Association of nut intake with risk factors, cardiovascular disease, and mortality in 16 countries from 5 continents: analysis from the Prospective Urban and Rural Epidemiology (PURE) study

Russell J de Souza,[1,2] Mahshid Dehghan,[2] Andrew Mente,[1,2] Shrikant I Bangdiwala,[1,2] Suad Hashim Ahmed,[3] Khalid F Alhabib,[4] Yuksel Altuntas,[5] Alicja Basiak-Rasała,[6] Gilles-R Dagenais,[7] Rafael Diaz,[8] Leela Itty Amma,[9] Roya Kelishadi,[10] Rasha Khatib,[11,12] Scott A Lear,[2,13] Patricio Lopez-Jaramillo,[14] Viswanathan Mohan,[15,16] Paul Poirier,[17] Sumathy Rangarajan,[2] Annika Rosengren,[18,19] Rosnah Ismail,[20] Sumathi Swaminathan,[21] Edelweiss Wentzel-Viljoen,[22] Karen Yeates,[23] Rita Yusuf,[24] Koon K Teo,[2,25] Sonia S Anand,[1,2,25] and Salim Yusuf,[2,25] for the PURE study investigators

[1]Department of Health Research Methods, Evidence, and Impact, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada; [2]Population Health Research Institute, Hamilton, ON, Canada; [3]Dubai Health Authority, Dubai, UAE; [4]Department of Cardiac Sciences, King Fahad Cardiac Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [5]Department of Endocrinology and Metabolism, University of Health Sciences, Sisli Hamidiye Etfal Teaching and Research Hospital , Istanbul, Turkey; [6]Department of Social Medicine, Wroclaw Medical University, Wroclaw, Poland; [7]Université Laval, Quebec, Canada; [8]Estudios Clinicos Latinoamerica (ECLA), Rosario, Santa Fe, Argentina; [9]Health Action by People/Amrita Institute of Medical Sciences, Kerala, India; [10]Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran; [11]Institute for Community and Public Health, Birzeit University, Birzeit, Palestine; [12]Advocate Research Institute, Advocate Health Care, Chicago, IL, USA; [13]Faculty of Health Sciences, Simon Fraser University, Vancouver, Canada; [14]Instituto Masira, Medical School, Facultad de Ciencias de la Salud, Universidad de Santander (UDES) and Fundacion Oftalmologica de Santander (FOSCAL), Bucaramanga, Colombia; [15]Madras Diabetes Research Foundation, Chennai, India; [16]Dr. Mohan's Diabetes Specialities Centre, Chennai, India; [17]Institut universitaire de cardiologie et de pneumologie de Québec, Quebec, Canada; [18]Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [19]Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden; [20]Community Health Department, Faculty of Medicine, National University of Malaysia, Kuala Lumpur, Malaysia; [21]St John's Research Institute, Koramangala, Bangalore, India; [22]Centre of Excellence for Nutrition, Faculty of Health Sciences, North-West University, Potchefstroom, South Africa; [23]Department of Medicine, Division of Nephrology, Queens University, Ontario, Canada; [24]School of Life Sciences, Independent University, Dhaka, Bangladesh; and [25]Department of Medicine, Faculty of Health Sciences, McMaster University, Ontario, Canada

ABSTRACT

Background: The association of nuts with cardiovascular disease and deaths has been investigated mostly in Europe, the USA, and East Asia, with few data available from other regions of the world or from low- and middle-income countries.

Objective: To assess the association of nuts with mortality and cardiovascular disease (CVD).

Methods: The Prospective Urban Rural Epidemiology study is a large multinational prospective cohort study of adults aged 35–70 y from 16 low-, middle-, and high-income countries on 5 continents. Nut intake (tree nuts and ground nuts) was measured at the baseline visit, using country-specific validated FFQs. The primary outcome was a composite of mortality or major cardiovascular event [nonfatal myocardial infarction (MI), stroke, or heart failure].

Results: We followed 124,329 participants (age = 50.7 y, SD = 10.2; 41.5% male) for a median of 9.5 y. We recorded 10,928 composite events [deaths (n = 8,662) or major cardiovascular events (n = 5,979)]. Higher nut intake (>120 g per wk compared with <30 g per mo) was associated with a lower risk of the primary composite outcome of mortality or major cardiovascular event [multivariate HR (mvHR): 0.88; 95% CI: 0.80, 0.96; P-trend = 0.0048]. Significant reductions in total (mvHR: 0.77; 95% CI: 0.69, 0.87; P-trend <0.0001), cardiovascular (mvHR: 0.72; 95% CI: 0.56, 0.92; P-trend = 0.048), and noncardiovascular mortality (mvHR: 0.82; 95% CI: 0.70, 0.96; P-trend = 0.0046) with a trend to reduced cancer mortality (mvHR: 0.81; 95% CI: 0.65, 1.00; P-trend = 0.081) were observed. No significant associations of nuts were seen with major CVD (mvHR: 0.91; 95% CI: 0.81, 1.02; P-trend = 0.14), stroke (mvHR: 0.98; 95% CI: 0.84, 1.14; P-trend = 0.76), or MI (mvHR: 0.86; 95% CI: 0.72, 1.04; P-trend = 0.29).

Conclusions: Higher nut intake was associated with lower mortality risk from both cardiovascular and noncardiovascular causes in low-, middle-, and high-income countries. *Am J Clin Nutr* 2020;112:208–219.

Keywords: nuts, mortality, cardiovascular disease, prospective cohort, global health

Introduction

Diet is an important modifiable risk factor for cardiovascular and other noncommunicable diseases. Many guidelines recommend a low-fat diet (<30% of energy) and replacing SFAs with unsaturated fatty acids (1, 2). Several prospective cohort studies found that diets replacing fat with carbohydrate are not associated with lower cardiovascular disease (CVD) risk (3–5), whereas diets that replace saturated fat or carbohydrate with unsaturated

fat or plant protein are associated with improvements in LDL cholesterol and HDL cholesterol and lower risk of CVD (5, 6). Nuts are good sources of fatty acids (predominantly unsaturated), fiber, plant protein, and minerals (notably magnesium and potassium) and contain bioactive compounds, such as polyphenols, tocopherols, phytosterols, and phenolics (7–9).

Meta-analyses of prospective cohort studies found that nut consumption is associated with a lower risk of CVD events and mortality (10–13). Most of these cohort studies were conducted in Europe and the USA, with limited information from other parts of the world with varying background diets and types of nuts consumed. The primary aims of this study were to assess the associations of nut intake with major CVD events and mortality in 124,329 participants in a prospective cohort study of high-, middle-, and low-income countries with a wide range of nut intake. We also examined associations between individual types of nuts with outcome events, and whether nut intake is associated with major CVD risk markers.

Methods

Study design and participants

The design and methods of the Prospective Urban Rural Epidemiology (PURE) study have been described previously (5, 14, 15). This prospective cohort study has enrolled 148,105 individuals aged 35–70 y in 21 low-, middle- and high-income countries between 1 January, 2003, and 3 July, 2019: Argentina, Bangladesh, Brazil, Canada, Chile, China, Colombia, India, Iran, Malaysia, occupied Palestine territory, Pakistan, the Philippines, Poland, South Africa, Saudi Arabia, Sweden, Tanzania, Turkey, United Arab Emirates, and Zimbabwe. We collected data at community, household, and individual levels with standardized questionnaires and case-report forms to record data on major cardiovascular events and mortality during follow-up.

The final baseline population for the analyses excluded participants from 5 countries where the FFQ did not ask about nut intake (n = 22,927 from Colombia, Chile, Malaysia, Pakistan, and the Philippines). We also excluded participants with missing or implausible FFQ data (<500 or >5000 kcal/d). For analyses of mortality we included 124,329 participants aged 50.5 y (SD = 10.0) from 16 countries; for the composite outcome of mortality and major CVD, as well as cardiovascular events, we excluded those with CVD [nonfatal myocardial infarction (MI), stroke, or heart failure; n = 10,866] at baseline, leaving 113,463 (**Online Supporting Material**, **Supplementary Figure 1**). Event definitions and adjudication processes have been published previously (Online Supporting Material, **Supplementary**

SY is supported by the Mary W Burke endowed chair of the Heart and Stroke Foundation of Ontario. The PURE study is an investigator-initiated study that is funded by the Population Health Research Institute, Hamilton Health Sciences Research Institute (HHSRI), the Canadian Institutes of Health Research, Heart and Stroke Foundation of Ontario; support from Canadian Institutes of Health Research's Strategy for Patient Oriented Research, through the Ontario Strategy for Patient-Oriented Research (SPOR) Support Unit, as well as the Ontario Ministry of Health and Long-Term Care and through unrestricted grants from several pharmaceutical companies [with major contributions from AstraZeneca (Canada), Sanofi-Aventis (France and Canada), Boehringer Ingelheim (Germany and Canada) Servier, and GlaxoSmithKline], and additional contributions from Novartis and King Pharma and from various national or local organizations in participating countries. These include: Argentina: Fundacion ECLA (Estudios Clínicos Latino America); Bangladesh: Independent University, Bangladesh and Mitra and Associates; Brazil: Unilever Health Institute, Brazil; Canada: this study was supported by an unrestricted grant from Dairy Farmers of Canada and the National Dairy Council (USA), Public Health Agency of Canada and Champlain Cardiovascular Disease Prevention Network; Chile: Universidad de La Frontera (DI13-PE11); China: National Center for Cardiovascular Diseases and ThinkTank Research Center for Health Development; Colombia: Colciencias (grant numbers: 6566-04-18062 and 6517-777-58228); India: Indian Council of Medical Research; Malaysia: Ministry of Science, Technology and Innovation of Malaysia [grant number: 100-IRDC/BIOTEK 16/6/21 (3/2007), and 07-05-IFN-BPH 010], Ministry of Higher Education of Malaysia [grant number: 600-RMI/LRGS/5/3 (2/2011)], Universiti Teknologi MARA, Universiti Kebangsaan Malaysia (UKM-Hejim-Komuniti-15-2010); occupied Palestinian territory: the United Nations Relief and Works Agency for Palestine Refugees in the Near East, occupied Palestinian territory; International Development Research Centre, Canada; Philippines: Philippine Council for Health Research and Development; Poland: Polish Ministry of Science and Higher Education (grant number: 290/W-PURE/2008/0), Wroclaw Medical University; Saudi Arabia: Saudi Heart Association, Saudi Gastroenterology Association, Dr. Mohammad Alfagih Hospital, The Deanship of Scientific Research at King Saud University, Riyadh, Saudi Arabia (research group number: RG - 1436-013); South Africa: The North-West University, SA and Netherlands Programme for Alternative Development, National Research Foundation, Medical Research Council of South Africa, The South Africa Sugar Association, Faculty of Community and Health Sciences; Sweden: grants from the Swedish state under the agreement concerning research and education of doctors; the Swedish Heart and Lung Foundation; the Swedish Research Council; the Swedish Council for Health, Working Life and Welfare, King Gustaf V's and Queen Victoria Freemason's Foundation, AFA Insurance; Turkey: Metabolic Syndrome Society, AstraZeneca, Sanofi-Aventis; United Arab Emirates: Sheikh Hamdan Bin Rashid Al Maktoum Award For Medical Sciences and Dubai Health Authority, Dubai.

A list of funding sources is given in the Online Supporting Materials (page 42). The external funders and sponsors of the study had no role in study design or conduct; data collection, analysis, or interpretation; the writing, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Data described in the manuscript, code book, and analytic code will not be made available as the PURE study is an ongoing study and during its conduct only the investigators who have participated/contributed to the study can have access to the data. Select summary data may be shared with policymakers for specific purposes. The study executive will consider specific requests for data analyses by noncontributing individuals 3 y after the study has been completed (i.e., complete recruitment and a minimum of 10-y follow-up in all) and the participating investigators have had an opportunity to explore questions that they are interested in. Costs related to data curating and related efforts will need to be met by anybody not contributing to the conduct of the study and requesting analyses.

Supplementary Tables 1–22, Supplementary Figure 1, and the Online Supporting Materials are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Address correspondence to RJdS (e-mail: desouzrj@mcmaster.ca).

Abbreviations used: CAD, coronary artery disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; mvHR, multivariable HR; PURE, Prospective Urban Rural Epidemiology study; MET, metabolic equivalent of task; MI, myocardial infarction; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Received December 4, 2019. Accepted for publication April 21, 2020.

First published online May 20, 2020; doi: https://doi.org/10.1093/ajcn/nqaa108.

Table 1) (16, 17). The Population Health Research Institute, Hamilton Health Sciences (Hamilton, Ontario, Canada) coordinated the study.

Ethics

The study was approved by the ethics committee at each participating center and at Hamilton Health Sciences, Hamilton, Ontario, Canada (see the Online Supporting Material for a list). All the participants provided written informed consent.

Assessment of diet

We recorded participants' habitual food intake at the baseline visit, using validated country-specific (region-specific in India) FFQs. For countries where a validated FFQ was not available, we developed and validated FFQs. These studies are described and referenced in **Supplementary Table 2**. Participants were asked "during the past year, on average, how often have you consumed the following foods or drinks" and the list of food items was given. For almost all countries, FFQs had the same format and frequencies of consumption (9 categories from "never" to ">6 times/d").

Exposure categories

Consumption of almonds, peanuts, walnuts, cashews, pistachios, hazelnuts, and chestnuts [which together account for 99.5% of global nut consumption (18)] and unspecified "other" or "mixed" nuts were assessed. Total nut intake was grouped as: <30 g per month, 30 g per month to <30 g per week, 30 g per week to <120 g per week, and ≥ 120 g per week. We chose these groupings to enhance comparability of our results with previous prospective studies (19–22).

Clinical outcomes

We included all outcome events known to us through to 3 July, 2019. We used standardized case-report forms to capture data on major cardiovascular events and death during follow-up, which were adjudicated centrally in each country by trained physicians using standardized definitions (Supplementary Table 1). To enhance comparability with other reports on single foods and nutrients in PURE, we chose a primary outcome which was a composite of mortality and major cardiovascular events [death from cardiovascular causes and nonfatal myocardial infarction (MI), stroke, and heart failure]. Secondary outcomes were mortality, MI, stroke, cardiovascular mortality, noncardiovascular mortality, and cancer mortality; and concentration of blood lipids [fasting total cholesterol (TC), LDL cholesterol, HDL cholesterol, triglycerides (TG), apo-A1, and apo-B], systolic and diastolic blood pressure, and fasting glucose.

Blood lipids

Study staff drew fasting blood samples (20 mL) from 95,852 participants. All participants were instructed not to have anything to eat or drink after 23:59 the evening prior to blood collection. When they arrived for blood collection (typically at 08:00 local time), they were asked whether they had adhered to this. The samples were frozen immediately at −20°C or −70°C after processing, and serum samples were shipped in nitrogen vapor tanks by courier from every site to a blood storage site, where they were stored at −160°C in nitrogen vapor (Hamilton, ON, Canada) or at −70°C (China, India, and Turkey). We analyzed blood samples for TC, LDL cholesterol, HDL cholesterol, TG, apo-A1, and apo-B in the Clinical Research and Clinical Trials Laboratory at Hamilton General Hospital (Hamilton, ON, Canada). Blood samples from China, India, and Turkey were analyzed in a central laboratory in each country after standardization with the laboratory in Hamilton (23).

Blood pressure

Blood pressure was recorded twice after 5 min of rest in a sitting position using an Omron automatic digital monitor (BP742 OMRON Healthcare Manufacturing Vietnam Co., Ltd.). We used the average of these measurements as the outcome.

Statistics

We calculated HRs using the Cox frailty model with random intercepts to account for center clustering (which also adjusts for region and country) (24). We present estimates of HRs and 95% CIs for categories of nuts, and per 30-g serving/d, adjusted for multiple confounding variables (mvHR). To test for trends across categories of nut intake, we used the score test of a linear association between a 1-category increase in nuts and risk (*P*-trend). The associations of nuts with mortality and the composite which included CVD were compared in the following subgroups: *1*) high versus low nut-consuming regions; *2*) high versus low urinary sodium excretion; *3*) across global regions (Europe/North America, South America, Africa, Middle East, South Asia, Southeast Asia, and China); *4*) higher versus lower carbohydrate intake; and *5*) type of nuts consumed (tree nuts compared with ground nuts; and specific associations of almonds, cashews, chestnuts, hazelnuts, peanuts, pistachio nuts, and walnuts). We performed 2 sensitvity analyses to assess the robustness of our findings: 1) we excluded those with CVD (or cancer for the cancer outcome) or diabetes at baseline; and 2) we also excluded those who experienced the outcome of interest during the first 2 y of follow-up.

For each participant, follow-up time accrued from the day of return of the baseline questionnaire and ended on the day of diagnosis of an event, or the end of the study period, whichever occurred first. Data collection across the PURE countries is ongoing, thus the dataset we used for the present analyses includes all outcome events known to us through to 3 July, 2019. For multivariate analyses, mvHR were adjusted for location (urban compared with rural), age (continuous), sex, education [categorized as none or primary school (first 6 y), secondary school (7 to 11 y) and college, trade school, or university (> 11 y)], smoking (categorized as never, former, or current smoker), BMI (weight in kg divided by height in meters, squared; continuous), waist-to-hip ratio (cm/cm, continuous), physical activity [categorized based on the metabolic equivalent of task (MET) per minute per week as low (<600 MET-min per week), moderate (600–3000 MET-min per week), or high (>3000 MET-min per week) activity], family history of CVD, diabetes, or cancer; and other dietary factors [fish, fruits,

TABLE 1 Characteristics of the study participants at enrollment by frequency of nut consumption

Characteristic	<30 g per month	30 g per month to <30 g per week	30 g per week to <120 g per week	≥120 g per week	Overall	*P*-trend[1]
No. of participants[2]	55,770 (44.9)	23,405 (18.8)	30,353 (24.4)	14,801 (11.9)	124,329	—
Nuts,[3] g/d	0.1 ± 0.3	2.4 ± 0.9	9.0 ± 3.7	35.0 ± 21.4	6.4 ± 13.0	<0.0001
Age,[3] y	50.7 ± 10.2	50.2 ± 9.8	50.1 ± 9.7	50.4 ± 9.9	50.5 ± 10.0	<0.0001
BMI,[3] kg/m^2	25.7 ± 5.5	25.2 ± 5.1	25.6 ± 5.3	26.3 ± 5.20	25.6 ± 5.3	0.0004
Waist-to-hip ratio,[3] cm/cm						
M	0.91 ± 0.08	0.91 ± 0.08	0.91 ± 0.08	0.91 ± 0.07	0.91 ± 0.08	0.034
F	0.85 ± 0.08	0.83 ± 0.08	0.83 ± 0.08	0.83 ± 0.08	0.84 ± 0.08	<0.0001
Male[2]	23,162 (41.5)	9640 (41.2)	13,528 (44.6)	6370 (43.0)	52,700 (42.4)	<0.0001
Urban[2]	27,655 (49.6)	11,735 (50.1)	17,504 (57.7)	9182 (62.0)	66,076 (53.2)	<0.0001
Current smoker[2]	12,371 (22.4)	5016 (21.7)	6231 (20.7)	2460 (16.7)	26,078 (21.2)	<0.0001
Consume alcohol,[2] yes	13,558 (26.6)	7530 (33.5)	10,395 (40.2)	5067 (42.9)	36,550 (32.9)	<0.0001
Hypertension[2]	18,201 (33.7)	6293 (27.7)	8007 (27.2)	3830 (27.3)	36,331 (30.2)	<0.0001
Diabetes[2]	4699 (8.4)	1510 (6.5)	2161 (7.1)	1254 (8.5)	9624 (7.8)	<0.0001
Family history of CVD[2]	14,956 (29.0)	6857 (34.2)	10,301 (39.3)	5301 (38.6)	37,415 (33.8)	<0.0001
Family history of diabetes[2]	10,402 (20.5)	4500 (22.5)	6762 (25.8)	3822 (27.8)	25,486 (23.0)	<0.0001
Family history of cancer[2]	8525 (16.9)	4356 (21.8)	6201 (23.7)	3044 (22.2)	22,126 (20.0)	<0.0001
Region[2]						<0.0001
Europe/North America	2718 (4.9)	3322 (14.2)	6496 (21.4)	3249 (22.0)	15,785 (12.7)	
South America	9.657 (17.3)	2457 (10.5)	1011 (3.3)	233 (1.6)	13,358 (10.7)	
Africa	3368 (6.0)	599 (2.6)	1201 (4.0)	1120 (7.6)	6, 288 (5.0)	
Middle East	4080 (7.3)	1711 (7.3)	5002 (16.5)	3544 (23.9)	14,337 (11.5)	
South Asia	14,438 (25.9)	6203 (26.5)	6797 (22.4)	1561 (10.6)	28,999 (23.3)	
China	21,509 (38.6)	9113 (38.9	9846 ± 32.4	5094 (34.4)	45,562 (36.7)	
Energy intake,[3] kcal	1960 ± 744	2026 ± 727	2200 ± 755	2639 ± 840	2112 ± 786	<0.0001
Energy from carbohydrate,[3] %	62.4 ± 12.4	63.2 ± 12.0	60.8 ± 11.1	55.9 ± 9.2	61.4 ± 11.8	<0.0001
Fibre,[3] g/d	20 ± 13	19 ± 12	24 ± 15	33 ± 19	23 ± 15	<0.0001
Energy from fat,[3] %	22.2 ± 10.1	21.8 ± 9.3	24.2 ± 8.8	28.9 ± 7.5	23.4 ± 9.6	<0.0001
Saturated fat,[3] %	8.0 ± 4.6	8.0 ± 4.5	8.1 ± 4.0	8.6 ± 3.3	8.1 ± 4.3	<0.0001
Monounsaturated fat,[3] %	7.4 ± 3.6	7.3 ± 3.4	8.3 ± 3.5	10.3 ± 3.6	7.9 ± 3.7	<0.0001
Polyunsaturated fat,[3] %	4.6 ± 3.2	4.6 ± 2.3	5.5 ± 2.3	7.5 ± 3.0	5.2 ± 3.0	<0.0001
Energy from protein,[3] %	15.0 ± 3.8	14.7 ± 3.5	15.1 ± 3.4	16.0 ± 3.2	15.1 ± 3.6	<0.0001
Dietary cholesterol,[3] mg/d	293 ± 277	260 ± 187	293 ± 205	357 ± 225	295 ± 241	<0.0001
Fish,[4] g/d	6.0 (20.2)	9.7 (27.3)	11.8 (27.3)	20.1 (44.9)	9.4 (26.3)	<0.0001
Fruits,[4] g/d	92.7 (170.8)	102.7 (193.8)	168.3 (278.0)	272.4 (364.0)	124.7 (240.9)	<0.0001
Vegetables,[4] g/d	222.7 (157.6)	250.0 (145.6)	250.8 (140.0)	257.1 (186.3)	250.0 (142.9)	<0.0001
Red and processed meat,[4] g/d	30.0 (79.7)	35.7 (66.6)	46.1 (75.3)	64.9 (83.7)	40.0 (79.0)	<0.0001
Legumes,[4] g/d	30.0 (67.9)	40.1 (69.2)	42.9 (64.9)	50.1 (72.9)	39.0 (69.7)	<0.0001
Almonds,[4] g/d	0.0 (0.0)	0.3 (0.5)	0.7 (1.4)	4.0 (5.9)	0.6 (2.4)	<0.0001
Chestnuts,[4] g/d	0.0 (0.0)	0.4 (0.7)	1.5 (2.7)	3.4 (6.2)	0.8 (2.7)	<0.0001
Cashew,[4] g/d	0.0 (0.0)	0.3 (1.0)	1.0 (1.8)	6.3 (8.5)	2.3 (5.7)	<0.0001
Hazelnut,[4] g/d	0.0 (0.1)	0.4 (0.7)	0.7 (1.7)	4.4 (7.7)	1.1 (3.7)	<0.0001
Peanuts,[4] g/d	0.1 (0.2)	1.5 (1.2)	4.5 (4.4)	17.6 (17.5)	3.3 (8.2)	<0.0001
Pistachio,[4] g/d	0.0 (0.2)	0.4 (0.6)	1.0 (1.5)	4.6 (6.2)	1.5 (3.5)	<0.0001
Walnuts,[4] g/d	0.0 (0.1)	0.5 (0.8)	2.7 (3.8)	10.9 (14.7)	1.9 (6.1)	<0.0001

[1]To test for trend across categories of nut intake, we used the score test of a linear association between a 1-category increase in nuts and the continuous risk factor (*P*-trend); we used the Cochran-Mantel-Haenszel test of association between a 1-category increase in nuts and the distribution of the categorical risk factor (*P*-trend).

[2]Presented as count (%).

[3]Presented as mean ± SD.

[4]Presented as median (IQR).

CVD, cardiovascular disease.

vegetables, red/processed meat, legumes (in g/d), and total energy intake (kcal/d)], using the complete-case method for covariates. Participants lost to follow-up contributed person-time through their final contact. We did not adjust for diabetes or hypertension in our models because the impact of nuts on mortality or CVD might occur through these risk factors.

We assessed the cross-sectional association of nut intake with blood lipids and glucose using a linear mixed-effects model (with a random effect for center), across the same categories of nut intake as described for clinical events (above), and per 30-g serving/d. Additional adjustments were made for use of antihypertensive medications (for the association of nuts with blood pressure), lipid-lowering medications (for the association of nuts with TC, LDL cholesterol, HDL cholesterol, TC:HDL cholesterol, and TG), and antidiabetic medications (for the association of nuts with glucose).

Results

Over a median of 9.5 y (IQR: 8.0, 11.1), we documented 8662 deaths (including 2039 from CVD and 4949 from noncardiovascular causes), 10,928 composite events (deaths and CVD), and 5979 major CVD cases, (including 2915 strokes and 2559 MIs).

Table 1 presents participant characteristics by category of baseline nut intake. Overall, 55,770 participants (44.9%) consumed <30 g nuts per month, and 14,801 (11.9%) consumed ≥ 120 g per week. Higher nut consumers were younger, had a marginally higher BMI and lower waist-to-hip ratio; and were more likely to be male, live in an urban area, and have a family history of CVD, diabetes, or cancer, and less likely to be a current smoker or have hypertension. Greater nut consumption was associated with a higher intake of energy, fibre, cholesterol, and percent of energy from fat and protein, and a lower percent of energy from carbohydrate.

UAE, Zimbabwe, Iran, Canada, Poland, Turkey, Tanzania, and Palestine were high nut-consuming countries, where 64.5% of participants consumed ≥30 g of nuts/wk, and the median nut intake was 7.4 g/d (IQR: 2.0, 17.6 g). India, China, South Africa, Brazil, Sweden, Argentina, Bangladesh, and Saudi Arabia were low nut-consuming countries where 51.7% of participants consumed <30 g of nuts per month, and the median nut intake was 1.0 g/d (IQR: 0.0, 4.9 g) (**Supplementary Tables 3** and **4**).

Clinical outcomes

A higher intake of nuts (>120 g per week compared with <30 g per month) was associated with a lower risk of the composite outcome (mvHR: 0.88; 95% CI: 0.80, 0.96; *P*-trend = 0.0048 or 0.90; 95% CI: 0.84, 0.97 per 30 g), mortality (mvHR: 0.77; 95% CI: 0.69, 0.87; *P*-trend <0.0001 or 0.85; 95% CI: 0.78, 0.93 per 30 g), cardiovascular mortality (mvHR: 0.72; 95% CI: 0.56, 0.92; *P*-trend = 0.048 or 0.82; 95% CI: 0.69, 0.99 per 30 g), and noncardiovascular mortality (mvHR: 0.82; 95% CI: 0.70, 0.96; *P*-trend = 0.0046 or 0.88; 95% CI: 0.78, 1.00 per 30 g). There was a trend towards a lower risk of cancer mortality (mvHR: 0.81; 95% CI: 0.65, 1.00; *P*-trend = 0.081). No significant associations of nuts were seen with major CVD (mvHR: 0.91; 95% CI: 0.81, 1.02; *P*-trend = 0.14 or 0.91; 95% CI: 0.84, 0.99 per 30 g), stroke (mvHR: 0.98; 95% CI: 0.84, 1.14; *P*-trend = 0.76 or 0.93; 95% CI: 0.84, 1.04 per 30 g), or MI (mvHR: 0.86; 95% CI: 0.72, 1.04; *P*-trend = 0.29 or 0.92; 95% CI: 0.81, 1.07 per 30 g) (**Figure 1** and **Table 2**, **Supplementary Tables 5–7**).

Risk factors

Higher nut consumption was associated with lower systolic blood pressure (SBP), diastolic blood pressure (DBP), and HDL cholesterol:LDL cholesterol ratio; and small increases in TC, HDL cholesterol, and LDL cholesterol, after adjustment for the same factors as for the clinical outcomes, as well as use of antihypertensives, cholesterol medications, or oral hypoglycemic medications (**Table 3**).

Sensitivity analyses

Associations of nuts with outcomes were not altered when we excluded participants experiencing the event in the first 2 y of follow-up, when we excluded those with CVD or diabetes at baseline who experienced the event within the first 2 y of follow-up, or both (**Supplementary Tables 8 and 9**; **Figure 2**), or when we used 2 different approaches to handle missing covariate data (**Supplementary Tables 10 and 11**).

Subgroup analyses

Associations were stable across geographic regions, between high and low nut-consuming countries, and between high and low carbohydrate-consuming countries; between those with and without diabetes or hypertension; and across levels of urinary sodium excretion and BMI (**Figure 3**; **Supplementary Tables 12-18**).

Analyses by type of nut

The associations between tree nuts (almonds, cashews, chestnuts, hazelnuts, pistachios, walnuts, kweme, and nut clusters) and ground nuts (peanuts and ground nuts) and the composite outcome ($P_{heterogeneity}$ = 0.008; I^2 = 85.8%; data not shown) and mortality ($P_{heterogeneity}$ = 0.08; I^2 = 67%; Figure 3; **Supplementary Tables 19** and **20**) were heterogeneous. Tree nuts were associated with a decreased risk of mortality (mvHR: 0.75; 95% CI: 0.61, 0.93; *P*-trend <0.0001 or 0.75; 95% CI: 0.62, 0.89 per 30 g), and the composite outcome (mvHR: 0.83; 95% CI: 0.70, 0.99; *P*-trend = 0.021), whereas ground nuts (including peanuts) were associated with a nonsignificant trend towards a lower risk of mortality (mvHR: 0.86; 95% CI: 0.70, 1.03; *P*-trend = 0.068 or 0.92; 95% CI: 0.80, 1.06 per 30 g) but not the composite outcome (mvHR: 0.96; 95% CI: 0.83, 1.11; *P*-trend = 0.90 or 0.99; 95% CI: 0.89, 1.10 per 30 g). There was no evidence of statistical heterogeneity for the associations of different nut types with mortality ($P_{heterogeneity}$ = 0.38; I^2 = 6%) (Figure 3; **Supplementary Table 21**).

Discussion

In a large, global, prospective cohort study with 9.5 y of follow-up, nut consumption is associated with a lower risk of total and cardiovascular mortality after adjustment for lifestyle and dietary factors. We observed no significant association with MI or stroke. The findings are robust and change little with adjustment for potential confounding variables.

Our results agree with previous observational studies of nuts and mortality, mainly in North America and Europe, which report lower RRs with higher nut consumption ranging from 11 to 50% (12, 22, 25–31). A meta-analysis of these studies (n = 277,432 participants and 49,232 deaths) for mortality, found a pooled RR of 0.81 (95% CI: 0.77, 0.85) (10). Another dose-response meta-analysis of studies from mostly high- and middle-income countries (USA and Europe) found pooled RRs of 0.71 for coronary artery disease (CAD) , 0.93 for stroke, 0.79 for CVD, 0.85 for cancer, and 0.78 for mortality (per 28 g/d). Our study independently confirms the lower risk of death associated with higher nut intake, in a population derived from different countries and different continents of the world where patterns of diet vary considerably.

Several nutrients in nuts may contribute to the association with reduced mortality. Almost 80% of energy from nuts comes from

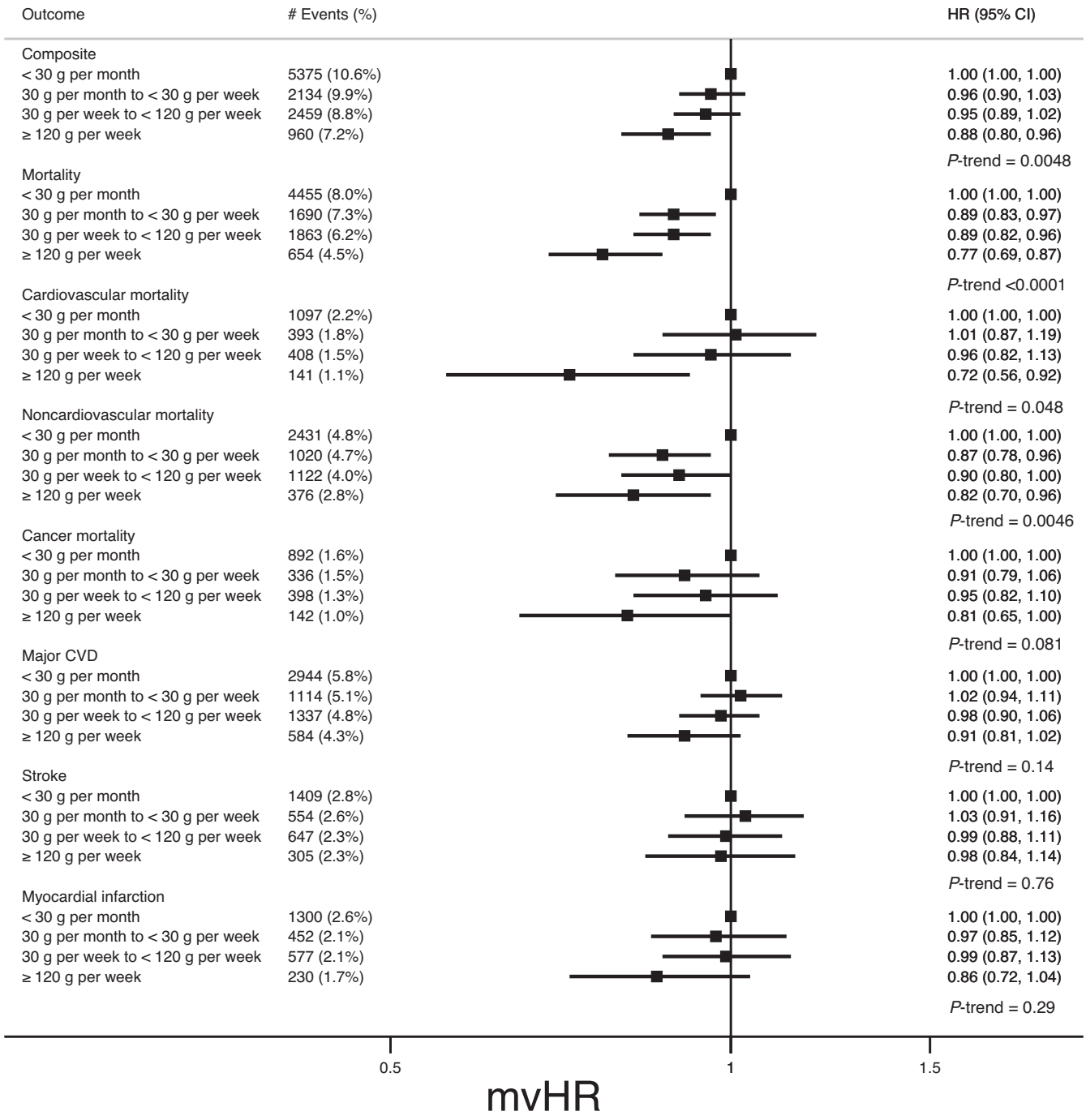

FIGURE 1 Association of highest (≥ 120 g/wk) compared with lowest (<30 g/mo) nut consumption with clinical outcomes. Models adjusted for follow-up time plus age, sex, location (urban/rural), and center (as a random effect); lifestyle factors (education, tobacco use, BMI, waist-to-hip ratio, and physical activity, family history of CVD, diabetes, and cancer); and diet factors (fish, fruits, vegetables, red/processed meat, legumes, and total energy). CVD, cardiovascular disease; mvHR, multivariable HR.

fat (32), but most nuts are low in saturated fat (4–16%) and contain no *trans* fat. Both monounsaturated and polyunsaturated fat (**Supplementary Table 22**) may have beneficial effects on inflammation, LDL cholesterol, and the LDL cholesterol:HDL cholesterol ratio, TG, and blood pressure; and are inversely associated with CVD outcomes (5, 7, 23, 33–36). In addition, nut consumption may displace the intake of less healthy foods such as highly refined sugars and starches, reducing the glycemic load (37), which has been linked with increased CVD, a major contributor to mortality (38). In our study, we found modest associations with lower levels of CVD risk factors, which may partially explain the lack of association with CVD and the failure to replicate findings of previous cohort studies, which have shown protective associations of nuts with CHD and CVD

TABLE 2 Association of nuts with clinical outcomes

		Category of nut consumption					
		<30 g per month	30 g per month to <30 g per week	30 g per week to <120 g per week	≥120 g per week	Per 30 g serving/d	Categorical trend-test[1]
Median intake (IQR, g/d)		0.0 (0.0 to 0.0)	2.2 (1.6 to 3.3)	8.2 (6.1 to 11.9)	28.6 (21.4 to 42.9)		
		# Cases (% in category)					
Composite outcome	Cases/Total	5375 (10.6%)	2134 (9.9%)	2459 (8.8%)	960 (7.2%)		
Age, sex, location,center-adjusted [2]	10,928/113,463	1.00	0.92 (0.87, 0.97)	0.88 (0.84, 0.93)	0.79 (0.74, 0.86)	0.86 (0.82, 0.91)	<0.0001
Multivariable-adjusted[3]	7362/88,202	1.00	0.96 (0.90, 1.03)	0.95 (0.89, 1.02)	0.88 (0.80, 0.96)	0.90 (0.84, 0.97)	0.0048
		# Cases (% in category)					
Mortality	Cases/Total	4455 (8.0%)	1690 (7.3%)	1863 (6.2%)	654 (4.5%)		
Age, sex, location,center-adjusted	8662/124,329	1.00	0.85 (0.80, 0.91)	0.80 (0.75, 0.85)	0.69 (0.63, 0.75)	0.78 (0.72, 0.83)	<0.0001
Fully-adjusted	5284/93,860	1.00	0.89 (0.83, 0.97)	0.89 (0.82, 0.96)	0.77 (0.69, 0.87)	0.85 (0.78, 0.93)	<0.0001
		# Cases (% in category)					
Cardiovascular mortality	Cases/Total	1097 (2.2%)	393 (1.8%)	408 (1.5%)	141 (1.1%)		
Age, sex, location,center-adjusted	2039/113,463	1.00	0.93 (0.82, 1.05)	0.89 (0.78, 1.01)	0.70 (0.57, 0.84)	0.79 (0.69, 0.91)	0.0003
Multivariable-adjusted	1253/85,713	1.00	1.01 (0.87, 1.19)	0.96 (0.82, 1.13)	0.72 (0.56, 0.92)	0.82 (0.69, 0.99)	0.048
		# Cases (% in category)					
Noncardiovascular mortality	Cases/Total	2431 (4.8%)	1020 (4.7%)	1122 (4.0%)	376 (2.8%)		
Age, sex, location,center-adjusted	4949/113,463	1.00	0.83 (0.77, 0.90)	0.79 (0.73, 0.85)	0.70 (0.62, 0.79)	0.78 (0.71, 0.87)	<0.0001
Multivariable-adjusted	2801/85,713	1.00	0.87 (0.78, 0.96)	0.90 (0.80, 1.00)	0.82 (0.70, 0.96)	0.88 (0.78, 1.00)	0.0046
		# Cases (% in category)					
Cancer mortality	Cases/Total	892 (1.6%)	336 (1.5%)	398 (1.3%)	142 (1.0%)		
Age, sex, location,center-adjusted	1768/121,433	1.00	0.89 (0.78, 1.02)	0.89 (0.79, 1.02)	0.71 (0.69, 0.86)	0.80 (0.70, 0.93)	0.0006
Multivariable-adjusted	1407/92,260	1.00	0.91 (0.79, 1.06)	0.95 (0.82, 1.10)	0.81 (0.65, 1.00)	0.89 (0.76, 1.04)	0.081
		# Cases (% in category)					
Major CVD	Cases/Total	2944 (5.8%)	1114 (5.1%)	1337 (4.8%)	584 (4.3%)		
Age, sex, location,center-adjusted	5979/113,463	1.00	0.98 (0.91, 1.06)	0.95 (0.89, 1.02)	0.86 (0.78, 0.94)	0.91 (0.85, 0.97)	<0.004
Multivariable-adjusted	4487/85,713	1.00	1.02 (0.94, 1.11)	0.98 (0.90, 1.06)	0.91 (0.81, 1.02)	0.91 (0.84, 0.99)	0.14
		# Cases (% in category)					
Stroke	Cases/Total	1409 (2.8%)	554 (2.6%)	647 (2.3%)	305 (2.3%)		
Age, sex, location,center-adjusted	2915/113,463	1.00	1.03 (0.93, 1.15)	0.98 (0.89, 1.09)	0.93 (0.81, 1.06)	0.92 (0.84, 1.01)	0.32
Multivariable-adjusted	2385/85,713	1.00	1.03 (0.91, 1.16)	0.99 (0.88, 1.11)	0.98 (0.84, 1.14)	0.93 (0.84, 1.04)	0.76
		# Cases (% in category)					
Myocardial Infarction	Cases/Total	1300 (2.6%)	452 (2.1%)	577 (2.1%)	230 (1.7%)		
Age, sex, location,center-adjusted	2559/113,463	1.00	0.90 (0.80, 1.01)	0.93 (0.84, 1.04)	0.81 (0.70, 0.95)	0.92 (0.82, 1.02)	0.014
Multivariable-adjusted	1788/85,713	1.00	0.97 (0.85, 1.12)	0.99 (0.87, 1.13)	0.86 (0.72, 1.04)	0.92 (0.81, 1.07)	0.29

[1]To test for trend across categories of nut intake, we used the score test of a linear association between a 1-category increase in nuts and risk (*P*-trend).

[2]Model adjusted for follow-up time plus age, sex, location (urban/rural), and center (as a random effect).

[3]Model adjusted for follow-up time plus age, sex, location (urban/rural), and center (as a random effect); lifestyle factors (education, tobacco use, BMI, waist-to-hip ratio, and physical activity, family history of CVD, diabetes, and cancer); and diet factors (fish, fruits, vegetables, red/processed meat, legumes, and total energy) (MV-adjusted, multivariable adjusted).

CVD, cardiovascular disease.

TABLE 3 Cross-sectional (baseline) associations of nut consumption with cardiovascular disease risk factors

Characteristic	<30 g per month (n = 42,159)[1]	30 g per month to <30 g per week (n = 18,869)[1]	30 g per week to <120 g per week (n = 23,919)[1]	≥120 g per week (n = 10,905)[1]	Overall (n = 95,852)[1]	P-trend[2]
SBP,[3] mmHg	154.74 (0.99)	154.32 (0.99)	153.92 (0.99)	153.84 (1.00)	154.20 (0.49)	<0.0001
SBP,[4] mmHg, no hypertension	122.51 (0.54)	122.32 (0.54)	122.24 (0.55)	121.89 (0.56)	122.24 (0.27)	0.0011
DBP,[3] mmHg	93.26 (0.69)	93.33 (0.69)	93.14 (0.69)	92.96 (0.69)	93.17 (0.34)	0.0432
DBP, mmHg, no hypertension	77.72 (0.41)	77.84 (0.41)	77.84 (0.41)	77.44 (0.42)	77.71 (0.21)	0.29
Total cholesterol,[5] mmol/L	3.92 (0.17)	4.02 (0.17)	3.99 (0.17)	3.94 (0.17)	3.97 (0.08)	0.0027
HDL cholesterol,[5] mmol/L	0.98 (0.04)	1.00 (0.04)	0.99 (0.04)	0.99 (0.04)	0.99 (0.02)	0.0279
LDL cholesterol,[5] mmol/L	2.30 (0.11)	2.36 (0.11)	2.34 (0.11)	2.31 (0.11)	2.33 (0.05)	0.024
Triglycerides,[5] mmol/L	1.91 (0.05)	1.92 (0.05)	1.92 (0.05)	1.90 (0.05)	1.91 (0.03)	0.72
TC:HDL[5]	4.25 (0.07)	4.26 (0.07)	4.27 (0.07)	4.24 (0.07)	4.26 (0.03)	0.56
HDL:LDL[5]	0.430 (0.008)	0.431 (0.008)	0.425 (0.008)	0.427 (0.008)	0.430 (0.005)	0.007
Apo-A,[5] mg/dL	0.14 (0.08)	0.15 (0.08)	0.14 (0.08)	0.15 (0.08)	0.15 (0.04)	0.67
Apo-B,[5] mg/dL	0.10 (0.06)	0.10 (0.06)	0.10 (0.06)	0.11 (0.06)	0.10 (0.03)	0.29
Apo-B:apo-A[5]	0.67 (0.05)	0.66 (0.05)	0.67 (0.05)	0.66 (0.05)	0.67 (0.03)	0.49
Glucose,[6] mmol/L	6.87 (0.07)	6.90 (0.07)	6.89 (0.07)	6.92 (0.07)	6.89 (0.04)	0.008
Glucose, mmol/L,[7] no diabetes	5.63 (0.09)	5.65 (0.09)	5.64 (0.09)	5.66 (0.08)	5.64 (0.04)	0.11

[1]Presented as mean (SE), adjusted for age, sex, location (urban/rural), and center (as a random effect); lifestyle factors (education, tobacco use, BMI, waist-to-hip ratio, and physical activity, family history of CVD, diabetes, and cancer), diet factors (fish, fruits, vegetables, red/processed meat, legumes, and total energy).

[2]Tests of trend assessed with generalized linear models.

[3]Additionally adjusted for use of antihypertensives.

[4]n = 60,072 without hypertension.

[5]Additionally adjusted for use of cholesterol medications.

[6]Additionally adjusted for use of oral hypoglycemic medications.

[7]n = 70,629 without diabetes.

DBP, diastolic blood pressure; SBP, systolic blood pressure; TC, total cholesterol.

(13). Differences in the predominant types of nuts consumed across countries, background CVD risk, and risk factors may also explain this (10).

We found that nut consumption was not associated with reduced risk of stroke. Previous cohort studies in European and US adults indicate that nut consumption is not associated with a reduced risk of total (13), ischemic (29, 39–43), or hemorrhagic (29, 39–41) stroke. In 134,265 participants in the Shanghai Women's Health Study (SWHS) and the Shanghai Men's Health Study (SMHS), a low intake of peanuts (median intake, 10.1 g/wk in men and 5.0 g/wk in women) was associated with a lower risk of ischemic (HR, 0.77; 95% CI: 0.60, 1.00 for the highest compared with lowest quintile of nut intake) and hemorrhagic stroke (HR, 0.77; 95% CI: 0.60, 0.99) (29). Our data from PURE China (n = 1662 strokes in 39,361 individuals) showed no association between total nuts (mvHR: 0.97; 95% CI: 0.81, 1.16 comparing ≥120 g/wk to <30 g/mo or 0.93; 95% CI: 0.81, 1.05 per 30 g; P-trend = 0.56) or peanuts (mvHR: 1.00; 95% CI: 0.88, 1.14 comparing >30 g/wk to <30 g/mo or 0.92; 95% CI: 0.78, 1.08 per 30 g; P-trend = 0.99) with stroke.

The PREDIMED (Prevención con Dieta Mediterránea) trial showed that those randomized to a Mediterranean diet supplemented with nuts experienced a 42% reduced risk of stroke (HR: 0.58; 95% CI: 0.42, 0.82) compared with the group advised to follow a low-fat diet (44). The inconsistent findings might be related to the type and amount of nuts consumed, differences in background CVD risk (e.g., blood pressure), or error inherent in dietary measurement by FFQ in cohort studies. In our study, we did not find that nut intake was associated with clinically important differences in blood pressure, which may also explain the lack of association with the risk of stroke.

In our study, the higher consumption of nuts was associated with marginally lower SBP and DBP but higher TC, HDL cholesterol, and LDL cholesterol. The magnitude of differences between the highest and lowest nut consumers is very small and likely not of clinical relevance, which may explain the lack of association with major CVD events in this study. Intervention trials consistently report significant reductions in TC with nuts (11). In a systematic review and meta-analysis of 61 trials (2582 participants followed for 3 to 26 wk), each daily serving of nuts lowered TC by 0.12 mmol/L, LDL cholesterol by 0.12 mmol/L, apo-B by 0.04 g/L, and TG by 0.02 mmol/L (45). Nuts did not affect SBP or DBP. In another meta-analysis of 33 randomized controlled trials, there were no differences in body weight, BMI, or waist circumference in people following diets including nuts compared with control diets (46). This suggests that any beneficial effect of nuts on mortality is probably independent of known CVD risk factors.

We found that tree nuts were more protective than ground nuts (peanuts). Tree nuts, such as walnuts, are good sources of n–6 and n–3 PUFAs (notably α-linolenic acid). Their consumption has been associated with cardioprotective properties (47) such as healthy lipid profiles and reduced inflammatory biomarkers (48), but evidence from large prospective studies with events is sparse. Almonds, another tree nut, are a rich source of monounsaturated fat (49), magnesium, potassium, and vitamin E, and they reduce LDL cholesterol (50). Almond skin flavonoids possess antioxidant activity in vitro and act synergistically

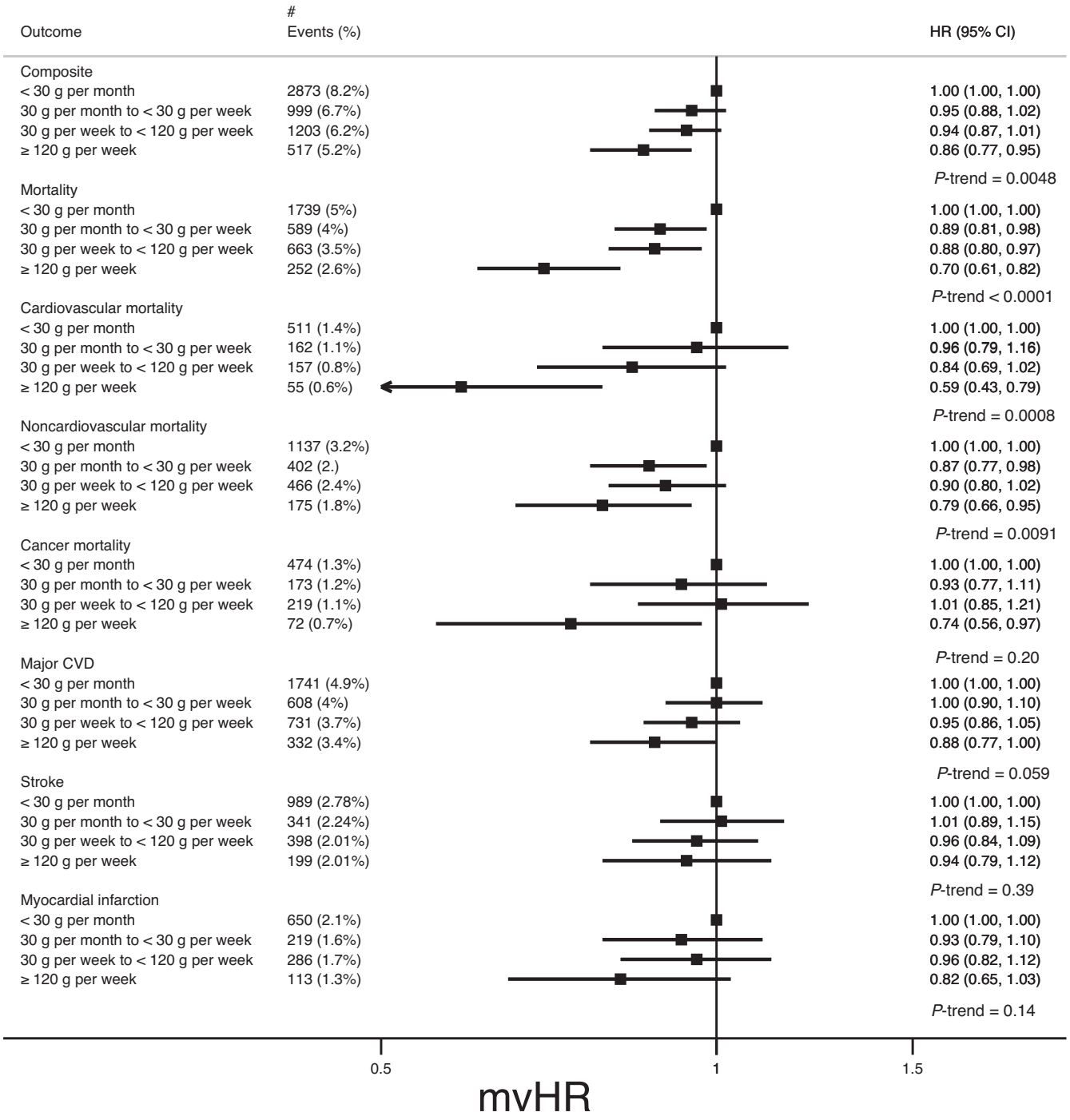

FIGURE 2 Association of highest (≥ 120 g/wk) compared with lowest (<30 g/mo) nut consumption with clinical outcomes, excluding those with diabetes or cancer (as appropriate), and who developed the outcome within the first 2 y of follow-up. Models adjusted for follow-up time plus age, sex, location (urban/rural), and center (as a random effect); lifestyle factors (education, tobacco use, BMI, waist-to-hip ratio, and physical activity, family history of CVD, diabetes, and cancer); and diet factors (fish, fruits, vegetables, red/processed meat, legumes, and total energy). CVD, cardiovascular disease; mvHR, multivariable HR.

with vitamin E to prevent oxidation of LDL in hamster models (51).

Most dietary guidelines do not make specific recommendations for nut consumption. The WHO (52) classifies the evidence supporting unsalted nuts for decreasing CVD risk as "probable," but the quality of the evidence was not assessed systematically and transparently. The American Heart Association's dietary guidelines recommend nut consumption as part of the DASH (Dietary Approaches to Stop Hypertension) diet (53). Canada's Food Guide recommends dry roasted nuts and seeds without

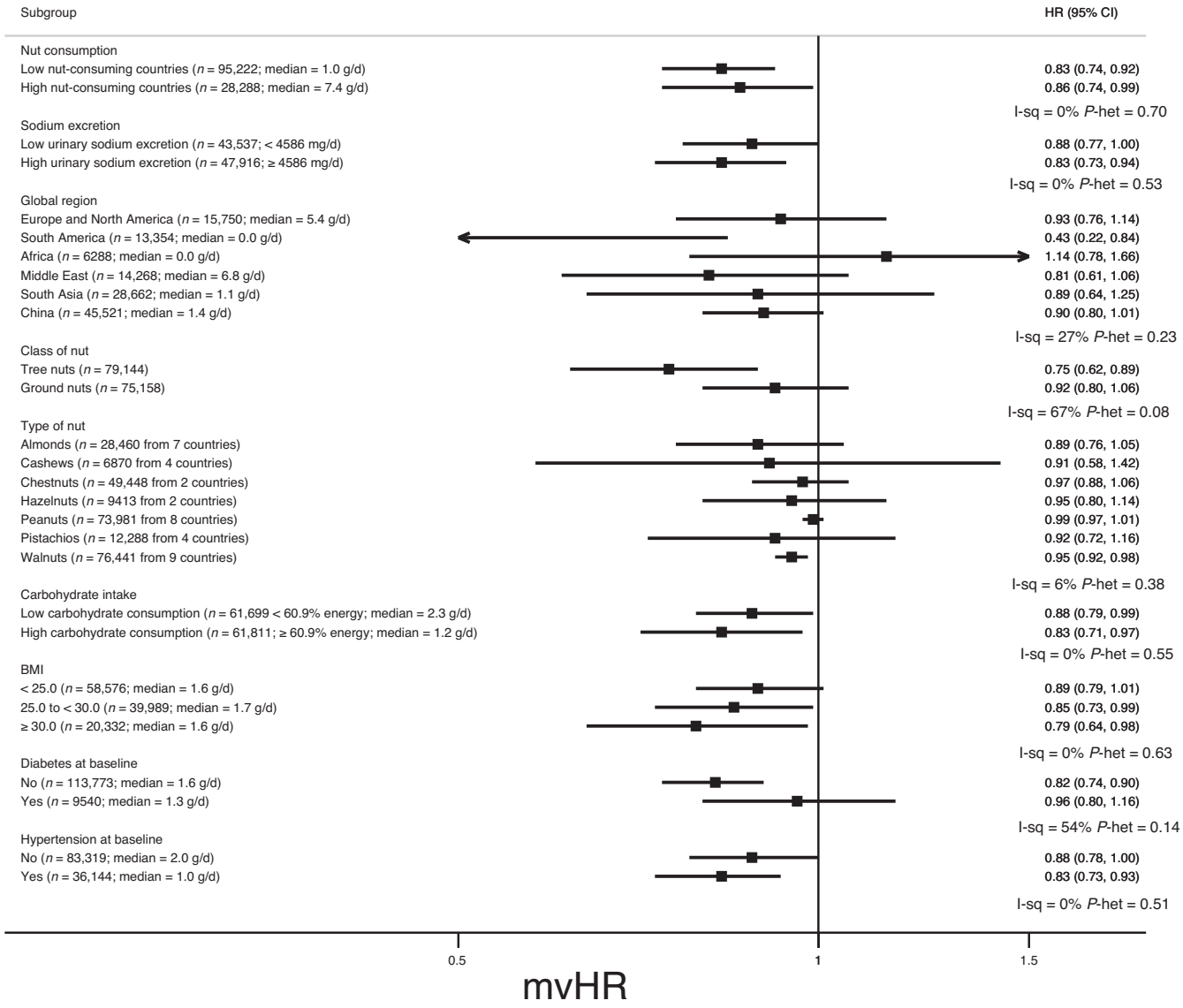

FIGURE 3 Association of nuts [per 30 g increase per day (or week for specific nuts only)] with mortality by subgroups. Models adjusted for follow-up time plus age, sex, location (urban/rural), and center (as a random effect); lifestyle factors (education, tobacco use, BMI, waist-to-hip ratio, and physical activity, family history of CVD, diabetes, and cancer); and diet factors (fish, fruits, vegetables, red/processed meat, legumes, and total energy). CVD, cardiovascular disease; mvHR, multivariable HR.

added sugars, fats, and sodium to meet the guideline to "eat protein foods" (54). The 2010 Dietary Guidelines for Americans state that nuts are a "nutrient-dense, high-fibre food and a good source of protein," and recommend 4 ounces (≈120 g) of nuts, seeds, or soya products/week for a 2000-kcal diet (55). These guidelines state that "moderate" evidence exists to support the benefit of nut consumption for controlling CVD risk factors. Only the 2015 Dutch food-based dietary guidelines recommend eating ≥15 g of unsalted nuts daily, because consumption of nuts "convincingly" reduces CAD risk (56).

PURE is the first large-scale multinational cohort study of the association of nuts with mortality and cardiovascular events. Our study has several strengths beyond its size and long follow-up with many adjudicated events. First, most of the countries are low- and middle-income countries, which provides information on a larger range of nut intake than previous studies conducted solely in North America and Europe. Second, we used standardized and validated methods to measure diet using a country-specific validated FFQ in each country. Third, we used standardized units for reporting nut intake, which makes findings between regions comparable. Fourth, we used standardized methods to document and adjudicate events. Fifth, we analyzed blood samples by standardized methods and applied calibration for countries where blood samples were analyzed locally. Sixth, we demonstrate reasonably consistent results across regions of the world (where the distribution of covariates, such as other lifestyle factors and potential confounders differ) which adds robustness to the findings.

Our study has some potential limitations. First, although we used a validated, semiquantitative FFQ to assess usual diet, we measured diet only at baseline. Therefore, we were unable to capture changes in diet that occurred over time, which can introduce some measurement error. Had we measured diet repeatedly, then one would expect the slope of the associations to be steeper. Second, as with any observational cohort study, residual confounding is a concern, and thus it remains plausible that nuts are surrogates for healthier lifestyles or increased wealth and ability to purchase healthier foods, in general, even though we adjusted for study center, and established and potential risk factors for CVD. Third, we did not ask information about nut consumption on FFQs in Colombia, Chile, Pakistan, the Philippines, and Malaysia. Fourth, any recommendation to consume nuts must carefully weigh the costs and benefits of such a recommendation, for example, the price of nuts is much higher in some regions of the world than others; and tree nuts may be more expensive than ground nuts in some countries, such as India. Included in such a cost-benefit analysis would be the concern that in some countries, there is a higher probability of exposure to aflatoxin (a myocardial toxin), which may offset the beneficial effects on cardiovascular health. Finally, the impact of higher nut intake may be influenced by the overall diet, even though our analyses are adjusted for multiple dietary confounders and conducted within different strata. However, the consistency of results between regions with markedly different levels of nut intake makes it less likely that confounders, which are expected to vary in different regions (including background diet), explain our observations.

In conclusion, nut consumption was associated with a lower risk of mortality in a diverse multinational cohort, after adjusting for other lifestyle and dietary factors. These findings support recommendations to increase the intake of a variety of nuts, as part of a healthy dietary pattern, to reduce the risk of death.

Consent for publication: this manuscript contains no individual data.

The authors' contributions were as follows–RJdS, SY, MD, and AM: designed the analyses presented in this manuscript; the PURE study was designed by SY and collaborators in participating countries; RJdS, MD, and AM: conducted the analyses described in this manuscript; RJdS: wrote the manuscript; RJdS and SY: had primary responsibility for the final content; all other listed authors: participated in data collection and management; and all listed authors read and approved the final manuscript.

Author disclosures: RJdS has served as an external resource person to the WHO's Nutrition Guidelines Advisory Group on *trans* fats, saturated fats, and polyunsaturated fats. The WHO paid for his travel and accommodation to attend meetings from 2012–2017 to present and discuss this work. He has also done contract research for the Canadian Institutes of Health Research's Institute of Nutrition, Metabolism, and Diabetes, Health Canada, and the WHO for which he received remuneration. He has received speaker's fees from the University of Toronto and McMaster Children's Hospital. He has held grants from the Canadian Foundation for Dietetic Research, Population Health Research Institute, Canadian Institutes of Health Research, and Hamilton Health Sciences Corporation as a principal investigator, and is a co-investigator on several funded team grants from Canadian Institutes of Health Research. He serves as an independent director of the Helderleigh Foundation (Canada). All other listed authors report no conflicts of interest.

References

1. World Health Organization. Healthy diet [Internet]. 2015 [last updated 29 April, 2020]. Available from: http://www.who.int/mediacentre/factsheets/fs394/en/.
2. Sacks FM, Lichtenstein AH, Wu JHY, Appel LJ, Creager MA, Kris-Etherton PM, Miller M, Rimm EB, Rudel LL, Robinson JG, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. Circulation 2017;136(3):e1–e23.
3. Howard BV, Van Horn L, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, Kuller LH, LaCroix AZ, Langer RD, Lasser NL, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 2006;295(6):655–66.
4. Prentice RL, Aragaki AK, Van Horn L, Thomson CA, Beresford SA, Robinson J, Snetselaar L, Anderson GL, Manson JE, Allison MA, et al. Low-fat dietary pattern and cardiovascular disease: results from the Women's Health Initiative randomized controlled trial. Am J Clin Nutr 2017;106(1):35–43.
5. Dehghan M, Mente A, Zhang X, Swaminathan S, Li W, Mohan V, Iqbal R, Kumar R, Wentzel-Viljoen E, Rosengren A, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. Lancet 2017;390(10107):2050–62.
6. Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER, Conlin PR, Erlinger TP, Rosner BA, Laranjo NM, et al. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. JAMA 2005;294(19):2455–64.
7. Sabate J, Ros E, Salas-Salvado J. Nuts: nutrition and health outcomes. Br J Nutr 2006;96(Suppl 2):S1–2.
8. Brufau G, Boatella J, Rafecas M. Nuts: source of energy and macronutrients. Br J Nutr 2006;96(Suppl 2):S24–8.
9. Dreher ML, Maher CV, Kearney P. The traditional and emerging role of nuts in healthful diets. Nutr Rev 1996;54(8):241–5.
10. 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(2):212–25.
11. Schwingshackl L, Hoffmann G, Missbach B, Stelmach-Mardas M, Boeing H. An umbrella review of nuts intake and risk of cardiovascular disease. Curr Pharm Des 2017;23(7):1016–27.
12. 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(3):1038–49.
13. Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, Tonstad S, Vatten LJ, Riboli E, Norat T. 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(1):207.
14. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, Bahonar A, Chifamba J, Dagenais G, Diaz R, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA 2013;310(9):959–68.
15. Teo K, Chow CK, Vaz M, Rangarajan S, Yusuf S. The Prospective Urban Rural Epidemiology (PURE) study: examining the impact of societal influences on chronic noncommunicable diseases in low-, middle-, and high-income countries. Am Heart J 2009;158(1):1–7.e1. doi: 10.1016/j.ahj.2009.04.019.
16. Corsi DJ, Subramanian SV, Chow CK, McKee M, Chifamba J, Dagenais G, Diaz R, Iqbal R, Kelishadi R, Kruger A, et al. Prospective Urban Rural Epidemiology (PURE) study: baseline characteristics of the household sample and comparative analyses with national data in 17 countries. Am Heart J 2013;166(4):636–46.e4. doi: 10.1016/j.ahj.2013.04.019.
17. Dehghan M, Mente A, Rangarajan S, Sheridan P, Mohan V, Iqbal R, Gupta R, Lear S, Wentzel-Viljoen E, Avezum A, et al. Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study. Lancet North Am Ed 2018;392(10161):2288–97. doi: 10.1016/S0140-6736(18)31812-9.
18. Kiprop V. The most popular nuts in the world [Internet]. [last updated December 13, 2018]. Available from: https://www.worldatlas.com/articles/the-most-popular-nuts-in-the-world.html.

19. Guasch-Ferre M, Liu X, Malik VS, Sun Q, Willett WC, Manson JE, Rexrode KM, Li Y, Hu FB, Bhupathiraju SN. Nut consumption and risk of cardiovascular disease. J Am Coll Cardiol 2017;70(20):2519–32.
20. Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. Nut and peanut butter consumption and risk of type 2 diabetes in women. JAMA 2002;288(20):2554–60.
21. Hu FB, Stampfer MJ, Manson JE, Rimm EB, Colditz GA, Rosner BA, Speizer FE, Hennekens CH, Willett WC. Frequent nut consumption and risk of coronary heart disease in women: prospective cohort study. BMJ 1998;317(7169):1341–5.
22. Fraser GE, Shavlik DJ. Risk factors for all-cause and coronary heart disease mortality in the oldest-old. The Adventist Health Study. Arch Intern Med 1997;157(19):2249–58.
23. Mente A, Dehghan M, Rangarajan S, McQueen M, Dagenais G, Wielgosz A, Lear S, Li W, Chen H, Yi S, et al. Association of dietary nutrients with blood lipids and blood pressure in 18 countries: a cross-sectional analysis from the PURE study. Lancet Diabetes Endocrinol 2017;5(10):774–87.
24. Xue X, Brookmeyer R. Bivariate frailty model for the analysis of multivariate survival time. Lifetime Data Anal 1996;2(3):277–89.
25. Bao Y, Han J, Hu FB, Giovannucci EL, Stampfer MJ, Willett WC, Fuchs CS. Association of nut consumption with total and cause-specific mortality. N Engl J Med 2013;369(21):2001–11.
26. Blomhoff R, Carlsen MH, Andersen LF, Jacobs DR Jr. Health benefits of nuts: potential role of antioxidants. Br J Nutr 2006;96(Suppl 2):S52–60.
27. Fraser GE, Sumbureru D, Pribis P, Neil RL, Frankson MA. Association among health habits, risk factors, and all-cause mortality in a black California population. Epidemiology 1997;8(2):168–74.
28. Levitan EB, Lewis CE, Tinker LF, Eaton CB, Ahmed A, Manson JE, Snetselaar LG, Martin LW, Trevisan M, Howard BV, et al. Mediterranean and DASH diet scores and mortality in women with heart failure: The Women's Health Initiative. Circ Heart Fail 2013;6(6):1116–23.
29. Luu HN, Blot WJ, Xiang YB, Cai H, Hargreaves MK, Li H, Yang G, Signorello L, Gao YT, Zheng W, et al. Prospective evaluation of the association of nut/peanut consumption with total and cause-specific mortality. JAMA Intern Med 2015;175(5):755–66.
30. Fernandez-Montero A, Bes-Rastrollo M, Barrio-Lopez MT, Fuente-Arrillaga Cde L, Salas-Salvado J, Moreno-Galarraga L, Martinez-Gonzalez MA. Nut consumption and 5-y all-cause mortality in a Mediterranean cohort: the SUN project. Nutrition 2014;30(9):1022–7.
31. Mann JI, Appleby PN, Key TJ, Thorogood M. Dietary determinants of ischaemic heart disease in health conscious individuals. Heart 1997;78(5):450–5.
32. Nash SD, Nash DT. Nuts as part of a healthy cardiovascular diet. Curr Atheroscler Rep 2008;10(6):529–35.
33. Lorente-Cebrian S, Costa AG, Navas-Carretero S, Zabala M, Martinez JA, Moreno-Aliaga MJ. Role of omega-3 fatty acids in obesity, metabolic syndrome, and cardiovascular diseases: a review of the evidence. J Physiol Biochem 2013;69(3):633–51.
34. O'Neil CE, Keast DR, Nicklas TA, Fulgoni VL 3rd. Nut consumption is associated with decreased health risk factors for cardiovascular disease and metabolic syndrome in U.S. adults: NHANES 1999–2004. J Am Coll Nutr 2011;30(6):502–10.
35. Zong G, Li Y, Sampson L, Dougherty LW, Willett WC, Wanders AJ, Alssema M, Zock PL, Hu FB, Sun Q. Monounsaturated fats from plant and animal sources in relation to risk of coronary heart disease among US men and women. Am J Clin Nutr 2018;107(3):445–53.
36. Oh K, Hu FB, Manson JE, Stampfer MJ, Willett WC. Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the Nurses' Health Study. Am J Epidemiol 2005;161(7):672–9.
37. Viguiliouk E, Kendall CW, Blanco Mejia S, Cozma AI, Ha V, Mirrahimi A, Jayalath VH, Augustin LS, Chiavaroli L, Leiter LA, et al. Effect of tree nuts on glycemic control in diabetes: a systematic review and meta-analysis of randomized controlled dietary trials. PLoS One 2014;9(7):e103376.
38. Ma XY, Liu JP, Song ZY. Glycemic load, glycemic index and risk of cardiovascular diseases: meta-analyses of prospective studies. Atherosclerosis 2012;223(2):491–6.
39. Djousse L, Gaziano JM, Kase CS, Kurth T. Nut consumption and risk of stroke in US male physicians. Clin Nutr 2010;29(5):605–9.
40. Bernstein AM, Pan A, Rexrode KM, Stampfer M, Hu FB, Mozaffarian D, Willett WC. Dietary protein sources and the risk of stroke in men and women. Stroke 2012;43(3):637–44.
41. Haring B, Misialek JR, Rebholz CM, Petruski-Ivleva N, Gottesman RF, Mosley TH, Alonso A. Association of dietary protein consumption with incident silent cerebral infarcts and stroke: The Atherosclerosis Risk in Communities (ARIC) Study. Stroke 2015;46(12):3443–50.
42. di Giuseppe R, Fjeld MK, Dierkes J, Theoflylaktopoulou D, Arregui M, Boeing H, Weikert C. The association between nut consumption and the risk of total and ischemic stroke in a German cohort study. Eur J Clin Nutr 2015;69(4):431–5.
43. Yaemsiri S, Sen S, Tinker L, Rosamond W, Wassertheil-Smoller S, He K. Trans fat, aspirin, and ischemic stroke in postmenopausal women. Ann Neurol 2012;72(5):704–15.
44. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med 2018;378(25):e34.
45. Del Gobbo LC, Falk MC, Feldman R, Lewis K, Mozaffarian D. Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. Am J Clin Nutr 2015;102(6):1347–56.
46. Flores-Mateo G, Rojas-Rueda D, Basora J, Ros E, Salas-Salvado J. Nut intake and adiposity: meta-analysis of clinical trials. Am J Clin Nutr 2013;97(6):1346–55.
47. Kris-Etherton PM. Walnuts decrease risk of cardiovascular disease: a summary of efficacy and biologic mechanisms. J Nutr 2014;144(4 Suppl):547S–54S.
48. 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(1):56–63.
49. Ellis PR, Kendall CW, Ren Y, Parker C, Pacy JF, Waldron KW, Jenkins DJ. Role of cell walls in the bioaccessibility of lipids in almond seeds. Am J Clin Nutr 2004;80(3):604–13.
50. Musa-Veloso K, Paulionis L, Poon T, Lee HY. The effects of almond consumption on fasting blood lipid levels: a systematic review and meta-analysis of randomised controlled trials. J Nutr Sci 2016;5:e34.
51. Chen CY, Milbury PE, Lapsley K, Blumberg JB. Flavonoids from almond skins are bioavailable and act synergistically with vitamins C and E to enhance hamster and human LDL resistance to oxidation. J Nutr 2005;135(6):1366–73.
52. World Health Organization & Food and Agriculture Organization of the United Nations. Diet, Nutrition and the Prevention of Chronic Diseases: Report of a Joint WHO/FAO Expert Consultation. WHO technical report series 916. Geneva: Switzerland; 2003.
53. American Heart Association Nutrition Committee, Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, Franklin B, Kris-Etherton P, Harris WS, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation 2006;114(1):82–96.
54. Government of Canada. Canada's food guide: Eat protein foods [Internet]. [last updated 2019]. Available from: https://food-guide.canada.ca/en/healthy-eating-recommendations/make-it-a-habit-to-eat-vegetables-fruit-whole-grains-and-protein-foods/eat-protein-foods/ [accessed 18 March, 2019].
55. US Department of Agriculture & US Department of Health and Human Services. Dietary Guidelines for Americans. Washington, DC; 2010.
56. Kromhout D, Spaaij CJ, de Goede J, Weggemans RM. The 2015 Dutch food-based dietary guidelines. Eur J Clin Nutr 2016;70(8):869–78.