyoles E, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Ann Intern Med 2006;145:1–11.
49. Wien MA, Sabate JM, Ikle DN, Cole SE, Kandeel FR. Almonds vs complex carbohydrates in a weight reduction program. Int J Obes Relat Metab Disord 2003;27:1365–72.
50. Bes-Rastrollo M, Sabate J, Gomez-Gracia E, Alonso A, Martinez JA, Martinez-Gonzalez MA. Nut consumption and weight gain in a Mediterranean cohort: the SUN study. Obesity (Silver Spring) 2007;15:107–16.
51. Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follmann D, Klag MJ. Effects of oral potassium on blood pressure: meta-analysis of randomized controlled clinical trials. JAMA 1997;277:1624–32.
52. Soltani N, Keshavarz M, Sohanaki H, Zahedi Asl S, Dehpour AR. Relaxatory effect of magnesium on mesenteric vascular beds differs from normal and streptozotocin induced diabetic rats. Eur J Pharmacol 2005;508:177–81.
53. Sontia B, Touyz RM. Role of magnesium in hypertension. Arch Biochem Biophys 2007;458:33–9.
54. Mutanen M, Freese R. Polyunsaturated fatty acids and platelet aggregation. Curr Opin Lipidol 1996;7:14–9.
55. Knapp HR. Dietary fatty acids in human thrombosis and hemostasis. Am J Clin Nutr 1997;65(Suppl):1687S–98S.
56. Jenkins DJ, Kendall CW, Banach MS, Srichaikul K, Vidgen E, Mitchell S, Parker T, Nishi S, Bashyam B, de Souza R, et al. Nuts as a replacement for carbohydrates in the diabetic diet. Diabetes Care 2011;34:1706–11.
57. Jenkins DJ, Kendall CW, Josse AR, Salvatore S, Brighenti F, Augustin LS, Ellis PR, Vidgen E, Rao AV. Almonds decrease postprandial glycemia, insulinemia, and oxidative damage in healthy individuals. J Nutr 2006;136:2987–92.
58. Tapsell LC, Batterham MJ, Teuss G, Tan SY, Dalton S, Quick CJ, Gillen LJ, Charlton KE. Long-term effects of increased dietary polyunsaturated fat from walnuts on metabolic parameters in type II diabetes. Eur J Clin Nutr 2009;63:1008–15.