See corresponding editorial on page 8.

Nut consumption and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a systematic review and meta-analysis[1–4]

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ABSTRACT

Background: Epidemiologic studies have shown inverse associations between nut consumption and diabetes, cardiovascular disease (CVD), and all-cause mortality, but results have not been consistent.

Objective: We assessed the relation between nut intake and incidence of type 2 diabetes, CVD, and all-cause mortality.

Design: We searched PubMed and EMBASE for all prospective cohort studies published up to March 2013 with RRs and 95% CIs for outcomes of interest. A random-effects model was used to pool risk estimates across studies.

Results: In 31 reports from 18 prospective studies, there were 12,655 type 2 diabetes, 8862 CVD, 6623 ischemic heart disease (IHD), 6487 stroke, and 48,818 mortality cases. The RR for each incremental serving per day of nut intake was 0.80 (95% CI: 0.69, 0.94) for type 2 diabetes without adjustment for body mass index; with adjustment, the association was attenuated [RR: 1.03; 95% CI: 0.91, 1.16; NS]. In the multivariable-adjusted model, pooled RRs (95% CIs) for each serving per day of nut consumption were 0.72 (0.64, 0.81) for IHD, 0.71 (0.59, 0.85) for CVD, and 0.83 (0.76, 0.91) for all-cause mortality. Pooled RRs (95% CIs) for the comparison of extreme quantiles of nut intake were 1.00 (0.84, 1.19; NS) for type 2 diabetes, 0.66 (0.55, 0.78) for IHD, 0.70 (0.60, 0.81) for CVD, 0.91 (0.81, 1.02; NS) for stroke, and 0.85 (0.79, 0.91) for all-cause mortality.

Conclusions: Our meta-analysis indicates that nut intake is inversely associated with IHD, overall CVD, and all-cause mortality but not significantly associated with diabetes and stroke. The inverse association between the consumption of nuts and diabetes was attenuated after adjustment for body mass index. These findings support recommendations to include nuts as part of a healthy dietary pattern for the prevention of chronic diseases. *Am J Clin Nutr* 2014;100:256–69.

INTRODUCTION

Cardiovascular disease (CVD)[5] is a major public health concern in both developed and developing countries. The American College of Cardiology predicts that the number of people diagnosed with CVD will double to 25 million in the United States alone by 2050 (1). In individuals with CVD, stroke is associated with permanent disability, mortality, and major direct and indirect costs because of functional impairments (2, 3). The increase in diabetes over the past 20 y has been dramatic; the current prevalence is now estimated to be nearly 6.4% worldwide (4). For these reasons, the primary prevention of these chronic diseases is imperative.

Dietary factors are one of the major determinants of both type 2 diabetes and CVD. Of various dietary factors, nuts have received increasing attention because they are a good source of macronutrients and micronutrients. Nuts are rich in unsaturated fatty acids, fiber, high-quality vegetable protein, and minerals (eg, magnesium and potassium). Nuts also have high contents of bioactive compounds, such as polyphenols, tocopherols, phytosterols, and phenolics (5–7). Walnuts are especially rich in polyunsaturated acids, including α-linolenic acid. Previous clinical trials and epidemiologic studies have shown that nuts have beneficial effects on various mediators of chronic diseases, including lipid concentrations (8), inflammation (9), insulin resistance (10), and blood pressure (BP) (11).

A previous review concluded that the consumption of nuts $\geq$5 times/wk was associated with a reduced incidence of coronary heart disease (IHD) (12). In the past several years, additional studies have been published on CVD, diabetes, and all-cause mortality. However, the epidemiologic evidence has not been consistent. Therefore, we conducted this meta-analysis on all published cohort studies to date to quantify the relation between nut consumption and risk of type 2 diabetes, CVD, and all-cause mortality.

METHODS

Data sources and searches

We searched PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and EMBASE (http://www.embase.com/) databases for all English-language

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[5] Abbreviations used: BP, blood pressure; CVD, cardiovascular disease; IHD, ischemic heart disease; MI, myocardial infarction.

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prospective cohort studies published in peer-reviewed journals through March 2013. Search terms included human and nuts or almond or cashew or peanut or pecan or pine nut or pistachio nut or macadamia nut or hazelnut or walnut and diabetes or CVD or myocardial infarction (MI) or coronary or stroke or death or mortality or mortalities or fatal and risk or Cox or hazard or odds. We also reviewed references from retrieved articles to find additional studies.

Study selection

We selected studies on the basis of the following criteria: *1*) a prospective cohort study, *2*) nut-consumption exposure, *3*) the outcome of interest (ie, type 2 diabetes, CVD, or all-cause mortality), and *4*) RRs with 95% CIs. On the basis of reviews of titles and abstracts, we identified 122 pertinent articles (**Figure 1**). We excluded reviews, case-control studies, editorials, nonhuman studies, dietary pattern reports, and articles that examined associations with foods other than nuts. If data were published more than once, we included the largest number of incident cases from the study.

We included the following 18 studies in the meta-analysis: 5 studies (13–17) stratified analyses by sex; one study (18) used 2 independent cohorts; one study (19) reported findings for IHD, CVD, and mortality; 3 studies (20–22) had 2 different outcomes; one study (23) had results for hemorrhagic and ischemic strokes; 2 studies (24, 25) had outcomes for fatal IHD and nonfatal MI; and 5 studies (26–30) had one outcome. One study stratified diabetes by BMI (in kg/m^2) (31). We pooled data on fatal IHD and nonfatal MI to get an overall estimate. In total, 31 reports from 18 studies were included in the meta-analysis as follows: 5 reports were on diabetes, 6 reports were on IHD, 5 reported were on stroke, 4 reports were on total CVD, and 11 reports were on all-cause mortality.

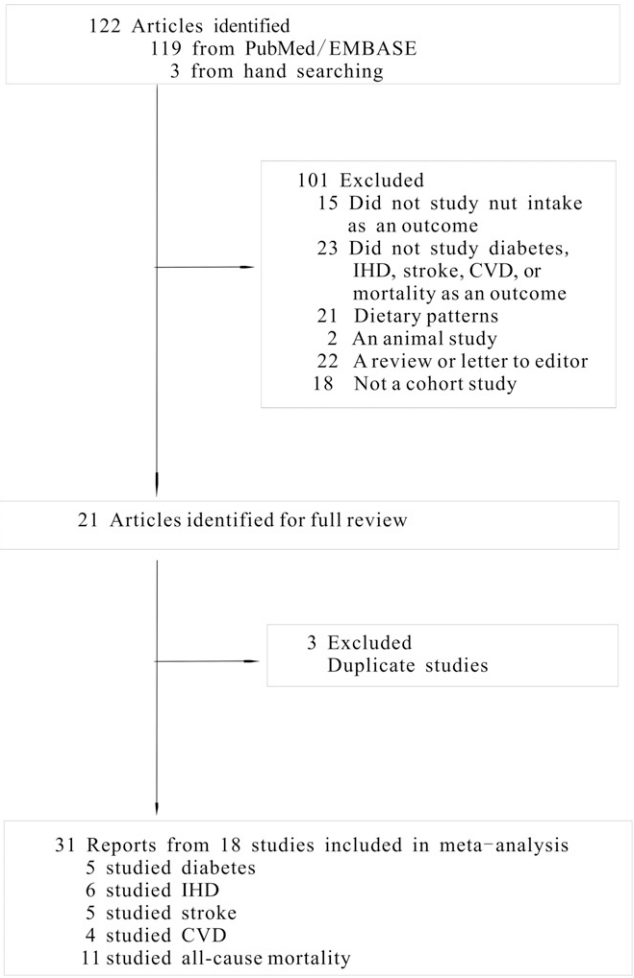

FIGURE 1. Flowchart of study selection. PubMed, http://www.ncbi.nlm.nih.gov/pubmed/; EMBASE, http://www.embase.com/. CVD, cardiovascular disease; IHD, ischemic heart disease.

Data extraction and quality assessment

Two independent investigators extracted data, including the name of the first author, year of publication, study title, sample size, sex and age range, type of nut (eg, with and without peanut butter), length of follow-up, country of study, inclusion and exclusion criteria, specific outcomes, number of cases, types of nuts consumed (ie, walnuts and total tree nuts), covariates that were adjusted, and RRs with corresponding 95% CIs for all categories of nut consumption. We extracted fully adjusted estimates. In addition, we extracted multivariable-adjusted estimates without adjustment for BMI when available.

We used the Meta-analysis of Observational Studies in Epidemiology (32) for quality assessment. This scoring system awards a maximum of 5 points as follows: study eligibility (1 point if inclusion and exclusion criteria are included), exposure (1 point if dietary assessment is validated and 1 point if nut intake is appropriately categorized), outcome (1 point for the assessment of outcome according to accepted clinical criteria), and statistical analysis (1 point for the control of confounding factors).

Statistical analysis

Results stratified by sex and stroke subgroups were treated as 2 separate reports. A random-effects model was used to calculate summary RRs and 95% CIs for a 1-serving/d increase of nut intake. For each study that used different cutoffs for nut categories, we evaluated the dose-response relation by computing RRs with 95% CIs for a 1-serving/d increment of nut consumption. For studies that provided results in servings per day, we used the original data to estimate RRs with 95% CIs for the 1-serving/d increase in nut intake. If outcomes were only shown by categories of nut intake, we used the method proposed by Greenland and Longnecker (33) and Orsini et al (34) to estimate RRs with 95% CIs for the 1-serving/d increase in nut intake. When the median or mean consumption per category was not reported, we assigned the midpoint of upper and lower boundaries in each category as the median consumption. For the highest consumption category, we assumed that the lower boundary plus a 25% increment was the median intake. For studies that reported categorical data in grams, we first converted nut intake into servings per day with a standard conversion (1 serving = 28 g) (35). We also used a random-effects model to calculate summary RRs and 95% CIs for highest compared with lowest intakes of nut consumption.

We used the I^2 statistic to assess heterogeneity. Low, moderate, and high degrees corresponded to I^2 values of 25%, 50%, and 75% (36, 37), respectively. The Egger test was used to assess publication bias (38). We performed subgroup analyses on

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TABLE 1
Characteristics of 18 prospective cohort studies on nut consumption and diabetes, IHD, stroke, CVD, and all-cause mortality events[1]

First author (ref), publication year, study name, location	Sex	Age	Follow-up time	No. of cases/subjects	Dietary category; RR (95% CI)	Exposure and case ascertainment[2]	Covariates in fully adjusted model
		y	*y*				
Parker (26), 2003, IWHS, United States	F	55–69	11	Diabetes 1831/134,486	<1/mo; 1.00 (1.00, 1.00) <1/wk; 0.98 (0.87, 1.10) 1–4/wk; 1.06 (0.93, 1.22) ≥5/wk; 1.51 (1.13, 2.04)	Validated FFQ 127 items/self-report	Age, smoking, family history of diabetes and physical activity, total energy intake, alcohol intake, BMI, diet, et al
Villegas (27), 2008, The Shanghai Women's Health Study, China	F	40–70	4.6	Diabetes 1608/64,227	0.1 g/d; 1.00 (1.00, 1.00) 0.4 g/d; 0.80 (0.69, 0.94) 0.7 g/d; 0.95 (0.82, 1.11) 1.4 g/d; 0.79 (0.68, 0.92) 3.1 g/d; 0.80 (0.68, 0.93)	Validated FFQ 77 items/symptoms plus FPG, OGTT, or taking antidiabetic medication	Age, energy intake, BMI, waist-to-hip ratio, smoking, alcohol, vegetable intake, fiber, physical activity, income, education, occupation, and hypertension
Kochar (28), 2010, PHS, United States	M	41–87	21.1	Diabetes 1828/20,224	0/wk; 1.00 (1.00, 1.00) <1/wk; 1.06 (0.93, 1.20) 1/wk; 1.10 (0.95, 1.26) 2–4/wk; 0.97 (0.82, 1.14) 5–6/wk; 0.99 (0.76, 1.30) >7/wk; 0.87 (0.61, 1.24)	Validated FFQ 19 items/self-report	Age, smoking, randomization arm, consumption of breakfast, cereal, dairy, and red meat, physical activity, BMI, and history of hypertension
Pan (18), 2013, NHS, United States	F	30–55	22	Diabetes 5121/116,4248	Fully adjusted model without BMI 0/wk; 1.00 (1.00, 1.00) <1/wk; 0.97 (0.91, 1.04) 1/wk; 1.00 (0.91, 1.09) 2–4/wk; 0.91 (0.80, 1.02) ≥5/wk; 0.87 (0.77, 0.99) Fully adjusted model 0/wk; 1.00 (1.00, 1.00), <1/wk; 0.99 (0.92, 1.05) 1/wk; 1.05 (0.96, 1.15) 2–4/wk; 0.98 (0.87, 1.11) ≥5/wk; 1.00 (0.87, 1.14)	Validated FFQ 130 items/symptoms plus FPG, OGTT, or use of antidiabetic medication	Age, smoking, family history of diabetes and physical activity, total energy intake, alcohol intake, BMI, diet, and magnesium
Pan (18), 2013, NHS II, United States	F	20–45	18	Diabetes 4098/159,9667	Fully adjusted model without BMI 0/wk; 1.00 (1.00, 1.00) <1/wk; 0.95 (0.88, 1.02) 1/wk; 0.89 (0.79, 0.99) 1–4/wk; 0.86 (0.73, 1.00) ≥5/wk; 0.77 (0.64, 0.92) Fully adjusted model 0/wk; 1.00 (1.00, 1.00) <1/wk; 0.99 (0.92, 1.06) 1/wk; 1.00 (0.89, 1.12) 1–4/wk; 1.00 (0.86, 1.17) ≥5/wk; 1.02 (0.85, 1.23)	Same as above	Same as above

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TABLE 1 (*Continued*)

First author (ref), publication year, study name, location	Sex	Age	Follow-up time	No. of cases/subjects	Dietary category; RR (95% CI)	Exposure and case ascertainment[2]	Covariates in fully adjusted model
Fraser (24), 1992, AHS, United States	Both	>25	6	Nonfatal MI 134 Fatal IHD 260/31,208	Fatal IHD <1/wk; 1.00 (1.00, 1.00) 1–4/wk; 0.74 (0.49, 1.11) >5/wk; 0.52 (0.30, 0.87) Nonfatal MI <1/wk; 1.00 (1.00, 1.00) 1–4/wk; 0.77 (0.61, 0.98) >5/wk; 0.67 (0.51, 0.88)	Semiquantitative FFQ 65 items/ medical records, autopsy report, death certificate	Age, sex, smoking, exercise, relative weight, high blood pressure, and consumption of other foods
Albert (25), 2002, PHS, United States	M	40–84	17	Nonfatal MI 1037 Fatal IHD 566/21,454	Fatal IHD <1/mo; 1.00 (1.00, 1.00) 1/wk; 0.90 (0.67, 1.22) 1–3/mo; 0.89 (0.67, 1.16) ≥2/wk; 0.70 (0.50, 0.98) Nonfatal MI <1/mo; 1.00 (1.00, 1.00) 1–3/mo; 1.22 (1.00, 1.51) 1/wk; 1.20 (0.96, 1.50) ≥2/wk; 1.04 (0.82, 1.33)	FFQ 20 items/self-report and medical records	Age, aspirin and carotene treatment, evidence of CVD, BMI, smoking, history of diabetes, hypercholesterolemia, hypertension, alcohol, exercise, and fish, red meat, fruit, vegetable, and dairy intake
Blomhoff (19), 2006, IWHS, United States	F	55–69	15	IHD death 948 CVD death 1675 Total death 5451/31,778	IHD death 0/wk; 1.00 (1.00, 1.00) <1/wk; 1.03 (0.84, 1.26) 1–4/wk; 0.82 (0.68, 0.98) ≥5/wk; 0.71 (0.55, 0.91) CVD death 0/wk; 1.00 (1.00, 1.00) <1/wk; 1.00 (0.86, 1.17) 1–4/wk; 0.84 (0.73, 0.96) ≥5/wk; 0.72 (0.60, 0.88) Total death 0/wk; 1.00 (1.00, 1.00) <1/wk; 0.93 (0.85, 1.02) 1–4/wk; 0.88 (0.81, 0.95) ≥5/wk; 0.89 (0.81, 0.99)	Peanut butter + nuts FFQ 127 items/ NS	BMI, waist-to-hip ratio, education, physical activity, use of estrogens, multivitamin supplements, alcohol, whole grain, refined grain, red meat, fish, seafood, and total fruit and vegetable intake
Li (21), 2009, NHS, United States	F	52.8 ± 8.5	22	CVD death 635 MI 452/6309	Nonfatal MI 0/wk; 1.00 (1.00, 1.00) <1/wk; 0.63 (0.41, 0.96) 2–4/wk; 0.74 (0.49, 1.13) ≥5/wk; 0.56 (0.33, 0.97) CVD 0/wk; 1.00 (1.00, 1.00) <1/wk; 0.72 (0.50, 1.02) 2–4/wk; 0.80 (0.56, 1.14) ≥5/wk; 0.56 (0.36, 0.89)	Peanut butter + nuts, semiquantitative FFQ 131 items/ADA diagnostic criteria	Age, time period, total energy, cereal fiber, alcohol, *trans* fat, BMI, smoking, menopausal status, parental history of early myocardial infarction, multivitamin, vitamin E, aspirin use, and exercise

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TABLE 1 (*Continued*)

First author (ref), publication year, study name, location	Sex	Age	Follow-up time	No. of cases/subjects	Dietary category; RR (95% CI)	Exposure and case ascertainment[2]	Covariates in fully adjusted model
Bernstein (29), 2010, NHS, United States	F	30–55	26	IHD 3162/34,492	0.00/wk; 1.00 (1.00, 1.00) 0.28/wk; 0.73 (0.65, 0.82) 0.49/wk; 0.91 (0.82, 1.00) 0.84/wk; 0.76 (0.67, 0.84) 2.8/wk; 0.68 (0.60, 0.76)	FFQ 131 items/medical records, symptoms plus electrocardiogram or enzymes ↑, National Death Index	Age, BMI, activity, alcohol, family history of MI, hormone use, menopausal status, smoking, aspirin intake, duration of diabetes years, hypertension, hypercholesterolemia, energy intake, cereal fiber, glycemic load, saturated fat, and *trans* fat
Djoussé (23), 2010, PHS, United States	M	41–87	21.1	Total stroke 1408/21,078	Hemorrhagic stroke 0/wk; 1.00 (1.00, 1.00) <1/wk; 1.13 (0.78, 1.62) 1/wk; 1.05 (0.70, 1.58) 2–4/wk; 0.49 (0.27, 0.89) 5–6/wk; 1.50 (0.79, 2.84) ≥7/wk; 1.84 (0.95, 3.57) Ischemic stroke 0/wk; 1.00 (1.00, 1.00) <1/wk; 0.93 (0.65, 1.34) 1/wk; 0.86 (0.74, 1.01) 2–4/wk; 0.94 (0.79, 1.11) 5–6/wk; 0.97 (0.80, 1.18) ≥7/wk; 1.06 (0.79, 1.43)	Semiquantitative FFQ 19 items/death certificates and medical records	Age, aspirin assignment, BMI, alcohol consumption, smoking, fruit and vegetable intake, exercise, breakfast cereal, red meat, fish, dairy consumption, prevalent hypertension, diabetes, atrial fibrillation, and IHD
Bernstein (15), 2012, HPFS, United States	Both	Men: 40–75 Women: 30–55	Men 26 Women 22	Total stroke Men 1397/43,150 Women 2633/84,010	Men 0.0/wk; 1.00 (1.00, 1.00) 0.5/wk; 0.94 (0.79, 1.12) 1.0/wk; 0.95 (0.80, 1.13) 1.8/wk; 1.01 (0.86, 1.20) 4.2/wk; 0.92 (0.77, 1.09) Women 0.0/wk; 1.00 (1.00, 1.00) 0.3/wk; 0.94 (0.83, 1.06) 0.5/wk; 0.91 (0.80, 1.04) 0.8/wk; 0.97 (0.85, 1.10) 2.4/wk; 0.86 (0.75, 0.98)	Validated FFQ 131 items/medical records	Age, time period, total energy, cereal fiber, alcohol, *trans* fat, BMI, smoking, menopausal status, parental history of early myocardial infarction, exercise, multivitamin, vitamin E supplement, aspirin use, fruit, vegetables, and other protein sources
Yaemsiri (30), 2012, WHI-OS, United States	F	50–79	4	Ischemic stroke 1049/87,025	Per 7/wk; 0.89 (0.66, 1.20)	FFQ 122 items/by centrally physicians and trained neurologists	Age, race, education, income, smoking, alcohol, history of IHD, AF, aspirin use, diabetes, BMI, BP, vitamin E, fruit, vegetables, fiber intake, and use of cholesterol-lowering, antihypertensive medication
Fraser (14), 1997, AHS, United States	Both	>25	—	All-cause mortality Men 257 Women 312/NS	Men <1/wk; 1.00 (1.00, 1.00) 1–4/ wk; 0.7 (0.4, 1.4)	Semiquantitative FFQ 65 items/NS	The food of interest as well as age, smoking, and exercise

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TABLE 1 (*Continued*)

First author (ref), publication year, study name, location	Sex	Age	Follow-up time	No. of cases/subjects	Dietary category; RR (95% CI)	Exposure and case ascertainment[2]	Covariates in fully adjusted model
					5/wk; 0.6 (0.2, 1.3) Women <1/wk; 1.00 (1.00, 1.00) 1–4/wk; 0.4 (0.2, 0.9) ≥5/wk; 0.5 (0.2, 1.2)		
Fraser (16), 1997, AHS, United States	Both	>85	12	All-cause mortality 1387/NS	Men <1/wk; 1.00 (1.00, 1.00) 1–4/wk; 0.84 (0.64, 1.09) ≥5/wk; 0.77(0.58, 1.02) Women <1/wk; 1.00 (1.00, 1.00) 1–4/wk; 0.89 (0.75, 1.06) ≥5/wk; 0.84 (0.70, 1.01)	Semiquantitative FFQ/by matching to California State death tapes and the National Death Index	Sex, smoking, BMI, exercise, bread, fish, beef, fruit, and sweet desserts
Mann (20), 1997, Oxford Vegetarian study, United Kingdom	Both	16–79	13.3	IHD death 64 All-cause mortality 392/10,802	IHD death <1/wk; 1.00 (1.00, 1.00) 1–4/wk; 1.19 (0.68, 2.10) ≥5/wk; 0.87 (0.45, 1.68) All-cause mortality <1/wk; 1.00 (1.00, 1.00) 1–4/wk; 0.99 (0.79, 1.25) ≥5/wk; 0.77 (0.58, 1.01)	Semiquantitative FFQ/collected with office for National Statistics and coded blinded	Age, sex, smoking, and social class
Van den Brandt (17), 2011, the Dutch study, Netherlands	Both	55–69	24	All-cause mortality Men 8019 Women 5248/NS	Men 0.0 g/d; 1.00 (1.00, 1.00) 11.1 g/d; 0.92 (0.87, 0.98) Women 0.0 g/d; 1.00 (1.00, 1.00) 6.2 g/d; 0.95 (0.90, 1.00)	Semiquantitative FFQ 150 items/by linkage to the Dutch Central Bureau of Genealogy	Age, smoking, BMI, nonoccupational physical activity, history of hypertension, highest level of education, and energy intake
Bao (13), 2013, NHS and HPFS, United States	Both	NHS 30–55 HPFS 40–75	NHS 30 HPFS 24	All-cause mortality NHS 16,200 HPFS 11,229 CVD death 6471/3,038,853	Women All-cause mortality 0/wk; 1.00 (1.00, 1.00) <1/wk; 0.94 (0.90, 0.98) 1/wk; 0.88 (0.83, 0.92) 2–4/wk; 0.85 (0.80, 0.90) 5–6/wk; 0.88 (0.78, 0.98) ≥7/wk; 0.79 (0.68, 0.91) Men: all-cause mortality 0/wk; 1.00 (1.00, 1.00) <1/wk; 0.85, 0.96) 1/wk; (0.86, 0.97) 2–4/wk; (0.83, 0.94) 5–6/wk; (0.76, 0.91) ≥7/wk; 0.80 (0.73, 0.88) CVD death	Validated FFQ 131 items/National Death Index, reports from family members and postal authorities	Age, race, BMI, physical activity, smoking, current multivitamin use, aspirin use, family history of diabetes, MI or cancer, hypertension, hypercholesterolemia, intake of total energy, alcohol, red or processed meat, fruit, and vegetables; and, in women, menopausal status and hormone use

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TABLE 1 (*Continued*)

First author (ref), publication year, study name, location	Sex	Age	Follow-up time	No. of cases/subjects	Dietary category; RR (95% CI)	Exposure and case ascertainment[2]	Covariates in fully adjusted model
					0/wk; 1.00 (1.00, 1.00)		
					<1/wk; 0.84 (0.78, 0.90)		
					1/wk; 0.83 (0.76, 0.89)		
					2–4/wk; 0.79 (0.73, 0.86)		
					≥5/wk; 0.75 (0.62, 0.84)		
Guasch-Ferré (22), 2013, the PREDIMED trial, Spain	Both	55–80	4.8	CVD death 81	CVD death	Semiquantitative FFQ 137 items/by the end-point adjudication committee	Age, sex, and intervention group, BMI, smoking, educational, activity, history of diabetes, hypercholesterolemia, use of oral antidiabetic medication, antihypertensive medication, statins, total energy intake, dietary variables, alcohol intake, and Mediterranean diet adherence
				All-cause mortality 323/31,077	0/wk; 1.00 (1.00, 1.00)		
					1–3/wk; 0.42 (0.24, 0.74)		
					>3/wk; 0.45 (0.25, 0.81)		
					All-cause mortality		
					0/wk; 1.00 (1.00, 1.00)		
					1–3/wk; 0.71 (0.54, 0.93)		
					>3/wk; 0.61 (0.45, 0.83)		

[1] ADA, American Diabetes Association; AF, atrial fibrillation; AHS, The Adventist Health Study; BP, blood pressure; CVD, cardiovascular disease; FFQ, food-frequency questionnaire; FPG, fasting plasma glucose; HPFS, Health Professionals Follow-Up Study; IHD, ischemic heart disease; IWHS, Iowa Women's Health Study; MI, myocardial infarction; NHS, Nurses' Health Study; OGTT, oral-glucose-tolerance test; PHS, Physicians' Health Study; ref, reference; PREDIMED, PREvención con DIeta MEDiterránea; WHI-OS, Women's Health Initiative Observational Study.

[2] Exposure refers to how the data were collected.

possible sources of heterogeneity [ie, sex, type of nut, IHD subtypes (fatal IHD or nonfatal MI), and stroke subtypes (ischemic and hemorrhagic)]. Sensitivity analyses were used to evaluate the effect of removing a single study from the analysis. Results of subgroup analyses are RRs (95% CIs) for comparison of highest with lowest categories of nut consumption because of a lack of data for person-years in some studies.

BMI might mediate the relation between nut consumption and respective health outcomes. Whenever possible, we separately performed a meta-analysis on the multivariable-adjusted model with and without adjustment for BMI to explore the possible mediating effect of BMI on the relation of nut intake with health outcomes.

In addition, we used restricted cubic splines with 4 knots at percentiles 5%, 35%, 65%, and 95% to evaluate potential linear curve associations between nut consumption and risk of diabetes, CVD, and all-cause mortality. Two-sided analyses were conducted with Stata 12.0 software (StataCorp). $P < 0.05$ was considered statistically significant.

RESULTS

Study characteristics

We used a total of 31 reports from 18 studies in our main analysis; 14 studies were conducted in the United States, 1 study was conducted in China, 1 study was conducted in the Netherlands, 1 study was conducted in the United Kingdom, and 1 study was conducted in Spain. We identified 12,655 cases of type 2 diabetes, 8862 cases of CVD, 6623 cases of IHD, 6487 cases of stroke, and 48,818 cases of mortality. Characteristics of these studies are presented in **Table 1** (13–30). Follow-up periods ranged from 4 to 30 y, and the age range was from 20 to 87 y. Nut consumption was assessed by food frequency questionnaires in all studies. Highest categories of nut intake ranged from ≥2 to ≥7 servings/wk; the lowest category of nut intake ranged from 0 to ≤1 serving/wk.

Most of the studies included other dietary variables, such as protein sources and total caloric intake. All but 2 reports from one study (20) used multivariate models without adjustment for dietary factors, which could have caused confounding. Two studies (19, 21) examined the relation between intakes of peanut butter as well as all nuts and disease outcomes. Other studies examined peanuts and/or nuts without peanut butter. Seven studies (13, 18, 21–23, 25, 28) reported the relation between nut intake and other dietary and lifestyle factors at baseline. Participants who consumed more nuts were leaner, exercised more frequently, smoked less, and ate more fruit and vegetables, fish, whole grains, and dairy. Study quality scores ranged from 3 to 5. The mean quality score was 4.6.

Nut consumption and diabetes

Four reports reported age-adjusted estimates. Pooled results from these 4 reports suggested an inverse association between nut intake and diabetes (RR: 0.88; 95% CI: 0.84, 0.92; $I^2 = 0.0\%$, $P = 0.60$) for a 1-serving/d increment in nut consumption (*see* Supplemental Figure 1 under "Supplemental data" in the online issue). Two reports (one study with 2 large cohorts) reported multivariable-adjusted estimates without BMI. When we repeated the meta-analysis and used multivariable-adjusted estimates

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without BMI, results were not substantially changed (RR: 0.80; 95% CI: 0.69, 0.94; I^2 = 51.4%, P = 0.15) (**Figure 2**). Four reports reported multivariable-adjusted estimates with adjustment for BMI. When the primary meta-analysis was repeated by using fully adjusted estimates, the summary estimate was attenuated to null) RR: 1.03; 95% CI: 0.91, 1.16; I^2 = 63.9%, P = 0.04; NS) (Figure 2).

Pooled RRs for the comparison of extreme quantiles of nut intake for type 2 diabetes are also shown in Figure 2. Subgroup analyses were performed by sex, BMI, and type of nuts. From stratified analyses by type of nuts, we showed an inverse association between nut intake and diabetes in the multivariate model without BMI. In the BMI-adjusted model, the only remaining inverse association was with walnuts. When studies were stratified by BMI, studies conducted in populations with lower BMI (<25) suggested a borderline inverse association (RR: 0.68; 95% CI: 0.45, 1.01; I^2 = 11.9%, P = 0.29). In studies conducted in populations with higher BMI (≥25), the pooled RR was 0.78 (95% CI: 0.64, 0.95; I^2 = 0%, P = 0.66) (**Table 2**).

In the cubic spline model, we showed a nonlinear association between nut consumption and risk of type 2 diabetes by using data with multivariable-adjustment without adjustment for BMI (**Figure 3**A; P-nonlinearity < 0.001). However, with the use of data with full adjustment, we showed no significant association between nut consumption and risk of diabetes (Figure 3B; P-nonlinearity = 0.746).

Nut intake, IHD, and CVD

Results from the random-effects meta-analysis of the relation between nut intake and incidences of IHD and CVD are shown in **Figure 4**. For a 1-serving/d increment in nut consumption, pooled RRs (95% CIs) were 0.72 (0.64, 0.81) for IHD with no between-study heterogeneity (I^2 = 0%, P = 0.64) and 0.71 (0.59, 0.85) for overall CVD with modest between-study heterogeneity (I^2 = 48.8%, P = 0.12) (Figure 4). After the removal of estimates that included peanut butter and all nuts, pooled RR estimates were 0.73 (95% CI: 0.64, 0.83) for IHD and 0.64 (95% CI: 0.43, 0.97) for CVD, respectively. With the exclusion of estimates without adjustment for dietary factors, the pooled RR for IHD was 0.73 (95% CI: 0.64, 0.83).

Pooled RRs for the comparison of extreme quantiles of nut intake were 0.66 (95% CI: 0.55, 0.78; I^2 = 62.5%, P = 0.02) for IHD and 0.70 (95% CI: 0.60, 0.81; I^2 = 22.8%, P = 0.27) for CVD (Figure 4). In stratified analyses by sex, an inverse relation between nut consumption and IHD was shown in women (RR: 0.68; 95% CI: 0.61, 0.76), with the I^2 value decreasing from 62.5% to 0.0%, but not in men (RR: 0.87; 95% CI: 0.59, 1.28; I^2 = 71.5%, P = 0.06; NS). For the type of IHD, nut intake was inversely associated with fatal IHD (RR: 0.68; 95% CI: 0.62, 0.75; I^2 = 0.0%, P = 0.54) but not nonfatal MI (RR: 0.70; 95% CI: 0.43, 1.17; I^2 = 75.7%, P = 0.02; NS). Similar results were shown in studies with and without peanut butter (Table 2). In

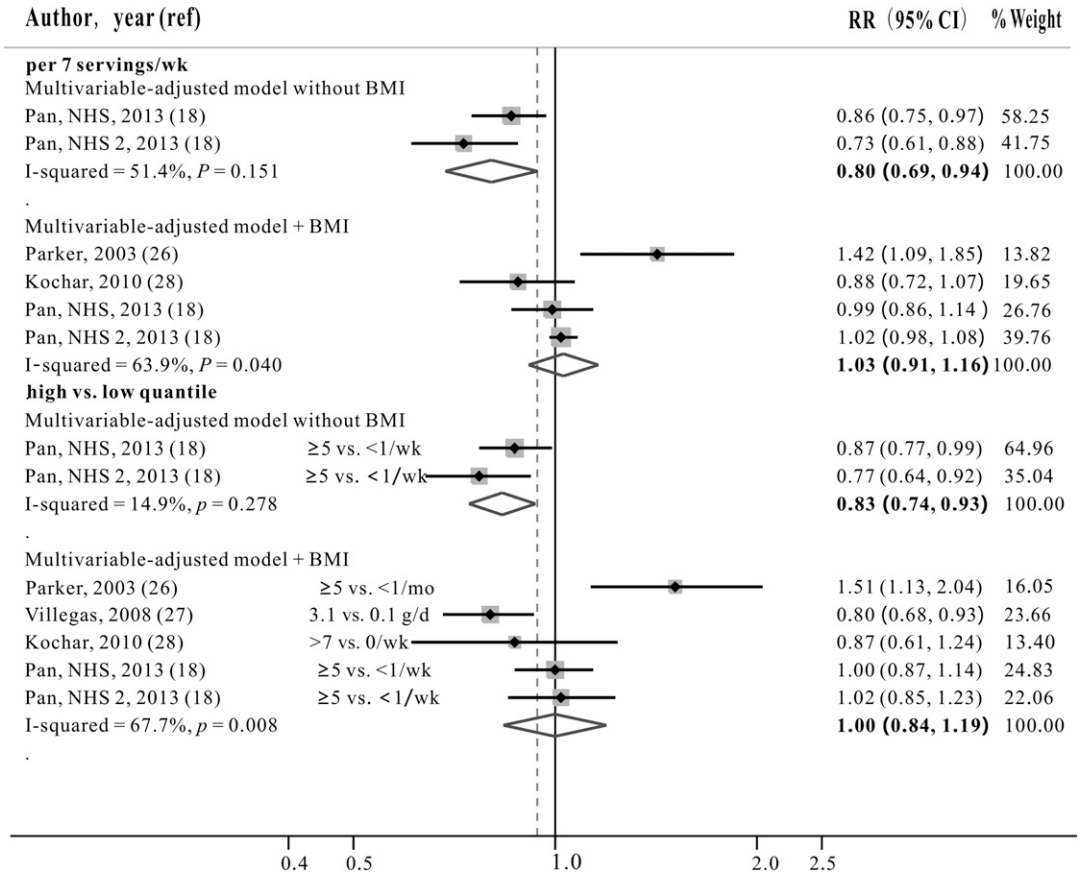

FIGURE 2. Pooled RRs and 95% CIs for type 2 diabetes. We obtained pooled estimates by using a random-effects model. Dots indicate adjusted RRs by comparing high with low quantiles or per 7-serving/wk increase in nut intakes; the dashed line indicates no significant association between exposure and outcome; the diamonds indicate the pooled RRs; the size of the shaded square is proportional to the percentage weight of each study; horizontal lines indicate 95% CIs. NHS, Nurses' Health Study; ref, reference.

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TABLE 2
Subgroup analyses (highest compared with lowest categories)[1]

Source	No. of reports	RR (95% CI)	Homogeneity	
			P-heterogeneity	I^2 (%)
Subgroup analyses for type 2 diabetes				
Multivariate-adjusted model without BMI				
Type of nuts				
Total tree nuts	2	0.85 (0.75, 0.95)	—	—
Walnuts	2	0.67 (0.54, 0.82)	—	—
Multivariate-adjusted model + BMI				
Type of nuts				
Total tree nuts	2	0.98 (0.87, 1.10)	—	—
Walnuts	2	0.76 (0.62, 0.94)	—	—
Sex				
F	3	0.94 (0.77, 1.15)	0.03	70.8
M	1	0.87 (0.61, 1.24)	—	—
BMI				
<25 kg/m^2	2	0.68 (0.45, 1.01)	0.29	11.9
≥ 25 kg/m^2	2	0.78 (0.64, 0.95)	0.66	0
Subgroup analyses for IHD				
Multivariate-adjusted model + BMI				
IHD subgroup				
Fatal IHD	5	0.68 (0.62, 0.75)	0.54	0
Nonfatal MI	3	0.70 (0.43, 1.17)	0.02	75.7
Sex				
F	3	0.68 (0.61, 0.76)	0.74	0
M	2	0.87 (0.59, 1.28)	0.06	71.5
Type of nuts				
Peanut butter + nuts	2	0.66 (0.52, 0.84)	<0.01	75.7
Nuts	4	0.70 (0.55, 0.89)	0.59	0
Subgroup analyses for stroke				
Multivariate-adjusted model + BMI				
Stroke subgroup				
Ischemic stroke	3	0.95 (0.84, 1.08)	0.87	0
Hemorrhagic stroke	2	1.17 (0.54, 2.54)	0.04	77.3
Sex				
F	2	0.87 (0.77, 0.98)	0.84	0
M	2	0.95 (0.82, 1.11)	0.40	0
Subgroup analyses for all-cause mortality				
Multivariate-adjusted model + BMI				
Sex				
F	5	0.88 (0.81, 0.96)	0.07	54.2
M	4	0.85 (0.75, 0.95)	0.05	60.7
Type of nuts				
Peanut butter + nuts	1	0.89 (0.81, 0.99)	—	—
Nuts	10	0.85 (0.79, 0.91)	<0.01	60.2

[1] Pooled estimates were obtained by using a random-effects model. IHD, ischemic heart disease; MI, myocardial infarction.

the cubic spline model, we showed a nonlinear association between nut consumption and risk of CVD (Figure 3C; *P*-nonlinearity < 0.001).

Nut intake and stroke

The pooled RR of total stroke for the comparison of extreme quantiles of nut intake was 0.91 (95% CI: 0.81, 1.02; $I^2 = 20.4\%$, $P = 0.285$; NS) (Figure 4). In a stratified analysis, an inverse association between nut consumption and stroke was shown in women (RR: 0.87; 95% CI: 0.77, 0.98; $I^2 = 0\%$, $P = 0.84$) but not men (RR: 0.95; 95% CI: 0.82, 1.11; $I^2 = 0\%$, $P = 0.40$; NS). In addition, pooled RRs were not statistically significant for either stroke type (Table 2).

Nut intake and all-cause mortality

For all-cause mortality, the pooled RR with a 1-serving/d increment in nut intake was 0.83 (95% CI: 0.76, 0.91) with moderately high heterogeneity ($I^2 = 62.1\%$, $P = 0.032$) (**Figure 5**). After the exclusion of estimates that included peanut butter as well as all nuts, the pooled RR was 0.80 (95% CI: 0.71, 0.90). When we excluded estimates without adjustment for dietary factors, the pooled RR was 0.84 (95% CI: 0.76, 0.92).

The pooled RR for the comparison of extreme quantiles of nut intake was 0.85 (95% CI: 0.79, 0.91) for all-cause mortality with moderately high heterogeneity ($I^2 = 60.2\%$, $P = 0.005$) (Figure 5). Similar results were shown in studies conducted in women and men and in studies with and without peanut butter (Table 2).

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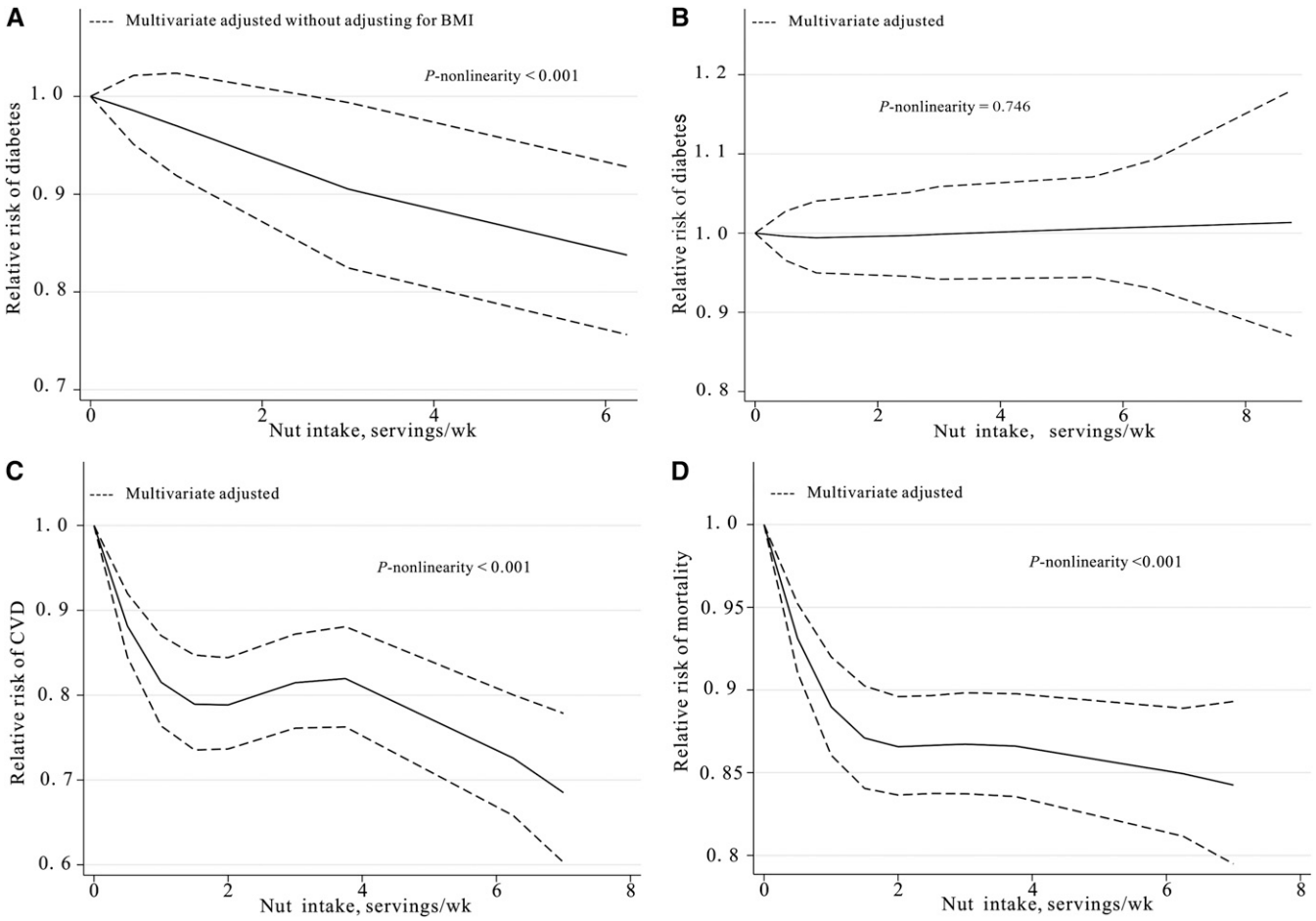

FIGURE 3. Dose-response relation plots between nut intakes (servings/wk) and risk of type 2 diabetes (A and B), cardiovascular disease (C), and all-cause mortality (D) were estimated by using random-effects metaregression. Dotted lines represent the 95% CIs for the fitted trend. RR estimates with multivariable-adjustment except adjustment for BMI were used in panel A; RR estimates with multivariable-adjustment were used in panels B–D. CVD, cardiovascular disease.

In the cubic spline model, we showed a nonlinear association between nut consumption and risk of all-cause mortality (Figure 3D; *P*-nonlinearity = <0.001).

Sensitivity analysis

When we recalculated the overall homogeneity and effect size by removing one report at a time, we showed that none of the single studies substantially changed the pooled estimates for IHD, overall CVD, and mortality (*see* Supplemental Table 1 under "Supplemental data" in the online issue). For stroke, the pooled estimate changed from 0.91 (95% CI: 0.81, 1.02) to 0.89 (95% CI: 0.80, 0.98; I^2 = 0.0%, P = 0.932) when the hemorrhagic stroke result from the Physicians' Health Study (23) was excluded. For diabetes, the pooled estimate was not substantially influenced with the omission of the study of Parker et al (26), which was from correspondence and not a peer-reviewed publication. The omission of the other studies one at a time did not materially change the pooled estimate.

Assessment of publication bias

No significant evidence of substantial publication bias was observed [P = 1.00 for diabetes, P = 1.00 for IHD, P = 0.31 for CVD, P = 0.46 for mortality (high compared with low analyses) and P = 0.81 for diabetes, P = 1.00 for IHD, P = 0.09 for CVD, P = 0.31 for stroke, and P = 0.21 for mortality (dose-response analyses)]. The assessment of publication bias was based on the fully adjusted model.

DISCUSSION

This meta-analysis indicated that nut intake is inversely associated with IHD, overall CVD, stroke in women, and all-cause mortality but not with diabetes and total stroke in the fully adjusted model. A significant inverse association seen between nut intake and type 2 diabetes was attenuated by adjustment for BMI, which indicated that the association was largely mediated through BMI.

Frequent nut intake may improve health outcomes via multiple mechanisms. First, nuts are high in fat, but most of the fat is unsaturated fatty acids (39) that can reduce risk of CVD and diabetes (40, 41). Second, nuts contain few carbohydrates and, thus, contribute little to postprandial glycemia (42). Third, inflammation has been linked to risk of CVD and diabetes (43), and evidence has suggested that frequent nut consumption has an inverse association with circulating inflammatory cytokines and a positive relation with plasma adiponectin (44). Fourth, nuts have high amounts of protein, L-arginine, folate, fiber, and

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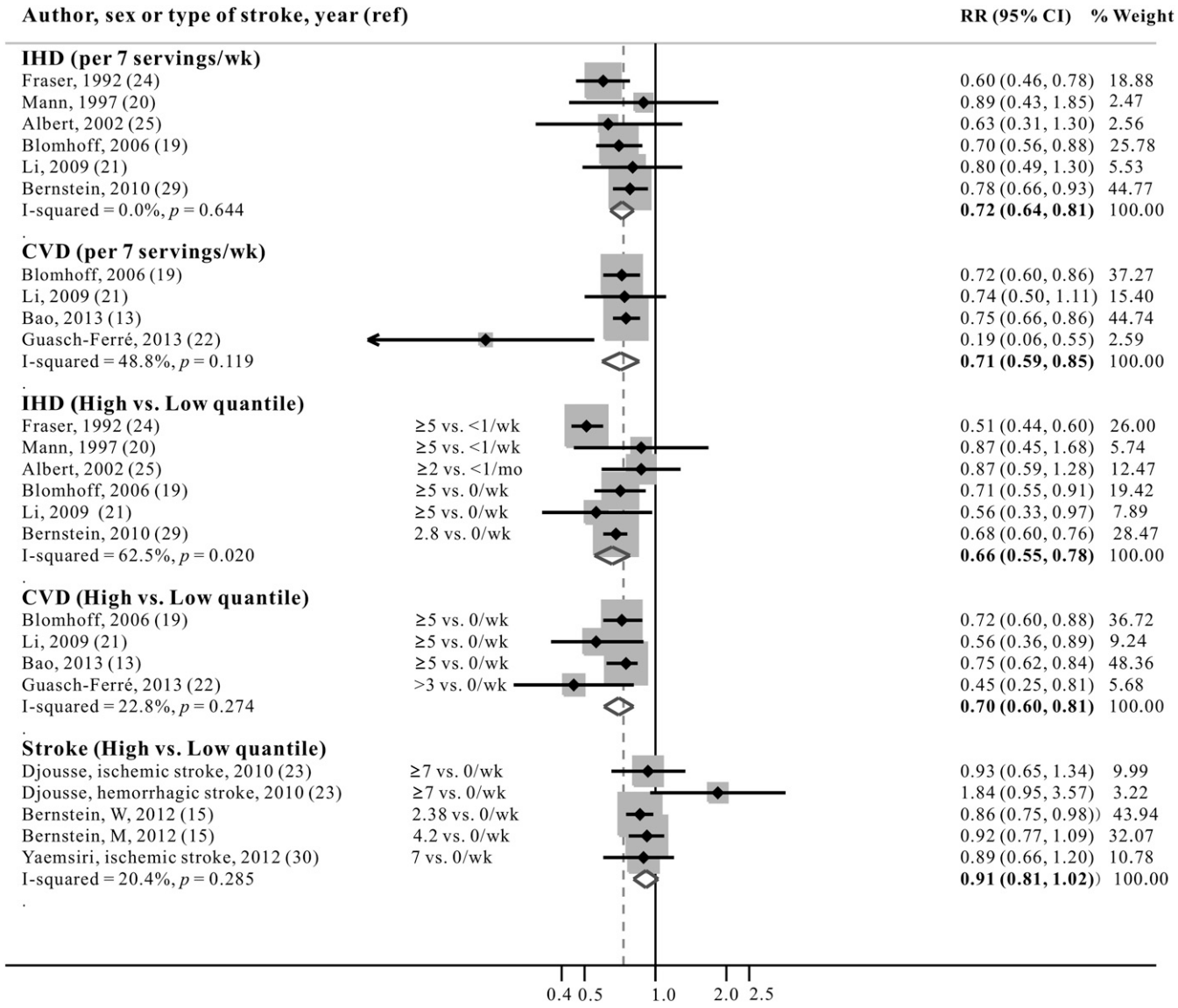

FIGURE 4. Pooled RRs and 95% CIs for IHD, stroke, and CVD. We obtained pooled estimates by using a random-effects model. Dots indicate adjusted RRs by comparing high with low quantiles or per 7-serving/wk increase in nut intakes; the dashed line indicates no significant association between exposure and outcome; the diamonds indicate the pooled RRs; the size of the shaded square is proportional to the percentage weight of each study; and horizontal lines indicate 95% CIs. CVD, cardiovascular disease; IHD, ischemic heart disease; ref, reference; W, women.

phytosterols (39). Unsalted varieties of nuts have low sodium contents. Nuts are also rich in minerals (eg, calcium, magnesium, and potassium) (39), which are associated with decreased overall cardiovascular risk (45).

In addition, frequent nut intake can improve lipid profiles. A recent pooled analysis of 25 clinical studies on various kinds of nuts showed a dose-response cholesterol-lowering effect. With an average daily intake of 67 g nuts, mean reductions in total and LDL cholesterol were 11 mg/dL and 10 mg/dL, respectively (8). Another meta-analysis of 13 clinical trials indicated that diets supplemented with walnuts were associated with a 13.7% decrease in LDL cholesterol (46). Because a large body of consistent evidence has supported the beneficial effects of frequent nut intake on various intermediate mediators of chronic diseases, it is plausible that nuts protect against IHD, overall CVD, and all-cause mortality.

Heterogeneity was present in our analyses. The heterogeneity for IHD and stroke were partly explained, and some meaningful results were obtained in subgroup analyses. For both IHD and stroke, results were stronger in women than men. These observed differences may be the result of a different hormonal milieu between sexes or just due to chance because of limited study. By IHD type, the result was stronger for fatal IHD than for MI. Data from Albert et al (25) showed a significant inverse relation between nut intake and sudden cardiac death but no significant inverse relation between nut intake and nonsudden IHD death or nonfatal MI. Separate analyses by stroke type did not show significant effects for either ischemic or hemorrhagic stroke. Greater intake of nuts has been associated with improved BP in a previous meta-analysis (47). If nuts decrease BP, it seems logical that frequent nut consumption would reduce the incidence of ischemic stroke. Our nonsignificant finding on ischemic stroke may have been attributable to the small number of cases in included studies, which limited the power of the analysis. In addition, stroke is a heterogeneous disease that is difficult to accurately

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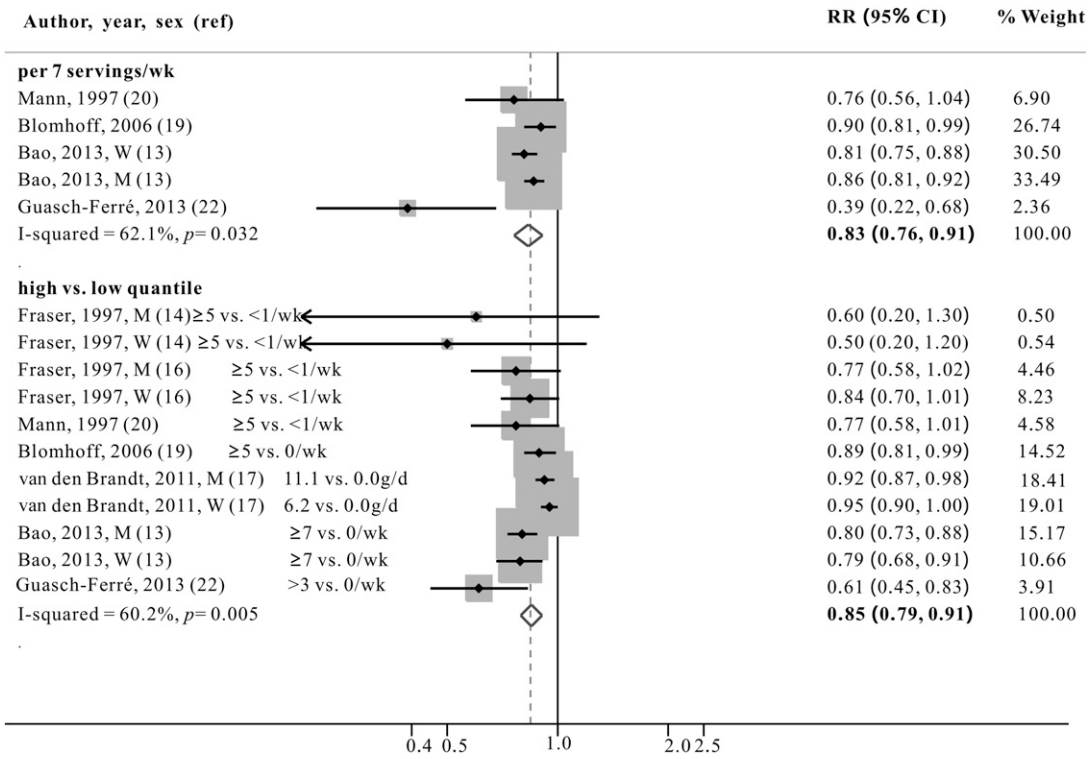

FIGURE 5. Pooled RRs and 95% CIs for all-cause mortality. We obtained pooled estimates by using a random-effects model. Dots indicate adjusted RRs by comparing high with low quantiles or per a 7-serving/wk increase in nut intakes; the dashed line indicates no significant association between exposure and outcome; the diamonds indicate the pooled RRs; the size of the shaded square is proportional to the percentage weight of each study; and horizontal lines indicate 95% CIs. ref, reference; W, women.

diagnose. Additional studies are warranted to investigate the association between the consumption of nuts and ischemic stroke and investigate the inverse relation between nut intake and stroke in women.

Long-term, double-blind, randomized controlled trials provide the best evidence on the effect between nutrients and disease. In the PREvención con DIeta MEDiterránea (PREDIMED) trial, Mediterranean diets supplemented with 30 g nuts/d (almonds, hazelnuts, and walnuts) significantly reduced systolic BP (48), risk of metabolic syndrome (49), and incidence of diabetes (50) compared with a low-fat diet. Recently, long-term results from this trial showed reduced risk of stroke, total CVD, and all-cause mortality for the group assigned to the Mediterranean diet with mixed nuts compared with the control group (51).

A recent meta-analysis showed no association between nut consumption and diabetes (47). However, the results did not consider models with and without adjustment for BMI. Obesity is the most-important determinant of type 2 diabetes. Previous studies have shown that frequent nut consumption is associated with less weight gain (52). Thus, BMI can be considered a mediating variable in the association between nut intake and diabetes. The inverse association between walnut consumption and diabetes risk remained significant even after adjustment for BMI. Note that walnuts have the highest α-linolenic acid content of all nuts (53). In addition, Guasch-Ferré et al (22) showed an inverse relation between walnuts and cancer mortality but not with other nuts in the PREvención con DIeta MEDiterránea trial and concluded this effect could be attributable to the rich free and total polyphenols contents in walnuts compared with other nuts. More studies are needed to elucidate the effect of different types of nuts separately on multiple health outcomes. Note the inverse associations between frequent nut consumption and risk of CVD and total mortality were not altered substantially after adjustment for BMI.

We included prospective cohort studies with high-quality scores, large sample sizes, and long-term follow-ups. We conducted several sensitivity analyses to evaluate the robustness of our findings. In addition, we obtained as much data as possible for dose-response analyses, which complemented the results from categorical analyses.

Our meta-analysis had several limitations. First, we may have overlooked some studies and did not include unpublished or non–English-language reports. Second, there are many kinds of nuts, with varying effects on health outcomes. However, we could only single out walnuts and peanuts. Our findings should be interpreted as the average associations with different types of nuts. Third, various preparation and processing methods may alter the availability of bioactive compounds in nuts (54), but it is beyond the scope of large epidemiologic studies to assess these factors in modifying health effects of nuts. Fourth, significant heterogeneity was present for the meta-analyses of nut consumption and mortality. Sources of heterogeneity were not completely clear, but they might be due to different types and amounts of nuts consumed in different populations. Finally, observational studies cannot exclude the effects of some unknown confounding factors or residual confounding attributable to other dietary and lifestyle factors because nut eaters tend to follow a healthy dietary pattern. Therefore, it is difficult to tease

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out the independent effects of nut consumption from other dietary factors in observational analyses. For this reason, our results should be interpreted in the context of mechanistic studies and human intervention studies.

In conclusion, our meta-analysis indicates significant inverse associations between frequent nut intake and IHD, overall CVD, and all-cause mortality. These findings support recommendations to include nuts as part of healthy dietary patterns for the prevention of chronic diseases.

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The authors' responsibilities were as follows—LL and FBH: were the guarantors, had full access to all study data, took responsibility for the study integrity and accuracy of data analyses, designed the study, and reviewed or revised the final manuscript; CL: led the conception and drafting of the protocol, analyzed data, drafted the manuscript, provided a critical review of the content of the manuscript, and revised the manuscript for important intellectual content; YZ and YD: searched databases according to inclusion and exclusion criteria, reviewed search results by titles and abstracts, and retrieved full-text articles to identify eligible trials; ZS and SC: extracted data and evaluated the methodological quality by using criteria that were previously established; MY: settled discrepancies by discussion in accordance with the authors' selection criteria and gave advice on the meta-analysis methodology; and all authors: contributed to the manuscript. None of the authors had a conflict of interest.

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