JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2017 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 70, NO. 20, 2017
ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2017.09.035

Nut Consumption and Risk of Cardiovascular Disease

Marta Guasch-Ferré, PhD,[a] Xiaoran Liu, PhD,[a] Vasanti S. Malik, PhD,[a,b] Qi Sun, MD, ScD,[a,b] Walter C. Willett, MD, DrPH,[a,b,c] JoAnn E. Manson, MD, DrPH,[c,d] Kathryn M. Rexrode, MD, MPH,[c,d] Yanping Li, MD, PhD,[a] Frank B. Hu, MD, PhD,[a,b,c] Shilpa N. Bhupathiraju, PhD[a,b]

ABSTRACT

BACKGROUND The associations between specific types of nuts, specifically peanuts and walnuts, and cardiovascular disease remain unclear.

OBJECTIVES The authors sought to analyze the associations between the intake of total and specific types of nuts and cardiovascular disease, coronary heart disease, and stroke risk.

METHODS The authors included 76,364 women from the Nurses' Health Study (1980 to 2012), 92,946 women from the Nurses' Health Study II (1991 to 2013), and 41,526 men from the Health Professionals Follow-Up Study (1986 to 2012) who were free of cancer, heart disease, and stroke at baseline. Nut consumption was assessed using food frequency questionnaires at baseline and was updated every 4 years.

RESULTS During 5,063,439 person-years of follow-up, the authors documented 14,136 incident cardiovascular disease cases, including 8,390 coronary heart disease cases and 5,910 stroke cases. Total nut consumption was inversely associated with total cardiovascular disease and coronary heart disease after adjustment for cardiovascular risk factors. The pooled multivariable hazard ratios for cardiovascular disease and coronary heart disease among participants who consumed 1 serving of nuts (28 g) 5 or more times per week, compared with the reference category (never or almost never), were 0.86 (95% confidence interval: 0.79 to 0.93; p for trend = 0.0002) and 0.80 (95% confidence interval: 0.72 to 0.89; p for trend <0.001), respectively. Consumption of peanuts and tree nuts (2 or more times/week) and walnuts (1 or more times/week) was associated with a 13% to 19% lower risk of total cardiovascular disease and 15% to 23% lower risk of coronary heart disease.

CONCLUSIONS In 3 large prospective cohort studies, higher consumption of total and specific types of nuts was inversely associated with total cardiovascular disease and coronary heart disease. (J Am Coll Cardiol 2017;70:2519–32)

Cardiovascular disease (CVD) remains a leading cause of death worldwide, and hence prevention of CVD has become a top public health priority (1). In recent years, dietary recommendations have shifted toward diets high in plant-based foods and low in animal-based foods for the prevention of chronic diseases (2). Most of these plant-based dietary patterns highlight the intake of nuts as a key component. Nuts have a unique nutritional composition (3) and are good sources of unsaturated fatty acids, dietary fiber, minerals, vitamins, and other bioactive compounds (4).

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Department of Nutrition, Harvard TH Chan School of Public Health, Boston, Massachusetts; [b]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [c]Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, Massachusetts; and the [d]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. This study was supported by research grants UM1 CA186107, R01 HL034594, R01 HL088521, UM1 CA176726, UM1 CA167552, R01 HL35464, and R01 HL60712 from the National Institutes of Health (NIH). Dr. Bhupathiraju is supported by a Career Development Grant from the NIH (K01 DK107804). Dr. Malik has received research support from the Peanut Institute. Drs. Li and Hu have received research support from the California Walnut Commission. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received June 13, 2017; revised manuscript received September 1, 2017, accepted September 12, 2017.

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CHD = coronary heart disease

CI = confidence interval

CVD = cardiovascular disease

FFQ = food frequency questionnaire

HR = hazard ratio

ICD-9 = International Classification of Diseases-9th Revision

NHS = Nurses' Health Study

Frequent nut consumption has been associated with reduced cardiovascular risk factors including dyslipidemia, type 2 diabetes, and metabolic syndrome, as well as with lower risk of coronary heart disease (CHD) (5–8). Findings from prospective cohort studies were confirmed by a randomized primary prevention trial conducted in a Mediterranean population at high cardiovascular risk (9). Participants randomized to a Mediterranean diet supplemented with mixed nuts—hazelnuts, almonds, and walnuts—had a 28% reduction in the incidence of major cardiovascular events after about 5 years of follow-up (9). Recent findings from the NHS (Nurses' Health Study) and the HPFS (Health Professionals Follow-Up Study) have also provided further evidence that the frequency of nut consumption is inversely associated with total and cause-specific mortality (10).

Most of the previous prospective studies have focused on total nut consumption in relation to the risk of CVD (11,12). However, the associations between peanut butter and specific types of nuts, such as peanuts and walnuts, with major cardiovascular events, and specifically the relation with stroke, remain unclear. Of note, because the nutritional composition of peanuts and walnuts differs from other nuts (13), evaluating the health effects of specific types of nuts is of particular interest.

SEE PAGE 2533

Our primary hypothesis is that frequent nut consumption is associated with lower risk of CVD incidence. Therefore, we examined the associations between the intake of total and specific types of nuts with CVD in 3 large prospective cohort studies. Our cohorts provided repeated measures of diet (including separate data on peanuts, walnuts, tree nuts, and peanut butter), extensive data on cardiovascular risk factors, up to 32 years of follow-up, and a large number of incident CVD cases.

METHODS

STUDY POPULATION. The NHS study is a prospective cohort study of 121,700 female nurses, 30 to 55 years of age, from 11 U.S. states that began in 1976. The NHS II study was established in 1989 and consists of 116,671 younger female registered nurses, 25 to 42 years of age at baseline. The HPFS study is a prospective cohort study of 51,529 male health professionals 40 to 75 years of age at baseline that began in 1986. In all 3 cohorts, information about medical history, lifestyle, and health conditions was collected by self-administered questionnaires every 2 years since baseline. Detailed information on the cohorts has been described previously elsewhere (14–16).

For the present analysis, baseline year was defined as the first year the validated food frequency questionnaire (FFQ) was collected in each study—1980 for the NHS study, 1991 for the NHS II study, and 1986 for the HPFS study. We excluded from the analysis those participants who reported CVD or cancer at baseline, participants who did not provide information on nut consumption, those who left more than 70 food items blank in the FFQ, or had daily energy intakes <600 or >3,500 kcal for women and <800 or >4,200 kcal for men. The final analyses included 76,364 women in the NHS study, 92,946 women in the NHS II study, and 41,526 men in the HPFS study. The institutional review boards of Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health approved the study protocol.

ASCERTAINMENT OF CVD. Our primary outcome measure was major CVD defined as a combined endpoint of myocardial infarction, stroke, or fatal CVD (fatal stroke, fatal myocardial infarction, and cardiovascular death). We further assessed the following secondary outcome measures: total CHD, which was defined as fatal or nonfatal myocardial infarction; and total stroke, which included all fatal and nonfatal stroke cases (ischemic, hemorrhagic, and undetermined subtypes). When a participant (or family members of deceased participants) reported an incident event, permission was requested to examine their medical records by physicians who were blinded to participant risk factor status. For each endpoint, the month and year of diagnosis were recorded as the diagnosis date. Nonfatal events were confirmed through review of medical record by study investigators blinded to participant risk factor status. Myocardial infarction was confirmed if World Health Organization criteria were met on the basis of symptoms plus diagnostic electrocardiogram changes or elevated cardiac enzymes (17). If medical records were unavailable, we considered myocardial infarction probable when the participant provided additional confirmatory information. Information on angina and coronary revascularization procedures (percutaneous transluminal coronary angioplasty or coronary artery bypass grafting surgery) was self-reported, and we included only events that occurred before a manifest cardiovascular event.

Strokes were confirmed if data in the medical records fulfilled the National Survey of Stroke criteria

requiring evidence of a neurological deficit with sudden or rapid onset that persisted for >24 h or until death (18). We excluded cerebrovascular pathology due to infection, trauma, or malignancy, as well as "silent" strokes discovered only by radiological imaging. Radiology reports of brain imaging (computed tomography or magnetic resonance imaging) were available in 89% of those with medical records. We classified strokes as ischemic stroke (thrombotic or embolic occlusion of a cerebral artery), hemorrhagic stroke (subarachnoid and intraparenchymal hemorrhage), or stroke of probable/unknown subtype (a stroke was documented, but the subtype could not be ascertained owing to medical records being unobtainable).

Deaths were identified by reports of families, the U.S. postal system, or using death certificates obtained from state vital statistics departments and the National Death Index, and confirmed through review of medical records or autopsy reports. Follow-up for deaths was >98% complete (19). Fatal CVD was defined as fatal CHD disease, fatal stroke, or fatal CVD. Fatal CHD was defined as ICD-9 (International Classification of Diseases-Ninth Revision) codes 410 to 412 and was considered confirmed if fatal CHD was confirmed via medical records or autopsy reports or if CHD was listed as the cause of death on the death certificate and there was prior evidence of CHD in the medical records. We designated as probable those cases in which CHD was the underlying cause on the death certificates, but no prior knowledge of CHD was indicated and medical records concerning the death were unavailable. Similarly, we used ICD-9 codes 430 to 434 to define fatal stroke and followed the same procedures to classify cases of confirmed or probable fatal stroke. Lastly, fatal CVD was defined by ICD-9 codes 390 to 458.

DIETARY ASSESSMENT. A semiquantitative food-frequency questionnaire with over 130 items administered every 2 to 4 years was used to assess dietary intake. In the 1980 and 1984 dietary questionnaires, we asked participants how often they had consumed a serving of nuts (serving size 28 g [1 oz]) during the preceding year: never or almost never, 1 to 3 times a month, once a week, 2 to 4 times a week, 5 or 6 times a week, once a day, 2 or 3 times a day, 4 to 6 times a day, or more than 6 times a day. In subsequent FFQs, the question regarding nuts was split into 2 items: peanuts and other nuts. A specific question about walnut consumption was first introduced on the questionnaires in 1998 in the NHS and HPFS studies, and 1999 in the NHS II study. Total nut consumption was defined as the intake of peanuts, other nuts, and walnuts (if available). Intake of peanut and peanut butter or other forms of peanuts was assessed and analyzed separately in the current analysis. Tree nuts included all types of tree nuts including walnuts (not including peanuts, which are botanically a legume, but with a similar fatty acid and nutrient profile as other nuts). Consumption of peanut butter was assessed in 1980, 1984, 1986, 1990, and 1994, with the same 9 responses as those for nut consumption (serving size 15 g [1 tablespoon]). A validation study indicated that nut consumption was reported with reasonable accuracy; the corrected coefficient was 0.75 between the FFQ and 4 1-week diet records for total nuts and peanut butter (20).

STATISTICAL ANALYSIS. We calculated each individual's person-time from the date of the return of the baseline questionnaire to the date of death or the end of follow-up (June 2012 in the NHS study, June 2013 in the NHS II study, and January 2012 in the HPFS study), whichever came first. The cumulative average nut consumption was calculated to better represent long-term diet and to minimize within-person variation. We stopped updating dietary variables on a report of cancer, coronary artery bypass, or angina because changes in diet after development of these conditions may confound the relation between diet and chronic diseases.

We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of developing total CVD, CHD, and stroke according to nut consumption categories. Separate analyses were conducted for fatal and nonfatal CVD, nonfatal myocardial infarction, fatal CHD, fatal and nonfatal stroke, and ischemic stroke. We did not analyze hemorrhagic stroke separately due to the lower number of cases. Multivariable models were adjusted for updated over time covariates: age (continuous); Caucasian (yes/no); body mass index (BMI) (<23, 23 to 24.9, 25 to 29.9, 30 to 34.9, ≥35 kg/m^2); physical activity (metabolic equivalents/week, quintiles); smoking status (never, past, current 1 to 14 cigarettes/day, current 15 to 24 cigarettes/day, current ≥25 cigarettes/day); physical examination for screening purposes (yes/no); current multivitamin use (yes/no); current aspirin use (yes/no); family history of diabetes mellitus (yes/no), myocardial infarction (yes/no), or cancer (yes/no); history of diabetes mellitus (yes/no), hypertension (yes/no), or hypercholesterolemia (yes/no); intakes of total energy (kcal/day), alcohol (g/day); red or processed meat (servings/day), fruits (servings/day), and vegetables (servings/day) (all in quintiles); and in women, menopausal status and hormone use (premenopausal, postmenopausal never users,

TABLE 1 Characteristics of Person-Years According to Frequency of Nut Consumption

	Frequency of Nut Consumption (Servings/Day)				
	Never or Almost Never	Less Than Once per Week	Once per Week	2 to 4 Times per Week	5 or More Times per Week
Nut Intake (Servings/Day)	0.00	0.01–0.09	0.10–0.19	0.20–0.59	≥0.60
Nurses' Health Study (1980)					
Age, yrs	56.2 ± 11.1	59.5 ± 10.9	60.5 ± 11.0	62.1 ± 11.1	65.2 ± 11.8
BMI, kg/m^2	26.1 ± 5.4	26.1 ± 5.2	25.8 ± 5.0	25.4 ± 4.8	25.0 ± 4.8
Physical activity, metabolic equivalents/week	14.7 ± 22.7	16.3 ± 21.5	18.1 ± 22.4	19.7 ± 24.0	21.3 ± 24.3
Family history of diabetes mellitus	28.3	28.8	28.2	28.0	26.4
Family history of myocardial infarction	19.5	19.0	18.5	18.1	17.8
Current smoker	19.5	15.0	13.3	13.1	12.7
Current menopausal hormone use	15.9	21.8	22.9	22.8	18.2
Baseline hypertension	40.2	39.1	37.3	36.0	34.6
Baseline hypercholesterolemia	36.8	42.0	42.4	41.7	39.6
Baseline diabetes	7.9	6.7	6.3	6.0	6.4
Multivitamin supplement use	43.5	50.5	54.1	57.6	60.5
Current aspirin use	43.5	48.2	49.2	50.7	48.0
Total energy intake, kcal/day	1,524 ± 499	1,643 ± 507	1,780 ± 530	1,873 ± 552	1,956 ± 582
Alcohol intake, g/day	4.0 ± 8.6	4.7 ± 9.1	5.6 ± 9.6	6.1 ± 10.2	6.6 ± 11.0
Red or processed meat intake, servings/day	1.3 ± 0.8	1.2 ± 0.7	1.3 ± 0.7	1.2 ± 0.7	1.2 ± 0.8
Fruit intake, servings/day	2.0 ± 1.3	2.1 ± 1.2	2.2 ± 1.2	2.4 ± 1.2	2.5 ± 1.4
Vegetable intake, servings/day	2.1 ± 1.1	2.3 ± 1.1	2.5 ± 1.1	2.7 ± 1.2	2.7 ± 1.3
Peanuts intake, servings/day	0.0 ± 0.1	0.0 ± 0.1	0.1 ± 0.1	0.2 ± 0.2	0.3 ± 0.4
Tree nuts intake, servings/day	0.0 ± 0.0	0.0 ± 0.1	0.1 ± 0.1	0.1 ± 0.2	0.2 ± 0.3
Walnuts intake, servings/day	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.1	0.1 ± 0.1	0.1 ± 0.2
Peanut butter intake, servings/day	0.2 ± 0.3	0.2 ± 0.3	0.2 ± 0.3	0.3 ± 0.3	0.3 ± 0.4
AHEI score, excluding nuts	46.4 ± 9.8	47.1 ± 9.3	48.1 ± 9.3	49.3 ± 9.5	50.9 ± 9.6
Nurses' Health Study II (1991)					
Age, yrs	43.2 ± 7.5	47.5 ± 7.4	47.0 ± 7.9	49.5 ± 7.6	50.2 ± 7.6
BMI, kg/m^2	26.8 ± 6.4	26.8 ± 6.3	26.4 ± 6.2	25.8 ± 6.0	25.2 ± 5.7
Physical activity, metabolic equivalents/week	19.5 ± 25.4	20.1 ± 26.4	21.7 ± 27.3	24.4 ± 31.8	26.7 ± 35.5
Family history of diabetes mellitus	34.2	34.5	34.1	34.2	34.9
Family history of myocardial infarction	37.6	37.1	36.8	36.5	34.5
Current smoker	9.0	8.5	9.1	8.6	9.6
Current menopausal hormone use	8.8	9.2	9.2	9.2	9.6
Baseline hypertension	19.3	19.9	18.8	17.5	15.4
Baseline hypercholesterolemia	30.8	32.3	31.6	31.5	29.7
Baseline diabetes	1.0	0.9	0.9	0.8	1.0
Multivitamin supplement use	33.1	35.2	34.8	36.5	38.5
Current aspirin use	24.0	29.2	30.0	30.8	30.1
Total energy intake, kcal/day	1,646 ± 527	1,803 ± 547	1,965 ± 564	2,088 ± 578	2,266 ± 602
Alcohol intake, g/day	3.3 ± 6.8	4.3 ± 7.9	5.2 ± 8.8	5.7 ± 9.4	5.6 ± 9.9
Red or processed meat intake, servings/day	0.9 ± 0.6	0.9 ± 0.6	1.0 ± 0.6	1.0 ± 0.6	0.9 ± 0.8
Fruit intake, servings/day	1.1 ± 0.9	1.2 ± 0.8	1.3 ± 0.9	1.5 ± 0.9	1.7 ± 1.2
Vegetable intake, servings/day	3.1 ± 1.9	3.5 ± 1.8	3.8 ± 2.0	4.3 ± 2.2	4.7 ± 2.6
Peanuts intake, servings/day	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.0	0.2 ± 0.1	0.4 ± 0.4
Tree nuts intake, servings/day	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.1	0.2 ± 0.1	0.6 ± 0.4
Walnuts intake, servings/day	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.1	0.1 ± 0.1	0.2 ± 0.5
Peanut butter intake, servings/day	0.1 ± 0.2	0.2 ± 0.2	0.2 ± 0.2	0.2 ± 0.3	0.3 ± 0.4
AHEI score, excluding nuts	46.4 ± 9.7	46.7 ± 9.3	47.5 ± 9.5	49.5 ± 9.6	51.6 ± 9.9

Continued on the next page

postmenopausal past users, postmenopausal current users). In the NHS II study, the multivariable model was further adjusted for oral contraceptive use (never, past, and current users). The aforementioned covariates were updated every 2 or 4 years using the most recent data for each 2-year follow-up interval. The p values for trend were calculated with the use of the Wald test of a continuous variable on the basis of the median number of servings of nuts consumed per day for each category.

We performed separate analyses for peanuts, tree nuts, walnuts, and peanut butter intake. Peanut

TABLE 1 Continued

	Frequency of Nut Consumption (Servings/Day)				
	Never or Almost Never	Less Than Once per Week	Once per Week	2 to 4 Times per Week	5 or More Times per Week
Health Professional's Follow-Up Study (1986)					
Age, yrs	60.3 ± 11.2	62.6 ± 10.7	61.8 ± 10.8	63.2 ± 10.9	64.4 ± 10.9
BMI, kg/m^2	25.7 ± 3.5	26.0 ± 3.5	26.0 ± 3.5	25.9 ± 3.6	25.5 ± 3.4
Physical activity, metabolic equivalents/week	28.0 ± 36.7	33.2 ± 39.2	35.3 ± 41.1	37.6 ± 41.9	39.0 ± 44.3
Family history of diabetes mellitus	17.6	20.0	18.9	19.4	19.0
Family history of myocardial infarction	32.3	30.8	30.8	30.5	30.9
Current smoker	8.1	5.7	6.4	6.2	7.0
Baseline hypertension	34.8	35.8	35.2	35.1	32.1
Baseline hypercholesterolemia	33.7	41.6	40.7	40.9	37.1
Baseline diabetes	5.9	6.0	5.8	6.2	6.3
Multivitamin supplement use	38.6	46.5	46.2	49.3	50.3
Current aspirin use	45.1	56.5	55.2	56.7	54.2
Total energy intake, kcal/day	1,768 ± 564	1,837 ± 567	1,980 ± 593	2,136 ± 624	2,363 ± 668
Alcohol intake, g/day	9.5 ± 14.2	10.4 ± 14.3	11.6 ± 14.9	12.8 ± 15.8	14.1 ± 17.3
Red or processed meat intake, servings/day	1.0 ± 0.8	1.0 ± 0.7	1.1 ± 0.7	1.1 ± 0.8	1.1 ± 0.8
Fruit intake, servings/day	2.2 ± 1.6	2.2 ± 1.3	2.4 ± 1.4	2.5 ± 1.5	2.8 ± 1.7
Vegetable intake, servings/day	2.8 ± 1.6	2.9 ± 1.5	3.1 ± 1.5	3.3 ± 1.6	3.6 ± 1.8
Peanuts intake, servings/day	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.0	0.2 ± 0.1	0.7 ± 0.5
Tree nuts intake, servings/day	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.0	0.1 ± 0.1	0.4 ± 0.4
Walnuts intake, servings/day	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.1	0.1 ± 0.1	0.1 ± 0.2
Peanut butter intake, servings/day	0.2 ± 0.4	0.2 ± 0.3	0.2 ± 0.3	0.3 ± 0.4	0.3 ± 0.5
AHEI score, excluding nuts	42.5 ± 10.1	43.4 ± 9.2	44.1 ± 9.1	45.3 ± 9.0	47.4 ± 9.4

Values are mean ± SD or %. All variables except age are age-standardized. Frequency of nut consumption pertains to 1 serving of nuts, defined as 28 g.
AHEI = Alternate Healthy Eating Index; BMI = body mass index.

butter models were additionally adjusted for quintiles of glycemic load, white bread, and soda intake, to control for dietary components associated with the consumption of peanut butter. For these analyses, we combined categories of high nut intake (≥2 servings/week) to maintain statistical power. We also analyzed nuts and types of nuts as a continuous variable (per 1 serving [28 g] increase).

We conducted several sensitivity analyses to test the robustness of the results. First, we conducted prespecified subgroup analyses by potential effect modifiers and the interaction between nut intake and covariates was examined using the likelihood ratio test. Second, to test whether our results were biased by selectively stopping updating diet after an intermediate outcome, we continuously updated diet until the end of follow-up. Third, instead of using repeated measures of diet, we used the most recent measure of diet. Fourth, we analyzed the association between baseline nut consumption and the incidence of CVD, CHD, and stroke. Fifth, we further adjusted the models for the number of natural teeth (0 to 10, 11 to 16, 17 to 32 teeth) in the NHS and HPFS studies, where the information was available, because tooth loss may be a marker for periodontal disease, which has been shown to be previously associated with CVD risk (21). Sixth, we further adjusted the models for the Alternate Healthy Eating Index (22), excluding the nut component. For the analysis including specific types of nuts, we mutually adjusted for other types of nuts (i.e., peanuts mutually adjusted for tree nuts and peanut butter). Finally, we conducted sensitivity analysis excluding BMI from the models.

The HRs from multivariable models in each cohort were pooled with the use of an inverse variance-weighted meta-analysis using a fixed-effects model. The p values for heterogeneity were calculated with the use of the Q statistics. Analyses were performed with the SAS statistical package (version 9.4, SAS Institute). Statistical tests were 2 sided, and p values of <0.05 were considered to indicate statistical significance.

RESULTS

During an average of 28.7 years of follow-up in the NHS, 21.5 years in the NHS II, and 22.5 years in the HPFS studies (and a total of 5,063,439 person-years across the 3 cohorts), we documented 14,136 incident CVD cases, including 8,390 CHD and 5,910 stroke cases. Compared with those participants who never or almost never consumed nuts, those who consumed

TABLE 2 Relative Risk (95% CI) of Cardiovascular Events According to Frequency of Nut Consumption

	Frequency of Nut Consumption						
	Never or Almost Never	Less Than Once per Week	Once per Week	2 to 4 Times per Week	5 or More Times per Week	p Value for Trend	HR (95% CI) per 28 g Increase
Total cardiovascular disease: fatal and nonfatal myocardial infarction + fatal and nonfatal stroke							
NHS median, g/day	0.00	1.68	3.92	9.24	27.00		
PY	384,331	972,973	391,790	331,935	117,245		2,198,274
Cases	1,278	3,005	1,131	972	341		6,727
Crude incidence/100,000 PY	333	309	289	293	291		
Age-adjusted model	1 (Ref.)	0.76 (0.71–0.81)	0.69 (0.63–0.74)	0.64 (0.58–0.69)	0.62 (0.54–0.71)	<0.001	0.68 (0.59–0.77)
Multivariable-adjusted model	1 (Ref.)	0.88 (0.82–0.94)	0.85 (0.78–0.93)	0.82 (0.75–0.90)	0.85 (0.75–0.97)	0.01	0.96 (0.90–1.00)
NHS II median, g/day	0.00	1.47	3.92	7.98	23.03		
PY	706,919	733,092	325,741	204,999	29,959		2,000,710
Cases	624	740	322	204	25		1,915
Crude incidence/100,000 PY	88	101	99	100	83		
Age-adjusted model	1 (Ref.)	0.92 (0.82–1.03)	0.92 (0.80–1.05)	0.82 (0.70–0.97)	0.66 (0.44–0.98)	<0.001	0.60 (0.43–0.83)
Multivariable-adjusted model	1 (Ref.)	0.91 (0.82–1.02)	0.95 (0.83–1.10)	0.89 (0.75–1.06)	0.75 (0.50–1.13)	0.15	0.69 (0.49–0.98)
HPFS median, g/day	0.00	1.96	3.92	7.84	24.08		
PY	121,404	218,753	209,348	230,225	84,725		864,455
Cases	885	1,406	1,251	1,390	562		5,494
Crude incidence/100,000 PY	729	646	598	604	663		
Age-adjusted model	1 (Ref.)	0.88 (0.80–0.95)	0.86 (0.78–0.93)	0.80 (0.73–0.87)	0.78 (0.70–0.87)	<0.001	0.87 (0.80–0.94)
Multivariable-adjusted model	1 (Ref.)	0.94 (0.86–1.02)	0.93 (0.85–1.01)	0.89 (0.81–0.97)	0.87 (0.78–0.97)	0.02	0.93 (0.85–1.00)
Pooled* multivariable-adjusted model	1 (Ref.)	0.91 (0.86–0.95)	0.90 (0.85–0.95)	0.86 (0.81–0.91)	0.86 (0.79–0.93)	0.0002	0.94 (0.89–0.99)
Coronary heart disease: fatal and nonfatal myocardial infarction							
NHS PY	384,646	973,970	392,199	332,232	117,369		2,200,416
Cases	783	1,609	560	460	140		3,552
Crude incidence/100,000 PY	204	165	143	139	119		
Age-adjusted model	1 (Ref.)	0.70 (0.65–0.77)	0.60 (0.54–0.67)	0.54 (0.48–0.61)	0.48 (0.40–0.58)	<0.001	0.68 (0.59–0.77)
Multivariable-adjusted model	1 (Ref.)	0.84 (0.76–0.91)	0.76 (0.68–0.86)	0.73 (0.64–0.82)	0.69 (0.56–0.83)	<0.001	0.84 (0.74–0.94)
NHS II PY	707,318	733,533	325,956	205,132	29,972		2,001,911
Cases	212	282	98	71	7		670
Crude incidence/100,000 PY	30	38	30	35	23		
Age-adjusted model	1 (Ref.)	0.93 (0.77–1.12)	0.74 (0.58–0.94)	0.72 (0.55–0.95)	0.46 (0.21–0.97)	0.001	0.37 (0.20–0.69)
Multivariable-adjusted model	1 (Ref.)	0.93 (0.77–1.13)	0.79 (0.61–1.02)	0.84 (0.63–1.12)	0.57 (0.27–1.23)	0.06	0.51 (0.27–0.95)
HPFS PY	121,568	219,074	209,641	230,514	84,833		865,630
Cases	693	1,071	934	1,046	424		4,168
Crude incidence/100,000 PY	571	490	446	454	500		
Age-adjusted model	1 (Ref.)	0.86 (0.78–0.94)	0.82 (0.74–0.90)	0.77 (0.70–0.85)	0.76 (0.67–0.86)	<0.001	0.85 (0.77–0.93)
Multivariable-adjusted model	1 (Ref.)	0.93 (0.84–1.03)	0.90 (0.81–0.99)	0.88 (0.79–0.97)	0.86 (0.76–0.98)	0.03	0.91 (0.82–0.99)
Pooled* multivariable-adjusted model	1 (Ref.)	0.88 (0.83–0.94)	0.83 (0.78–0.90)	0.82 (0.76–0.88)	0.80 (0.72–0.89)	<0.0001	0.87 (0.81–0.94)

Continued on the next page

nuts more frequently were older, had a lower BMI, were less likely to smoke, were more likely to exercise, and consumed more fruits and vegetables (**Table 1**). Participants' characteristics according to the frequency of peanut and walnut consumption are shown in Online Tables 1 and 2, respectively. Online Table 3 shows the Pearson correlations among different types of nuts in the 3 cohorts.

Age-adjusted and multivariable-adjusted analyses showed a consistent significant inverse association between total nut consumption and total CVD and CHD (**Table 2**). The pooled multivariable HRs, without heterogeneity by sex or cohort, for those who consumed nuts 5 or more times per week (1 serving of nuts = 28 g), as compared with those who never consumed nuts, were 0.86 (95% CI: 0.79 to 0.93; $p < 0.001$) for total CVD and 0.80 (95% CI: 0.72 to 0.89; $p < 0.001$) for CHD. Each serving increase of nuts was associated with 6% (HR: 0.94; 95% CI: 0.89 to 0.99) and 13% (HR: 0.87; 95% CI: 0.81 to 0.94) lower risk of CVD and CHD, respectively. Total nut consumption was inversely associated with both fatal (HR: 0.76; 95% CI: 0.70 to 0.84; $p = 0.0003$) and nonfatal (HR: 0.91; 95% CI: 0.85 to 0.98; $p = 0.005$) CVD in the pooled analysis of the 3 cohorts (Online Table 4).

In separate analyses of specific types of nuts (**Central Illustration, Table 3**), when comparing consumption of nuts 2 or more times per week with the reference category, the pooled multivariable-adjusted HRs for CVD were 0.87 (95% CI: 0.82 to 0.93) for peanuts,

TABLE 2 Continued

	Frequency of Nut Consumption						
	Never or Almost Never	Less Than Once per Week	Once per Week	2 to 4 Times per Week	5 or More Times per Week	p Value for Trend	HR (95% CI) per 28 g Increase
Stroke: fatal and nonfatal stroke							
NHS PY	384,731	973,952	392,151	332,238	117,328		2,200,400
Cases	536	1,462	590	529	205		3,322
Crude incidence/100,000 PY	139	150	151	159	175		
Age-adjusted model	1 (Ref.)	0.87 (0.78-0.96)	0.83 (0.74-0.93)	0.79 (0.70-0.89)	0.82 (0.69-0.89)	0.04	0.96 (0.89-1.04)
Multivariable-adjusted model	1 (Ref.)	0.97 (0.87-1.07)	0.98 (0.86-1.10)	0.96 (0.85-1.09)	1.05 (0.88-1.26)	0.50	1.02 (0.96-1.09)
NHS II PY	707,097	733,336	325,829	205,058	29,963		2,001,283
Cases	418	465	226	135	18		1,262
Crude incidence/100,000 PY	59	63	69	66	60		
Age-adjusted model	1 (Ref.)	0.91 (0.79-1.05)	1.02 (0.86-1.20)	0.88 (0.72-1.08)	0.78 (0.48-1.25)	0.29	0.75 (0.50-1.11)
Multivariable-adjusted model	1 (Ref.)	0.90 (0.79-1.04)	1.04 (0.88-1.24)	0.94 (0.76-1.15)	0.85 (0.52-1.37)	0.72	0.81 (0.54-1.22)
HPFS PY	121,724	219,328	209,870	230,827	84,959		866,708
Cases	192	335	317	344	138		1,326
Crude incidence/100,000 PY	158	153	151	149	163		
Age-adjusted model	1 (Ref.)	0.95 (0.79-1.13)	0.99 (0.83-1.19)	0.89 (0.74-1.07)	0.86 (0.69-1.07)	0.12	0.95 (0.81-1.10)
Multivariable-adjusted model	1 (Ref.)	0.97 (0.80-1.16)	1.02 (0.85-1.23)	0.93 (0.77-1.12)	0.91 (0.72-1.14)	0.32	0.99 (0.85-1.16)
Pooled* multivariable-adjusted model	1 (Ref.)	0.95 (0.88-1.03)	1.01 (0.92-1.10)	0.95 (0.87-1.04)	0.98 (0.86-1.13)	0.88	1.02 (0.96-1.08)

Values are n or HR (95% CI), unless otherwise indicated. Multivariable analyses were adjusted for updated over time covariates: age (continuous); Caucasian (yes/no); body mass index (<23, 23-24.9, 25-29.9, 30-34.9, ≥35 kg/m^2); physical activity (metabolic equivalents/week, quintiles); smoking status (never, past, current 1-14 cigarettes/day, current 15-24 cigarettes/day, current ≥25 cigarettes/day); physical examination for screening purposes (yes/no); current multivitamin use (yes/no); current aspirin use (yes/no); family history of diabetes mellitus (yes/no), myocardial infarction (yes/no), or cancer (yes/no); history of diabetes mellitus (yes/no), hypertension (yes/no), or hypercholesterolemia (yes/no); intake of total energy, alcohol, red or processed meat, fruits, and vegetables (quintiles); and in women, menopausal status and hormone use (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users). In the NHS II study, multivariable model was further adjusted for oral contraceptive use (never, past, and current users). Frequency of nut consumption pertains to 1 serving of nuts, defined as 28 g. (1 oz) *Results from the multivariable model were combined with the use of the fixed-effects model.

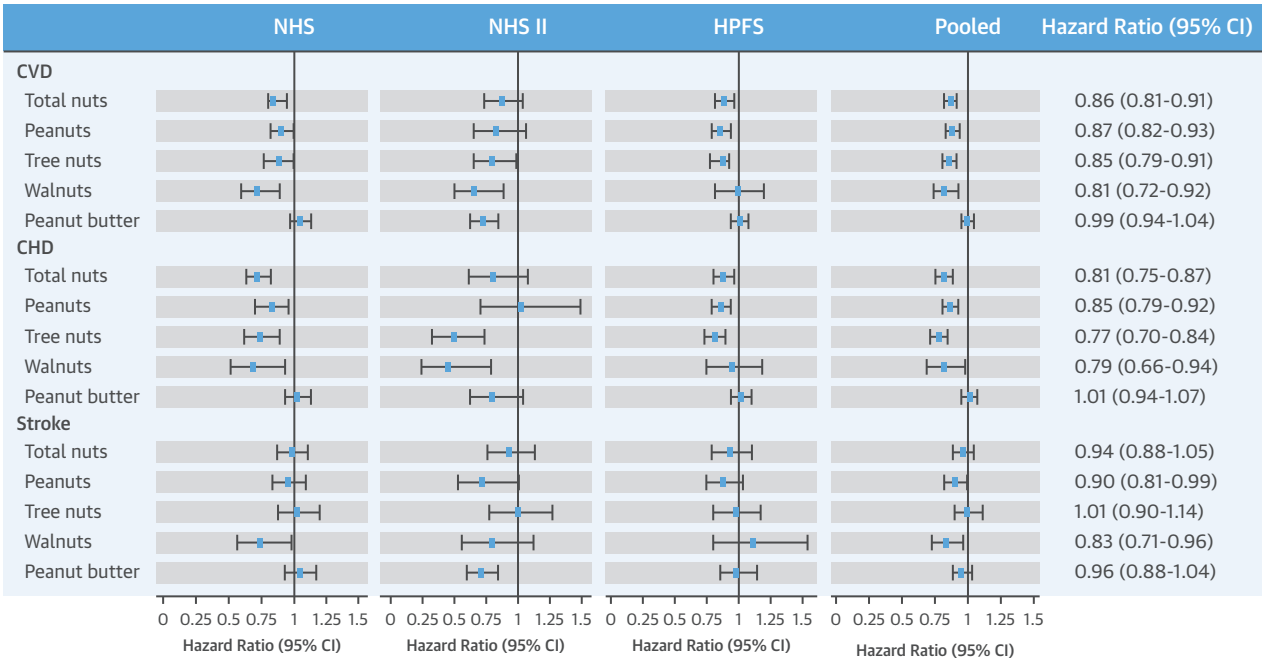
CI = confidence interval; HPFS = Health Professionals Follow-Up Study; HR = hazard ratio; NHS = Nurses' Health Study; PY = person-years.

and 0.85 (95% CI: 0.79 to 0.91) for tree nuts. Consuming walnuts 1 or more times per week was also associated with a lower risk of CVD (HR: 0.81; 95% CI: 0.71 to 0.91). Significant associations were also observed for each serving increase in peanuts, tree nuts, and walnuts. Peanut butter intake was not significantly associated with CVD. Significant inverse associations were observed between the intake of total nuts, peanuts, tree nuts, and walnuts, and CHD risk (**Central Illustration,** Online Table 5). Participants who consumed peanuts or tree nuts 2 or more times per week had, respectively, 15% (95% CI: 8% to 21%) and 23% (95% CI: 16% to 30%) lower risk of CHD compared with those who never or almost never consumed nuts. Consuming walnuts 1 or more times per week was associated with 21% (95% CI: 6% to 34%) lower risk of CHD. Pooled analyses of the 3 cohorts showed that total nut consumption was inversely associated with fatal CHD (HR: 0.69; 95% CI: 0.61 to 0.77; $p < 0.0001$), but nonsignificant associations were observed for nonfatal myocardial infarction (Online Table 6).

The pooled risk estimates for stroke among participants who consumed total nuts and peanuts 2 or more times per week was 0.94 (95% CI: 0.88 to 1.05; $p = 0.08$) and 0.90 (95% CI: 0.81 to 0.99; $p = 0.07$), respectively. Walnut intake was associated with a 17% (95% CI: 4% to 29%; $p = 0.10$) lower risk of stroke (**Central Illustration,** Online Table 5). Peanut butter and tree nuts were not associated with stroke risk (Online Table 5). Likewise, we found no significant associations between total nut consumption and the risk of fatal, nonfatal, or ischemic stroke (Online Table 7).

In analyses stratified by potential risk factors for CVD, the inverse association between total nut consumption and CVD persisted in most subgroups (**Figure 1**). No significant interactions were observed in pooled analysis. Our results remained robust in several sensitivity analyses. The results remained unchanged when we continuously updated the diet until the end of follow-up (pooled multivariable HR for CVD comparing nut consumption 5 or more times per week with no nut consumption: HR: 0.86; 95% CI: 0.78 to 0.94; $p < 0.001$) and when we used the most recent diet as our primary exposure (pooled multivariable HR for CVD comparing nut consumption 5 or more times per week with no nut consumption: HR: 0.88; 95% CI: 0.82 to 0.94; $p < 0.001$). Additional adjustment for tooth loss or the Alternate Healthy Eating Index (excluding the nut component) did not materially alter the associations (data not shown). When specific types of nuts were mutually adjusted for other nuts in individual cohorts, results were

CENTRAL ILLUSTRATION **CVD, CHD, and Stroke Based on Frequency of Nut Consumption and Type of Nut: HRs**



Guasch-Ferré, M. et al. J Am Coll Cardiol. 2017;70(20):2519–32.

Multivariable hazard ratios (HRs) for total cardiovascular disease (CVD) among study participants who consumed nuts 2 or more times per week (1 or more times per week for walnuts) versus those who never or almost never consumed nuts, were adjusted for updated covariates: age (continuous); Caucasian (yes/no); body mass index (<23, 23 to 24.9, 25 to 29.9, 30 to 34.9, ≥35 kg/m^2); physical activity (metabolic equivalents/week, quintiles); smoking status (never, past, current 1 to 14 cigarettes/day, current 15 to 24 cigarettes/day, current ≥25 cigarettes/day); physical examination for screening purposes (yes/no); current multivitamin use (yes/no); current aspirin use (yes/no); family history of diabetes mellitus (yes/no), myocardial infarction (yes/no), or cancer (yes/no); history of diabetes mellitus (yes/no), hypertension (yes/no), or hypercholesterolemia (yes/no); intake of total energy, alcohol, red or processed meat, fruits, and vegetables (quintiles); and in women, menopausal status and hormone use (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users). In the NHS II study, the multivariable model was further adjusted for oral contraceptive use (never, past, and current users). Peanut butter models were additionally adjusted for glycemic load, soda, and white bread intake (quintiles). Results were pooled with the use of the fixed-effects model. **Bars** represent 95% confidence intervals (CIs). CHD = coronary heart disease; NHS = Nurses' Health Study; NHS II = Nurses' Health Study II; HPFS = Health Professionals Follow-Up Study.

attenuated (i.e., peanuts mutually adjusted for tree nuts and peanut butter). However, significant inverse associations remained in the pooled analysis for peanuts and tree nuts (Online Table 8). Significant inverse associations between baseline nut consumption and risk of CVD and CHD were also observed (Online Table 9). Results were consistent with primary analysis when we excluded BMI from the multivariable-adjusted model (pooled multivariable HR for CVD comparing nut consumption 5 or more times per week with no nut consumption: HR: 0.85 (95% CI: 0.79 to 0.93; $p < 0.001$).

DISCUSSION

In 3 large prospective cohorts with up to 32 years of follow-up, we observed that nut consumption was associated with lower risk of developing CVD after adjusting for cardiovascular risk factors. As compared with those participants who never or almost never consumed nuts, those who consumed nuts 5 or more times per week had 14% lower risk of CVD and 20% lower risk of CHD. Results were similar for tree nuts, peanuts, and walnuts, and the inverse association persisted across all subgroups in stratified analysis. Significant inverse associations were observed for each increasing serving of nuts and risk of CVD and CHD. Although we found no evidence of an association between total nut consumption and risk of stroke, the intake of peanuts and walnuts was inversely associated with the risk of stroke.

Our results are in line with previous observational studies that reported inverse associations between nut consumption and CVD risk. However, the number

of studies that investigated specific types of nuts is limited, and few of them had repeated measures of diet (11,12). To date, 12 cohort studies have investigated the association between total nut consumption and CVD risk (11). Consistent with our findings, a recent meta-analysis of these 12 studies found a summary relative risk for high versus low intake of nuts of 0.81 (95% CI: 0.74 to 0.89) for CVD and 0.76 (95% CI: 0.69 to 0.84) for CHD (11). Our results are in agreement with a meta-analysis of 7 prospective studies that showed a 30% lower risk of CHD mortality in participants with higher nut consumption, and no significant associations for nonfatal CHD, but only 3 studies examined nut consumption in relation to nonfatal CHD (12).

Despite studies reporting consistent inverse associations between higher nut consumption and risk of CVD and CHD, studies evaluating associations with stroke remain limited (11). In the pooled analysis of our cohorts, we found that consumption of peanuts 2 or more times per week and walnuts 1 or more times per week was associated with a 10% and 17% lower risk of total stroke, respectively, but there was no significant associations for total nut intake. In a meta-analysis of 11 prospective studies, an inverse association was observed for total nut consumption and total stroke risk (HR: 0.89; 95% CI: 0.82 to 0.97 for high vs. low intake) (11). However, the associations were not significant in 8 of the individual studies included, and most of the studies did not differentiate between fatal and nonfatal stroke. Two studies evaluated the associations between intake of specific types of nuts and stroke death. The Shanghai Men's Health Study (23) reported an inverse trend between higher peanut intake and lower risk of ischemic stroke (HR comparing the 5th vs. 1st quintile 0.77 [0.60 to 1.00]; p for trend = 0.003). In the Netherlands Cohort Study (24), an intake of >5 g/day of peanuts was associated with a 29% (6% to 46%) lower risk of stroke death compared with those who did not consume peanuts. Another reason that may account for the lack of associations between nut intake and stroke is the lack of effect of nuts on blood pressure (25).

Walnuts are among the most widely consumed tree nut in the world and are high in n-6 and n-3 PUFA (especially in plant-derived α-linolenic acid). Their consumption has been associated with cardioprotective properties (26). Although numerous clinical studies have shown beneficial effects of walnuts on lipid profiles and inflammatory biomarkers (27), evidence from large prospective studies with long durations of follow-up is sparse. In a secondary analysis of the PREDIMED (Prevención con Dieta Mediterránea) trial, participants who consumed >3 servings per week of walnuts had 47% (2% to 71%) lower risk of cardiovascular mortality compared with those who did not consume walnuts (28). In the present study, we have also observed that consuming walnuts at least once per week was associated with 19% lower risk of CVD, 21% lower risk of CHD, and 17% lower risk of stroke.

Peanut butter intake was inversely associated with CVD and stroke in the NHS II study, but no significant associations were observed when pooling the 3 cohort studies together. Although we conducted several sensitivity analyses adjusting peanut butter models for foods associated with peanut butter consumption (such as soda, white bread, and glycemic load), residual confounding by dietary pattern remains a strong possibility. Further, it may be possible that peanut butter intake is not associated with disease risk. In a previous report of the NHS and HPFS studies, peanut butter intake was not associated with inflammatory biomarkers (29). Of note, in our cohorts, a serving of peanut butter was defined as 1 tablespoon (15 g), which is not consistent with the typical serving size of 2 tablespoons and may have misclassified intake levels. Further studies are needed to elucidate the health effects of peanut butter intake.

Findings from observational studies alone cannot be used to draw conclusions regarding whether associations are causal; however, the PREDIMED trial found that participants who were randomized to a Mediterranean diet supplemented with mixed nuts had 28% (95% CI: 0.54 to 0.96) reduced risk of a composite of cardiovascular events and 46% (95% CI: 0.35 to 0.84) reduced risk of stroke after 4.8 years of follow-up compared with a control diet (advice to reduce all types of dietary fat) (9).

Nuts are high in unsaturated fatty acids, dietary fiber, minerals, vitamins, and several bioactive compounds, which may in part explain their beneficial effects on cardiovascular health (30). There are several mechanisms that may account for the inverse associations between nut consumption and CVD. Randomized controlled trials have shown that consumption of nuts improves lipid profiles (5,27), attenuates inflammation (31), oxidative stress, improves endothelial function (32), and decreases insulin resistance (33). Nuts are also rich in polymerized polyphenols, which provide a substrate for gut microbiota. The compounds arising from this metabolism may modulate gut microbiota through prebiotic effects and antimicrobial activities and consequently contribute to cardiovascular benefits for the host (34). Despite nuts being an energy-dense food, there is no scientific

TABLE 3 Relative Risk (95% CI) of Cardiovascular Events According to Type of Nuts

	Frequency of Nut Consumption					
	Never or Almost Never	Less Than Once per Week	Once per Week	2 or More Times per Week	p Value for Trend	HR (95% CI) per 28 g increase
Nurses' Health Study						
Peanuts						
Median, g/day	0.00	1.30	3.92	12.04		
PY	999,858	829,970	204,015	164,431		2,198,274
Cases	3,158	2,544	567	458		6,727
Crude incidence/100,000 PY	316	307	278	279		
Multivariable-adjusted model	1 (Ref.)	0.92 (0.87–0.98)	0.95 (0.87–1.04)	0.90 (0.81–1.00)	0.09	0.82 (0.68–0.99)
Tree nuts						
Median, g/day	0.00	1.30	3.92	10.56		
PY	1,134,756	776,813	167,205	119,500		2,198,274
Cases	3,463	2,477	468	319		6,727
Crude incidence/100,000 PY	305	319	280	267		
Multivariable-adjusted model	1 (Ref.)	0.95 (0.90–1.00)	0.95 (0.86–1.05)	0.88 (0.78–0.99)	0.03	0.79 (0.62–1.00)
Walnuts						
Median, g/day	0.00	1.96	7.37			
PY	452,904	190,234	45,583			688,721
Cases	1,880	654	106			2,640
Crude incidence/100,000 PY	422	348	237			
Multivariable-adjusted model	1 (Ref.)	1.02 (0.93–1.12)	0.72 (0.59–0.88)		0.007	0.55 (0.34–0.89)
Peanut butter						
Median, g/day	0.00	0.90	2.10	6.30		
PY	402,929	728,603	405,168	661,574		2,198,274
Cases	1,028	2,358	1,284	2,057		6,727
Crude incidence/100,000 PY	255	324	317	311		
Multivariable-adjusted model	1 (Ref.)	1.06 (0.98–1.14)	1.06 (0.97–1.15)	1.04 (0.96–1.13)	0.75	0.95 (0.87–1.04)
Nurses' Health Study II						
Peanuts						
Median, g/day	0.00	1.17	3.92	8.02		
PY	909,678	876,295	139,660	75,077		2,000,710
Cases	837	869	135	74		1,915
Crude incidence/100,000 PY	92	99	97	99		
Multivariable-adjusted model	1 (Ref.)	0.90 (0.81–0.99)	0.88 (0.73–1.07)	0.83 (0.65–1.06)	0.09	0.55 (0.31–1.00)
Tree nuts						
Median, g/day	0.00	1.30 3.92 8.790	3.92	8.79		
PY	990,483	730,724	152,825	126,678		2,000,710
Cases	891	750	157	117		1,915
Crude incidence/100,000 PY	90	103	103	92		
Multivariable-adjusted model	1 (Ref.)	0.93 (0.83–1.03)	0.92 (0.77–1.10)	0.80 (0.65–0.98)	0.04	0.53 (0.33–0.85)
Walnuts						
Median, g/day	0.00	0.68	4.65			
PY	588,362	443,135	63,826			1,095,323
Cases	732	458	52			1,242
Crude incidence/100,000 PY	124	103	81			
Multivariable-adjusted model	1 (Ref.)	0.84 (0.74–0.95)	0.66 (0.50–0.89)		0.003	0.21 (0.06–0.73)
Peanut butter						
Median, g/day	0.00	1.05	2.10	6.10		
PY	351,026	701,495	400,266	547,923		2,000,710
Cases	390	661	397	467		1,915
Crude incidence/100,000 PY	111	94	99	85		
Multivariable-adjusted model	1 (Ref.)	0.77 (0.67–0.87)	0.87 (0.75–1.00)	0.73 (0.63–0.84)	0.004	0.84 (0.68–1.04)

Continued on the next page

TABLE 3 Continued

	Frequency of Nut Consumption					
	Never or Almost Never	Less Than Once per Week	Once per Week	2 or More Times per Week	p Value for Trend	HR (95% CI) per 28 g increase
Health Professionals Follow-Up Study						
Peanuts						
Median, g/day	0.00	1.96	3.92	12.04		
PY	177,482	370,105	145,053	171,815		864,455
Cases	1,288	2,234	875	1,097		5,494
Crude incidence/100,000 PY	726	604	603	638		
Multivariable-adjusted model	1 (Ref.)	0.91 (0.85–0.98)	0.93 (0.85–1.02)	0.85 (0.78–0.93)	0.002	0.95 (0.85–1.06)
Tree nuts						
Median, g/day	0.00	1.63	3.92	11.01		
PY	257,997	377,087	118,784	110,587		864,455
Cases	1,818	2,330	728	618		5,494
Crude incidence/100,000 PY	705	618	613	559		
Multivariable-adjusted model	1 (Ref.)	0.94 (0.88–1.00)	0.98 (0.90–1.07)	0.84 (0.76–0.92)	0.001	0.85 (0.72–1.00)
Walnuts						
Median, g/day	0.00	1.30	6.02			
PY	142,208	65,094	24,124			231,426
Crude incidence/100,000 PY						
Cases	895	349	129			1,373
Multivariable-adjusted model	1 (Ref.)	0.95 (0.83–1.08)	0.99 (0.81–1.20)		0.84	1.01 (0.65–1.56)
Peanut butter						
Median, g/day	0.00	1.05	2.10	6.45		
Person-years	227,180	233,480	134,685	269,109		864,454
Cases	1,454	1,431	832	1,777		5,494
Crude incidence/100,000 PY	705	618	613	559		
Multivariable-adjusted model	1 (Ref.)	0.97 (0.90–1.05)	1.02 (0.93–1.11)	1.01 (0.93–1.08)	0.55	1.03 (0.96–1.10)
Pooled*						
Peanuts						
Multivariable-adjusted model	1 (Ref.)	0.92 (0.88–0.95)	0.94 (0.88–1.00)	0.87 (0.82–0.93)	0.0002	0.91 (0.83–1.00)
Tree nuts						
Multivariable-adjusted model	1 (Ref.)	0.95 (0.91–0.98)	0.96 (0.90–1.03)	0.85 (0.79–0.91)	0.002	0.81 (0.71–0.92)
Walnuts						
Multivariable-adjusted model	1 (Ref.)	0.95 (0.89–1.02)	0.81 (0.71–0.92)		<0.001	0.71 (0.52–0.97)
Peanut butter						
Multivariable-adjusted model	1 (Ref.)	0.98 (0.93–1.02)	1.01 (0.96–1.07)	0.99 (0.94–1.04)	0.74	0.99 (0.94–1.05)

Values are n or HR (95% CI), unless otherwise indicated. Multivariable analyses were adjusted for updated over time covariates: age (continuous); Caucasian (yes/no); body mass index (<23, 23–24.9, 25–29.9, 30–34.9, ≥35 kg/m^2); physical activity (metabolic-equivalents/week, quintiles); smoking status (never, past, current 1–14 cigarettes/day, current 15–24 cigarettes/day, current ≥25 cigarettes/day); physical examination for screening purposes (yes/no); current multivitamin use (yes/no); current aspirin use (yes/no); family history of diabetes mellitus (yes/no), myocardial infarction (yes/no), or cancer (yes/no); history of diabetes mellitus (yes/no), hypertension (yes/no), or hypercholesterolemia (yes/no); intake of total energy, alcohol, red or processed meat, fruits, and vegetables (quintiles); and in women, menopausal status and hormone use (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users). In the NHS II study, the multivariable model was further adjusted for oral contraceptive (never, past, and current users). Peanut butter models were additionally adjusted for glycemic load, soda, and white bread intake (quintiles). Frequency of nut consumption pertains to 1 serving of nuts, defined as 28 g. *Results from the multivariable model were combined with the use of the fixed-effects model.

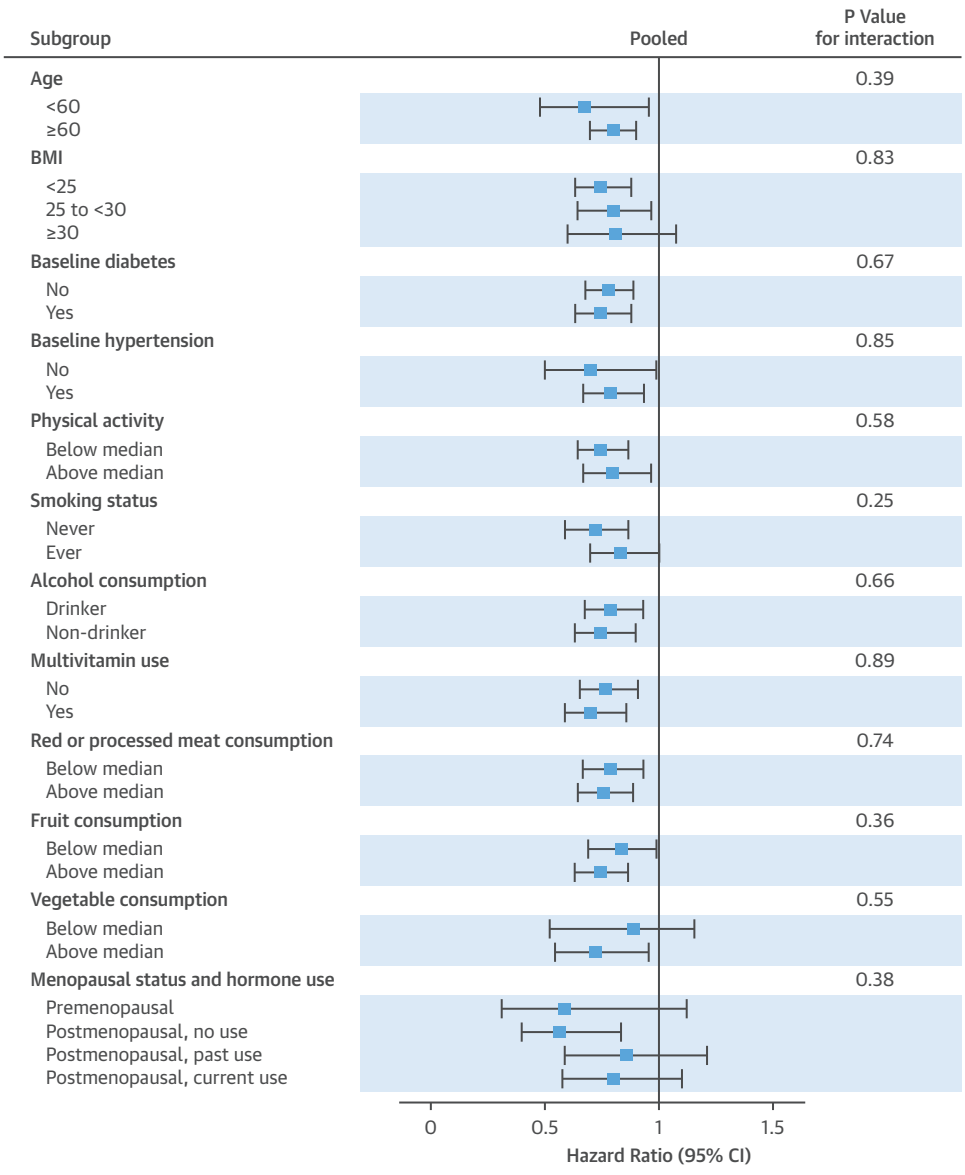
Abbreviations as in Table 2.

evidence supporting associations between weight gain and nut consumption. Indeed, they have been associated with lower weight gain and lower risk of obesity, probably because they can increase satiety and fullness, which may potentially reduce the consumption of unhealthy snacks (35–37).

STUDY STRENGTHS. The strengths of the present study include its prospective design, large sample size including men and women, long duration of follow-up with a high retention rate, repeated assessment of diet and lifestyle variables, and analyses of several CVD outcomes including fatal and nonfatal CVD, fatal and nonfatal CHD, and stroke (fatal, nonfatal, and ischemic). Moreover, we present strong evidence for the association between total nuts, peanuts, tree nuts, walnuts, and peanut butter with CVD risk in 3 large cohort studies with more than 13,500 CVD cases.

STUDY LIMITATIONS. First, given that our study sample was limited to white health professionals, this

FIGURE 1 HRs for CVD in Subgroups



Multivariable hazard ratios (HRs) for pooled analysis of the 3 cohorts (Nurses' Health Study I and II, and Health Professionals Follow-Up Study) for total cardiovascular disease (CVD) among study participants who consumed nuts 2 or more times per week versus those who never consumed nuts were adjusted for updated covariates: age (continuous); Caucasian (yes/no); body mass index (BMI) (<23, 23 to 24.9, 25 to 29.9, 30 to 34.9, ≥35 kg/m^2); physical activity (metabolic equivalents/week, quintiles); smoking status (never, past, current 1 to 14 cigarettes/day, current 15 to 24 cigarettes/day, current ≥25 cigarettes/day); physical examination for screening purposes (yes/no); current multivitamin use (yes/no); current aspirin use (yes/no); family history of diabetes mellitus (yes/no), myocardial infarction (yes/no), or cancer (yes/no); history of diabetes mellitus (yes/no), hypertension (yes/no), or hypercholesterolemia (yes/no); intake of total energy, alcohol, red or processed meat, fruits, and vegetables (quintiles); and in women, menopausal status and hormone use (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users). In Nurses' Health Study II, the multivariable model was further adjusted for oral contraceptive (never, past, and current users). Results were pooled with the use of the fixed-effects model. **Bars** represent 95% confidence intervals (CIs).

could limit generalizability of our findings. Still, because there is no reason to expect that the underlying biological mechanisms may be different, our results can be generalized to men and women of different ethnicities. Because nut intake was self-reported, some measurement error is inevitable. However, because dietary data was collected prospectively, misreporting is likely to be random, resulting in an underestimation of the association. By calculating the cumulative average of nut intake from multiple time points, we were able to reduce potential random measurement error. Further, inverse associations were consistent across pre-specified subgroup analysis and in several sensitivity analyses. Because we lacked data on how nuts were prepared (e.g., salted, raw, roasted), we were unable to test the influence of preparation methods.

CONCLUSIONS

Findings from 3 large prospective cohort studies indicate that frequent intake of nuts, tree nuts, peanuts, and walnuts was associated with a lower risk of CVD, independently from other cardiovascular risk, lifestyle, and dietary factors. Our findings support recommendations of increasing the intake of a variety of nuts as part of healthy dietary patterns to reduce the risk of chronic diseases in the general population.

ACKNOWLEDGMENTS The authors thank the participants and staff of the Nurses' Health Study, the Nurses' Health Study II, and the Health Professionals Follow-Up Study for their valuable contributions.

ADDRESS FOR CORRESPONDENCE: Dr. Marta Guasch-Ferré OR Dr. Shilpa N. Bhupathiraju, Department of Nutrition, Harvard TH Chan School of Public Health, 655 Huntington Avenue, Boston, Massachusetts 02115. E-mail: mguasch@hsph.harvard.edu OR sbhupath@hsph.harvard.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Consumption of peanuts and tree nuts 2 or more times per week and walnuts 1 or more times/week is associated with a lower risk of coronary artery disease and cardiovascular disease in general.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Increasing the intake of nuts, as part of a healthy diet, may help to reduce the risk of cardiovascular disease in the general population.

TRANSLATIONAL OUTLOOK: Further research is needed to investigate the mechanisms underlying the association between nut consumption and reduction in cardiovascular risk.

REFERENCES

1. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385:117–71.

2. 2015 Dietary Guidelines Advisory Committee. Scientific Report of the 2015 Dietary Guidelines Advisory Committee. Rockville, MD: Office of Disease Prevention and Health Promotion, U.S. Department of Health and Human Services, 2015.

3. Ros E. Health benefits of nut consumption. Nutrients 2010;2:652–82.

4. Ros E, Hu FB. Consumption of plant seeds and cardiovascular health: epidemiological and clinical trial evidence. Circulation 2013;128:553–65.

5. Sabate 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.

6. Kendall CW, Josse AR, Esfahani A, Jenkins DJ. Nuts, metabolic syndrome and diabetes. Br J Nutr 2010;104:465–73.

7. Luo C, Zhang Y, Ding Y, et al. Nut consumption and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a systematic review and meta-analysis. Am J Clin Nutr 2014;100:256–69.

8. Hu FB, Manson JE, Willett WC. Types of dietary fat and risk of coronary heart disease: a critical review. J Am Coll Nutr 2001;20:5–19.

9. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368:1279–90.

10. Bao Y, Han J, Hu FB, et al. Association of nut consumption with total and cause-specific mortality. N Engl J Med 2013;369:2001–11.

11. Aune D, Keum N, Giovannucci E, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. BMC Med 2016;14:207.

12. Mayhew AJ, de Souza RJ, Meyre D, Anand SS, Mente A. A systematic review and meta-analysis of nut consumption and incident risk of CVD and all-cause mortality. Br J Nutr 2016;115:212–25.

13. Sabaté J, Ros E, Salas-Salvadó J. Nuts: nutrition and health outcomes. Br J Nutr 2006;96 Suppl 2:S1–2.

14. Belanger C, Speizer FE, Hennekens CH, Rosner B, Willett W, Bain C. The Nurses' Health Study: current findings. Am J Nurs 1980;80:1333.

15. Colditz GA, Martin P, Stampfer MJ, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. Am J Epidemiol 1986;123:894–900.

16. 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.

17. Mendis S, Thygesen K, Kuulasmaa K, et al. World Health Organization definition of myocardial infarction: 2008-09 revision. Int J Epidemiol 2011;40:139–46.

18. Walker AE, Robins M, Weinfeld FD. The National Survey of Stroke. Clinical findings. Stroke 1981;12 Pt 2 Suppl 1:I13–44.

19. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. Am J Epidemiol 1984;119:837–9.

20. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol 1989;18:858–67.

21. Howell TH, Ridker PM, Ajani UA, Hennekens CH, Christen WG. Periodontal disease and risk of subsequent cardiovascular

disease in U.S. male physicians. J Am Coll Cardiol 2001;37:445–50.

22. McCullough ML, Willett WC. Evaluating adherence to recommended diets in adults: the Alternate Healthy Eating Index. Public Health Nutr 2006;9:152–7.

23. Luu HN, Blot WJ, Xiang Y-B, et al. Prospective evaluation of the association of nut/peanut consumption with total and cause-specific mortality. JAMA Intern Med 2015;175:755–66.

24. van den Brandt PA, Schouten LJ. Relationship of tree nut, peanut and peanut butter intake with total and cause-specific mortality: a cohort study and meta-analysis. Int J Epidemiol 2015;44:1038–49.

25. Mohammadifard N, Salehi-Abargouei A, Salas-Salvadó J, Guasch-Ferré M, Humphries K, Sarrafzadegan N. The effect of tree nut, peanut, and soy nut consumption on blood pressure: a systematic review and meta-analysis of randomized controlled clinical trials. Am J Clin Nutr 2015;101:966–82.

26. Kris-Etherton PM. Walnuts decrease risk of cardiovascular disease: a summary of efficacy and biologic mechanisms. J Nutr 2014;144:547S–54S.

27. Banel DK, Hu FB. Effects of walnut consumption on blood lipids and other cardiovascular risk factors: a meta-analysis and systematic review. Am J Clin Nutr 2009;90:56–63.

28. Guasch-Ferre M, Bullo M, Martinez-Gonzalez MA, et al. Frequency of nut consumption and mortality risk in the PREDIMED nutrition intervention trial. BMC Med 2013;11:164.

29. Yu Z, Malik VS, Keum N, et al. Associations between nut consumption and inflammatory biomarkers. Am J Clin Nutr 2016;104:722–8.

30. Ros E, Tapsell LC, Sabate J. Nuts and berries for heart health. Curr Atheroscler Rep 2010;12:397–406.

31. Salas-Salvado J, Garcia-Arellano A, Estruch R, et al. Components of the Mediterranean-type food pattern and serum inflammatory markers among patients at high risk for cardiovascular disease. Eur J Clin Nutr 2008;62:651–9.

32. Bulló M, Lamuela-Raventós R, Salas-Salvadó J. Mediterranean diet and oxidation: nuts and olive oil as important sources of fat and antioxidants. Curr Top Med Chem 2011;11:1797–810.

33. Casas-Agustench P, Bullo M, Salas-Salvado J. Nuts, inflammation and insulin resistance. Asia Pac J Clin Nutr 2010;19:124–30.

34. Lamuela-Raventos RM, St Onge M-P. Prebiotic nut compounds and human microbiota. Crit Rev Food Sci Nutr 2017;57:3154–63.

35. 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.

36. Bes-Rastrollo M, Wedick NM, Martinez-Gonzalez MA, Li TY, Sampson L, Hu FB. Prospective study of nut consumption, long-term weight change, and obesity risk in women. Am. J Clin Nutr 2009;89:1913–9.

37. Freisling H, Noh H, Slimani N, et al. Nut intake and 5-year changes in body weight and obesity risk in adults: results from the EPIC-PANACEA study. Eur J Nutr 2017 Jul 21 [E-pub ahead of print].

KEY WORDS cardiovascular disease, coronary heart disease, nuts, peanuts, stroke, tree nuts

APPENDIX For supplemental tables, please see the online version of this article.