Journal of the American Heart Association

ORIGINAL RESEARCH

Changes in Nut Consumption and Subsequent Cardiovascular Disease Risk Among US Men and Women: 3 Large Prospective Cohort Studies

Xiaoran Liu, PhD; Marta Guasch-Ferré, PhD; Jean-Philippe Drouin-Chartier, PhD; Deirdre K. Tobias, ScD; Shilpa N. Bhupathiraju, PhD; Kathryn M. Rexrode, MD, MPH; Walter C. Willett, MD, DrPH; Qi Sun, MD, PhD; Yanping Li, PhD

BACKGROUND: We aim to evaluate the association of within-individual changes in consumption of total and specific types of nuts and the subsequent risk of incident cardiovascular disease (CVD) in US men and women.

METHODS AND RESULTS: We included 34 103 men from the HPFS (Health Professionals Follow-Up Study) (1986–2012), 77 815 women from the NHS (Nurses' Health Study) (1986–2012), and 80 737 women from the NHS II (1991–2013). We assessed nut consumption every 4 years using validated food frequency questionnaires. We used multivariable Cox proportional hazards regression models to examine the association between 4-year changes in nut consumption and risk of confirmed CVD end points in the subsequent 4 years. Per 0.5 serving/day increase in total nut consumption was associated with lower risk of CVD (relative risk [RR], 0.92; 95% CI, 0.86–0.98), coronary heart disease (RR, 0.94; 95% CI, 0.89–0.99), and stroke (RR, 0.89; 95% CI, 0.83–0.95). Compared with individuals who remained nonconsumers in a 4-year interval, those who had higher consumption of total nuts (≥0.5 servings/day) had a lower risk of CVD (RR, 0.75; 95% CI, 0.67–0.84), coronary heart disease (RR, 0.80; 95% CI, 0.69–0.93), and stroke (RR, 0.68; 95% CI, 0.57–0.82) in next 4 years. Individuals who decreased nut consumption by ≥0.50 servings/day had a higher risk of developing CVD (RR, 1.14; 95% CI, 0.99–1.32), coronary heart disease (RR, 1.06; 95% CI, 0.88–1.28), and stroke (RR, 1.28; 95% CI, 1.02–1.60) when compared with those who maintained their nut consumption.

CONCLUSIONS: Increasing total consumption of nuts and intake of individual types of nuts (eg, walnuts, other tree nuts, and peanuts) was associated with a subsequent lower risk of CVD. These data support the role of nut intake in the primary prevention of CVD.

REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifiers: NCT00005152 and NCT00005182.

Key Words: cardiovascular disease ■ cohorts ■ nuts ■ peanuts ■ prevention ■ stroke

Cardiovascular disease (CVD) is the leading cause of death worldwide and largely preventable through improving diet quality and other lifestyle factors.[1,2] Diet quality has modestly improved among US adults over the past 2 decades, mainly because of increases in intakes of whole grains, nuts, and seeds and decreases in sugar-sweetened beverages and *trans* fatty acids.[3] As an important component of a healthy diet in the United States, nuts are nutrient-dense foods rich in unsaturated fatty acids, proteins, vitamins, minerals, and fibers.[4] At the same time, nuts are also rich in fats and thus energy dense, which may lead some to perceive nuts as an unhealthful food choice. However, considerable evidence from both

Correspondence to: Yanping Li, PhD, or Qi Sun, MD, PhD, Harvard T.H. Chan School of Public Health, 665 Huntington Ave, Boston, MA 02115. E-mails: yanping@hsph.harvard.edu; qisun@hsph.harvard.edu

Supplementary material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013877

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- We evaluated whether dynamic changes in total nut consumption and consumption of specific types of nuts over time (ie, from nonconsumers to consumers) are associated with lower risk of cardiovascular disease (CVD).
- Increasing intake of total consumption of nuts, and intake of specific types of nuts, including walnuts, other tree nuts, or peanuts, was associated with a subsequent lower risk of CVD.

What Are the Clinical Implications?

- Maintaining a regular consumption of nuts is associated with lower risk for CVD.
- Incorporating nuts into diet is beneficial for the prevention of CVD, even among those who previously did not consume nuts.
- Substituting less healthful food items with nuts is associated with reduced risk of developing CVD.

Nonstandard Abbreviations and Acronyms

CVD	cardiovascular disease
CHD	coronary heart disease
HPFS	Health Professionals Follow-Up Study
NHS	Nurses' Health Study
RR	relative risk
FFQ	food frequency questionnaire

epidemiological studies and clinical trials suggests that nuts are not associated with weight gain and may, in fact, help to lose weight when incorporated to an energy restricted diet.[5]

Nuts have cardioprotective benefits.[6,7] A recent meta-analysis of 12 prospective studies reported a dose-response, inverse association between nuts and risk of CVD. Each additional 28 g/d was associated with a 21% lower risk of CVD and a 29% lower risk of coronary heart disease (CHD).[6] Higher nut consumption was also associated with a lower risk of CHD mortality.[7] Results from the PREDIMED (Prevención con Dieta Mediterránea) study, a primary-prevention randomized trial, are consistent with findings from observational studies. In the PREDIMED trial, randomization to consume 30 g/d of mixed nuts in the context of a Mediterranean diet reduced major cardiovascular events by 28% over 5 years mean follow-up, and the risk reduction was similar to that among participants randomized to the Mediterranean diet supplemented with extra virgin olive oil.[8]

The consumption of nuts and seeds has played an increasingly important role in the US diet: the intake of these foods has increased from 0.5 servings/day in 1999 to 0.75 servings/day in 2012.[9] Despite consistent evidence demonstrating a dose-response association between nut consumption and CVD risk, there are no epidemiological studies evaluating whether dynamic within-person changes in nut consumption over time (ie, from nonconsumers to consumers) are associated with subsequent risk of CVD. Also, most previous studies have focused on total nut consumption; however, the consumption of specific types of nuts remains largely uninvestigated. Therefore, in the present analyses, we aim to examine the association of changes in total consumption of nuts, and in specific types of nuts (eg, walnuts, other tree nuts, and peanuts), with risk of developing major cardiovascular events in 3 large prospective cohorts of US men and women.

METHODS

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. Please see the study websites for more information: https://www.hsph.harvard.edu/hpfs/hpfs_collaborators.htm, and http://www.nurseshealthstudy.org/researchers.

Study Population

Population Characteristics

We conducted a pooled analysis of 3 large US prospective cohort studies: the HPFS (Health Professionals Follow-Up Study), the NHS (Nurses' Health Study), and the NHS II. In the HPFS, 51 529 male health professionals between 40 and 75 years of age were enrolled in 1986 from 50 states. The NHS was composed of 121 701 nurses between 35 and 55 years of age when they were enrolled in 1976 from 11 states, and the NHS II included 116 430 younger nurses aged 24 to 44 years when enrolled in 1989 from 14 states.[10] Approximately 97% of study participants are white.[11] Information on participants' medical history, newly diagnosed diseases, lifestyle, and dietary factors was collected at baseline and during follow-up through mailed questionnaires every 2 to 4 years. The response rate was ≈90% for each cycle in the 3 cohorts.[10] Participants gave informed consent via the return of questionnaires.

The study was approved by the institutional review boards of Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health. Completion of

self-administered information was considered to imply informed consent.

Outcome Ascertainment

Our primary end point was incident total CVD, a composite outcome including nonfatal myocardial infarction, fatal CHD, and stroke (nonfatal or fatal).

When participants reported nonfatal cardiovascular events on any biennial questionnaires, we requested permission from participants for study physicians to review their medical records. Nonfatal myocardial infarction was confirmed using the diagnostic criteria of the World Health Organization, specifically, on the basis of symptoms and either electrocardiographic changes or elevated cardiac enzyme concentrations.[12] Nonfatal stroke was defined according to the diagnostic criteria of National Survey of Strokes criteria, requiring evidence of a neurological deficit with sudden or rapid onset that persisted for >24 hours or until death.[13] CHD and stroke events that could not be confirmed by medical records but with other confirmatory information that was obtained through telephone interview or letter were classified as probable. In the current study, we included both confirmed and probable cases of CHD and stroke, as results including both confirmed and probable CVD events were nearly identical to those obtained with confirmed cases alone.[14]

Deaths were identified through searches of the National Death Index,[13] or were reported by family members or the postal authorities.[13] Fatal CHD was confirmed by medical records, autopsy reports, or death certificates, if CHD was listed as the underlying and only plausible cause of death on the death certificate with previous evidence of CHD in the medical records. Similarly, fatal stroke was identified and confirmed by reviewing death certificates, hospital records, or autopsy records.

Dietary Assessment

A semiquantitative validated food frequency questionnaire (FFQ) containing ≈130 foods was administrated to participants every 4 years starting in 1986 in the NHS and HPFS and in 1991 in the NHS II. These time points were used as baseline for the current analysis.

Participants were asked to report the frequency on consumption of a standard portion size of each food or beverage, from "never or less than once per month" to "≥6 times per day" on average over the past year. Validation of the questionnaire has been reported previously.[15–17] Nut consumption assessed by FFQ questionnaire provided reasonable accuracy in reflecting daily nut consumption when compared with a 7-days diet record, as evidenced by a correlation coefficient of 0.75 for both total nuts and peanut butter.[18]

For nuts, participants were asked how often they consumed 1 serving (28 g or 1 ounce) of nuts and peanuts. We converted frequency categories of nut consumption (never or less than once per month, 1–3 per month, 1 per week, 2–4 per week, 5–6 per week, 1 per day, 2–3 per day, 4–6 per day, or ≥6 times per day) to servings per day. Consumption of peanut butter was also assessed with the same 9 frequency categories in 1 tablespoon (15 g) servings.

Questions on walnuts and "other tree nuts" were first added to the FFQ in 1998 in NHS and HPFS, and in 1999 in NHS II, after which we derived total consumption of tree nuts as the sum of other tree nuts and walnuts. Botanically, peanuts are legumes[19]; however, in this analysis, we included peanuts within the total nut category, because they are considered as nuts by consumers and have a nutrient composition similar to tree nuts.[2] In the present study, we analyzed total consumption of nuts (ie, walnuts, other tree nuts, and peanuts), tree nuts (walnuts and other tree nuts), walnuts, other tree nuts not including walnuts, peanuts (without peanut butter), and peanut butter.

Statistical Analysis

We used Cox proportional-hazards regression models to examine the associations between changes in total nut intake or intake of specific types of nuts during a 4-year interval with the relative risk (RR) of developing CVD, CHD, and stroke during the subsequent 4 years with a total of up to 26 (NHS and HPFS) or 22 (NHS II) years of follow-up. Individuals contributed to person-time from the return of the baseline FFQ until the date of diagnosis of CVD, death, or the end of the follow-up period (January 2012 for HPFS, June 2012 for NHS, and June 2013 for NHS II), whichever came first.

We excluded participants who reported CVD, cancer, diabetes mellitus, or missing body mass index before or during the first 4-year interval. For individuals who had missing FFQ or missing data on nut consumption or reported implausible energy intake (<600 or >3500 kcal/d for women or <800 or >4200 kcal/d for men), we further excluded their person-time from corresponding intervals but otherwise continued to count their person-times in subsequent intervals with valid data.

Our basic model (model 1) was stratified by age, cohort, sex, and calendar year in 4-year intervals. In model 2, we further adjusted for the initial nut intake at the beginning of each 4-year period. In model 3, we further adjusted for race (white, other), family history of myocardial infarction, menopausal status (premenopausal or postmenopausal), hormone therapy use (never, past, or current), oral contraceptive

use (never, current, past, missing indicator, in NHS II), number of teeth at baseline (0, 1–16, 17–24, 25–32, in NHS and HPFS), updated teeth lost during follow-up (continuous, in NHS and HPFS), initial and change in smoking status (never to never, never to current, past to past, current to past, current to current, missing indicator), initial alcohol intake (g/d: 0.0, 0.1–4.9, 5.0–14.9, 15.0–29.9, and ≥30.0), change in alcohol intake (decrease, no change, increase), and initial (metabolic equivalent h/wk: quintiles), and change in physical activity level (metabolic equivalent h/wk: <–5.0, –5.0 to 4.9, ≥5.0). In the final model 4, we further adjusted for initial body mass index (kg/m^2: <21.0, 21.0–24.9, 25.0–29.9, 30.0–31.9, >32.0), updated history of hypercholesterolemia, and high blood pressure at the start of each 4-year interval, initial (kcal/d: quintiles) and changes in total energy intake (kcal/d: <–250, –250 to 250, ≥250), and initial and change in Alternative Healthy Eating Index score (calculated without the alcohol and nut components:<–2, –2 to 5, ≥5) over each 4-year period.

Changes in intakes of nuts and other dietary factors were modeled as continuous variables in 0.5 servings/day. Those with lower than the 0.5th percentile or higher than the 99.5th percentile were assigned to values of 0.5th percentile or 99.5th percentile, respectively, to minimize the influence of outliers.[20]

We categorized the change in nut consumption over 4 years into 5 groups: (1) minimal change (±0.00 servings/day), (2) increase between 0.01 and 0.49 servings/day, (3) decrease between 0.01 and 0.49 servings/day, (4) increase ≥0.50 servings/day, and (5) decrease ≥0.50 servings/day. Individuals with no change or relatively stable consumption were assigned as the reference group. The median values of each category were modeled as continuous variables to examine the linear trend. Missing data from categorical variables were assigned a missing indicator to minimize sample reduction caused by missing covariates.

We also categorized participants by their habitual nut intake, assessed by consistency across 2 consecutive FFQs into 9 groups (jointly defined by nonconsumer [0 servings/day], low intake [<0.5 servings/day], and high intake [≥0.50 servings/day] at the beginning and the assessment at 4 years of each 4-year interval) and subsequently examined the association with risk of total CVD, CHD, and stroke. Those who were nonconsumers at both time points were assigned as the reference group.

We conducted statistical substitution analysis to estimate the potential effect of substituting nuts for other foods on CVD risk. We further adjusted model 3 for initial and change in intake (serving/day) of red meat, processed meat, refined grain, French fries, dessert, and chips. We calculated the differences in β coefficients of changes of nuts and other food items, which can be interpreted as the estimated effects on CVD risk when increasing 0.5 servings/day (3.5 servings/week) of nuts while simultaneously decreasing the equal serving of other foods.

We also conducted prespecified subgroup analyses by potential effect modifiers of the association between changes in nut intake and CVD risk. We stratified the analyses on the basis of participants' age (<60 or ≥60 years), smoking status (never smoking or ever smoking), and changes in energy, alcohol intake, physical activity level, Alternative Healthy Eating Index score, and body weight. Two change categories were used: "no changes or decreased" and "increased." We conducted 2 sensitivity analyses to test the robustness of our results. First, we further adjusted our final model (model 4) for concurrent 4-year changes in body weight to estimate the extent to which weight change mediates the association between changes in nut intake with CVD risk. Second, we further censored follow-up of men and women who developed incident diabetes mellitus during the follow-up period.

We pooled data from the 3 cohorts for the main analysis, and considered the cohort-specific results for secondary analyses. We used SAS version 9.4 (SAS Institute) to analyze the data, and set statistical significance at a 2-tailed $P<0.05$.

RESULTS

Baseline Characteristics

The current study included 34 103 men in the HPFS, 77 815 women in the NHS, and 80 737 women in the NHS II. Table 1 presents participants' characteristics based on baseline 4-year change in nut consumption. Individuals who increased nut consumption over time had a lower initial consumption, higher initial energy intake, and better diet quality (higher Alternative Healthy Eating Index score) than those who maintained a stable nut consumption. Decrease in nut consumption was observed along with decrease in energy intake and diet quality and a higher initial consumption.

Changes in Nut Consumption and Risk of CVD, CHD, and Stroke

Table 2 shows the associations between changes in nut consumption and risks of CVD, CHD, and stroke. Compared with individuals who did not change their total intake of nuts, those who increased nut consumption ≥0.50 servings/day were associated with lower risk of CVD (RR, 0.86; 95% CI, 0.78–0.94), CHD (RR, 0.88; 95% CI, 0.78–1.00), and stroke (RR, 0.82; 95% CI, 0.71–0.96) independent of initial nut consumption and other lifestyle factors. In contrast, participants who

Table 1. Age-Adjusted Characteristics of Participants According to the First 4-Year Changes in Total Nut Consumption

Variable	Changes in Total Nut Consumption (Servings/d)*				
	Decrease		No Change	Increase	
	≥0.50	0.01–0.49	0.00	0.01–0.49	≥0.50
HPFS					
Participants, n	2243	10 576	10 339	9180	1765
Initial nut intake, servings/d	1.3 (1.1)	0.3 (0.2)	0.1 (0.2)	0.1 (0.2)	0.3 (0.4)
Change in nut intake, servings/d	−1.1 (0.9)	−0.2 (0.1)	0.0 (0.0)	0.2 (0.1)	1.0 (0.8)
Age, y†	58.8 (9.8)	57.7 (9.8)	58.1 (9.9)	58.4 (9.8)	60.8 (9.4)
Initial body mass index, kg/m^2	25.3 (3.1)	25.5 (3.2)	25.4 (3.2)	25.5 (3.2)	25.2 (3.2)
Weight change, kg	0.6 (4.8)	0.6 (4.1)	0.6 (4.2)	0.7 (4.2)	0.5 (4.9)
Current smoker, %	7.4	8.1	8.6	8.3	8.4
Initial physical activity, metabolic equivalent h/wk	22.6 (30.7)	19.9 (24.0)	19.5 (26.0)	19.7 (26.2)	21.7 (25.4)
Change in physical activity, metabolic equivalent h/wk	1.0 (30.0)	1.7 (22.8)	1.8 (24.6)	2.0 (25.3)	1.9 (23.1)
Initial alcohol intake, g/d	13.6 (16.6)	11.5 (14.9)	10.6 (14.8)	11.3 (15.0)	12.6 (16.0)
Change in alcohol intake, g/d	−1.5 (11.7)	−1.1 (10.1)	−0.7 (10.2)	−0.2 (10.6)	0.1 (11.0)
Initial total energy intake, kcal/d	2383.8 (653.8)	2022.3 (604.5)	1898.0 (590.5)	1951.7 (588.1)	2129.0 (638.1)
Change in total energy intake, kcal/d	−327.3 (563.9)	−133.6 (504.2)	−37.0 (490.9)	60.6 (504.7)	228.5 (566.5)
Initial Alternate Healthy Eating Index score	45.4 (10.4)	43.1 (9.9)	42.7 (10.2)	42.7 (10.1)	43.9 (10.4)
Change in Alternate Healthy Eating Index score	−0.3 (7.4)	0.9 (7.3)	1.0 (7.5)	1.2 (7.2)	2.8 (7.8)
Family history of myocardial infarction, %	31.3	31.8	32.8	31.6	30.2
Initial high blood pressure, %	21.1	21.0	20.8	21.6	21.4
Initial hypercholesterolemia, %	16.7	16.9	16.8	18.4	20.2
NHS					
Participants, n	2839	23 544	32 269	17 016	2147
Initial nut intake, servings/d	1.1 (0.8)	0.2 (0.2)	0.0 (0.1)	0.1 (0.1)	0.2 (0.3)
Change in nut intake, servings/d	−1.0 (0.7)	−0.1 (0.1)	0.0 (0.0)	0.1 (0.1)	1.0 (0.8)
Age, y†	58.9 (7.8)	57.7 (7.8)	58.4 (8.0)	58.7 (7.9)	61.0 (8.1)
Initial body mass index, kg/m^2	24.7 (4.4)	25.3 (4.7)	25.6 (4.9)	25.5 (4.8)	25.0 (4.7)
Weight change, kg	1.0 (5.2)	1.0 (5.3)	1.2 (5.4)	1.4 (5.2)	0.8 (5.4)
Current smoker, %	17.8	18.0	19.3	18.3	17.7
Initial physical activity, metabolic equivalent h/wk	17.0 (25.7)	14.9 (20.8)	14.2 (20.7)	15.0 (21.1)	16.9 (22.1)
Change in physical activity, metabolic equivalent h/wk	2.1 (26.6)	1.9 (21.5)	1.7 (22.5)	1.9 (23.2)	2.0 (22.7)
Initial alcohol intake, g/d	7.4 (11.1)	6.3 (10.4)	5.3 (9.8)	6.1 (10.7)	6.7 (10.6)
Change in alcohol intake, g/d	−1.2 (7.7)	−1.0 (7.4)	−0.6 (6.8)	−0.5 (7.5)	−0.2 (7.6)
Initial total energy intake, kcal/d	2151.4 (553.8)	1823.4 (524.8)	1663.6 (510.1)	1762.3 (519.7)	1877.9 (537.4)
Change in total energy intake, kcal/d	−260.3 (490.3)	−88.7 (455.0)	−9.8 (442.1)	74.5 (455.5)	223.9 (484.5)
Initial Alternate Healthy Eating Index score	47.9 (9.9)	45.0 (9.7)	44.3 (10.0)	44.5 (9.8)	46.0 (10.5)
Change in Alternate Healthy Eating Index score	−0.7 (7.7)	0.8 (7.5)	0.9 (7.6)	1.3 (7.4)	3.0 (8.1)
Family history of myocardial infarction, %	23.9	25.3	24.8	24.3	23.4
Baseline premenopausal, %	23.0	22.9	23.2	23.6	22.5
Initial high blood pressure, %	22.9	25.1	27.3	27.4	23.9
Initial hypercholesterolemia, %	20.3	20.8	22.5	24.1	27.2

(Continued)

Table 1. Continued

Variable	Changes in Total Nut Consumption (Servings/d)*				
	Decrease		No Change	Increase	
	≥0.50	0.01–0.49	0.00	0.01–0.49	≥0.50
NHS II					
Participants, n	1011	18 883	41 799	17 450	1594
Initial nut intake, servings/d	1.0 (0.6)	0.2 (0.1)	0.0 (0.1)	0.0 (0.1)	0.1 (0.2)
Change in nut intake, servings/d	−0.9 (0.6)	−0.1 (0.1)	0.0 (0.0)	0.1 (0.1)	1.0 (0.7)
Age, y†	45.0 (7.4)	41.1 (5.5)	40.8 (5.2)	42.2 (5.8)	46.5 (6.7)
Initial body mass index, kg/m^2	24.1 (5.2)	24.7 (5.4)	24.8 (5.3)	24.7 (5.4)	24.1 (5.4)
Weight change, kg	2.8 (6.3)	2.9 (6.2)	3.1 (6.6)	3.0 (6.5)	1.9 (6.5)
Current smoker, %	13.7	11.9	11.0	12.0	11.2
Initial physical activity, metabolic equivalent h/wk	27.2 (33.5)	24.0 (34.9)	23.5 (33.9)	23.3 (33.3)	26.9 (42.9)
Change in physical activity, metabolic equivalent h/wk	−0.3 (31.3)	−3.0 (32.7)	−3.0 (32.1)	−2.8 (32.3)	−0.6 (33.8)
Initial alcohol intake, g/d	4.3 (7.7)	3.7 (6.8)	3.0 (6.0)	3.5 (6.5)	4.0 (7.6)
Change in alcohol intake, g/d	0.2 (6.6)	0.2 (5.5)	0.3 (5.2)	0.7 (5.6)	0.7 (6.2)
Initial total energy intake, kcal/d	2223.3 (586.6)	1919.3 (549.2)	1702.1 (527.9)	1814.1 (541.8)	1969.5 (570.0)
Change in total energy intake, kcal/d	−258.1 (560.0)	−77.5 (503.3)	20.6 (481.1)	127.3 (505.1)	267.1 (594.1)
Initial Alternate Healthy Eating Index score	46.0 (10.6)	41.7 (9.8)	41.8 (10.0)	41.8 (9.9)	44.0 (10.2)
Change in Alternate Healthy Eating Index score	−1.1 (8.2)	0.5 (8.0)	0.3 (8.3)	0.7 (8.2)	3.8 (9.4)
Family history of myocardial infarction, %	37.5	40.3	40.6	39.1	36.7
Baseline premenopausal, %	87.4	86.0	86.3	86.2	85.8
Baseline use of oral contraceptive, %	7.1	8.2	8.5	9.1	8.5
Initial high blood pressure, %	6.7	7.1	7.1	7.2	6.0
Initial hypercholesterolemia, %	15.6	15.8	15.6	16.4	14.2

HPFS indicates Health Professionals Follow-Up Study; and NHS, Nurses' Health Study.

*The first 4-year period refers to the first period during which changes in nut consumption were calculated for each subjects. Values are means (SDs) or percentages and are standardized to the age distribution of the study population.

†Value is not age adjusted.

decreased nut consumption by ≥0.50 servings/day had a higher risk of CVD (RR, 1.14; 95% CI, 0.99–1.32), CHD (RR, 1.06; 95% CI, 0.88–1.28), and stroke (RR, 1.28; 95% CI, 1.02–1.60) when compared with individuals who maintained their nut consumption stable over 4 years (model 2–4 adjusted for initial intake). An increase of 0.5 servings/day in total nut consumption was associated with an 8% lower risk of CVD (RR, 0.92; 95% CI, 0.86–0.98), 6% lower risk of CHD (RR, 0.94; 95% CI, 0.89–0.99), and 11% lower risk of stroke (RR, 0.89; 95% CI, 0.83–0.95) (Figure 1). Increasing intakes of tree nuts, walnuts, and peanuts, per 0.5 servings/day, were each significantly associated with lower risk of CVD. Increase in consumption of tree nuts and peanuts (0.5 servings/day) was associated with lower risk of CHD. An increase in walnut consumption was associated with lower risk of stroke.

We evaluated the joint association of habitual nut intake at the beginning and end of each 4-year interval with the risk of developing CVD, CHD, and stroke in subsequent 4 years throughout study follow-up (Figure 2). Compared with individuals who remained nonconsumers over 4 years, those who maintained consistently high nut consumption of ≥0.5 servings/day over 4 years had a lower risk of CVD (RR, 0.75; 95% CI, 0.67–0.84), CHD (RR, 0.80; 95% CI, 0.69–0.93), and stroke (RR, 0.68; 95% CI, 0.57–0.82). When compared with nonconsumers, individuals who increased their nut consumption over 4-year period from 0 to ≥0.5 servings/day also had lower risks of developing CVD, CHD, and stroke in the next 4 years. The magnitude of this joint association was consistent across the 3 cohorts (Table S1).

Statistically substituting nuts for meat, processed meat, refined grain, French fries, and dessert (including chocolates, candy bars, cookies, cakes, sweet roll, pies, and donuts) was associated with lower risks of CVD, CHD, and stroke (Figure S1). For example, increasing nut intake by 0.5 servings/day (3.5 servings/week) with a simultaneous decrease in red meat

Table 2. Multivariable Adjusted RR (95% CI) for Incident Cardiovascular Disease According to Categories of Updated 4-Year Changes in Total Nut Consumption Based on Pooled Data of NHS, NHS II, and the HPFS

Variable	Changes in Total Nut Consumption Frequency (Servings/d)					*P* Trend
	Decrease		No Change	Increase		
Range	≤−0.50	−0.49 to −0.01	0	0.01 to 0.49	≥0.50	
Cumulative initial intake, mean (SD)	1.37 (0.99)	0.26 (0.27)	0.06 (0.16)	0.11 (0.21)	0.26 (0.37)	
Cumulative 4-y changes, mean (SD)	−1.04 (0.79)	−0.15 (0.11)	0	0.16 (0.11)	1.05 (0.77)	
Cardiovascular disease						
Cases, n	384	2085	3075	2355	561	
Model 1	0.87 (0.78–0.97)	0.92 (0.87–0.98)	1.0 (Reference)	0.87 (0.82–0.92)	0.74 (0.68–0.82)	0.0001
Model 2	1.18 (1.02–1.36)	0.97 (0.91–1.03)	1.0 (Reference)	0.88 (0.83–0.93)	0.78 (0.71–0.85)	<0.0001
Model 3	1.17 (1.01–1.35)	1.00 (0.94–1.06)	1.0 (Reference)	0.93 (0.88–0.98)	0.85 (0.77–0.93)	<0.0001
Model 4	1.14 (0.99–1.32)	0.99 (0.94–1.05)	1.0 (Reference)	0.93 (0.88–0.99)	0.86 (0.78–0.94)	<0.0001
Coronary heart disease						
Cases, n	225	1268	1745	1405	334	
Model 1	0.85 (0.74–0.98)	0.95 (0.88–1.02)	1.0 (Reference)	0.89 (0.83–0.96)	0.75 (0.67–0.85)	0.007
Model 2	1.11 (0.92–1.33)	0.99 (0.92–1.07)	1.0 (Reference)	0.90 (0.83–0.96)	0.78 (0.69–0.88)	<0.0001
Model 3	1.10 (0.91–1.32)	1.03 (0.95–1.11)	1.0 (Reference)	0.96 (0.89–1.03)	0.86 (0.76–0.97)	0.002
Model 4	1.06 (0.88–1.28)	1.02 (0.94–1.10)	1.0 (Reference)	0.96 (0.89–1.03)	0.88 (0.78–1.00)	0.01
Stroke						
Cases, n	159	817	1330	950	227	
Model 1	0.91 (0.77–1.08)	0.89 (0.81–0.97)	1.0 (Reference)	0.85 (0.78–0.92)	0.73 (0.64–0.85)	0.005
Model 2	1.31 (1.04–1.63)	0.94 (0.86–1.03)	1.0 (Reference)	0.86 (0.79–0.93)	0.77 (0.67–0.89)	<0.0001
Model 3	1.29 (1.03–1.61)	0.96 (0.87–1.05)	1.0 (Reference)	0.90 (0.82–0.98)	0.83 (0.71–0.96)	0.0003
Model 4	1.28 (1.02–1.60)	0.96 (0.87–1.05)	1.0 (Reference)	0.89 (0.82–0.97)	0.82 (0.71–0.96)	0.0004

Model 1 was stratified by age, sex, and calendar year in 4-year intervals; model 2 was model 1 further adjusted for initial total nut intake; model 3 was model 2 further adjusted for race (white or nonwhite), family history of myocardial infarction, initial and change in smoking status (never to never, never to current, past to past, current to past, current to current, missing indicator), menopausal status and postmenopausal hormone use (premenopausal, postmenopausal+current use, postmenopausal+past use, postmenopausal+never use, missing indicator, in NHS and NHS II), number of teeth at baseline (0, 1–16, 17–24, 25–32, in NHS and HPFS) and updated teeth loss during follow-up (continuous, in NHS and HPFS), oral contraceptive use (never, current, past, missing indicator, in NHS II), initial (g/d: 0, 0.1–4.9, 5–14.9, 15–29.9, and ≥30) and change in alcohol intake (decrease, no change, or increase), and initial (metabolic equivalent h/wk, quintiles) and change in physical activity level (metabolic equivalent h/wk: <−5, −5 to 4.9, or ≥5); model 4 was model 3 further adjusted for initial body mass index (<21.0, 21.0–24.9, 25.0–29.9, 30.0–31.9, or >32.0 kg/m^2), initial history of hypercholesterolemia and high blood pressure at the start of each 4-year interval, initial (quintiles) and changes in energy intakes (kcal/d: <−250, −250 to 250, or ≥250), and initial (calculated without the alcohol component and nuts, quintile) and change in Alternate Healthy Eating Index score (<−2, −2 to 5, or ≥5) over each 4-year period. HPFS indicates Health Professionals Follow-Up Study; NHS, Nurses' Health Study; and RR, relative risk.

by 0.5 servings/day was associated with 7% to 13% lower risks of CVD, CHD, and stroke. Replacing desserts, refined grains, and French fries by 0.5 servings/day with the equivalent of 0.5 servings of nuts per day has demonstrated similar inverse association with risks of major cardiovascular events (Figure S1).

The inverse associations of changes in nut consumption and CVD risk were consistent across subgroups stratified by age and 4-year changes in diet, lifestyle factors, and body weight (Table S2). Among participants who were ever smokers, nut consumption was associated with significant lower risk of stroke (RR, 0.81; 95% CI, 0.73–0.88; *P* for interaction=0.008). In sensitivity analyses of further adjustment for 4-year change in body weight, increasing total consumption of nuts by 0.5 servings/day remained associated with a lower risk of CVD (RR, 0.92; 95% CI, 0.88–0.96), CHD (RR, 0.94; 95% CI, 0.89–0.99), and stroke (RR, 0.89; 95% CI, 0.83–0.95). When we further censored participants with incident diabetes mellitus during follow-up period, the RRs were 0.91 for CVD (95% CI, 0.87–0.95), 0.93 for CHD (95% CI, 0.88–0.98), and 0.88 for stroke (95% CI, 0.82–0.94).

DISCUSSION

Compared with participants who made no changes to their nut intake, participants who increased their total nut consumption had a lower risk of CVD, CHD, and stroke in 3 prospective cohorts of US men and women followed for up to 26 years. Consistent inverse associations with the risk of CVD were observed with increases in the consumption of tree nuts, walnuts, and peanuts. We found

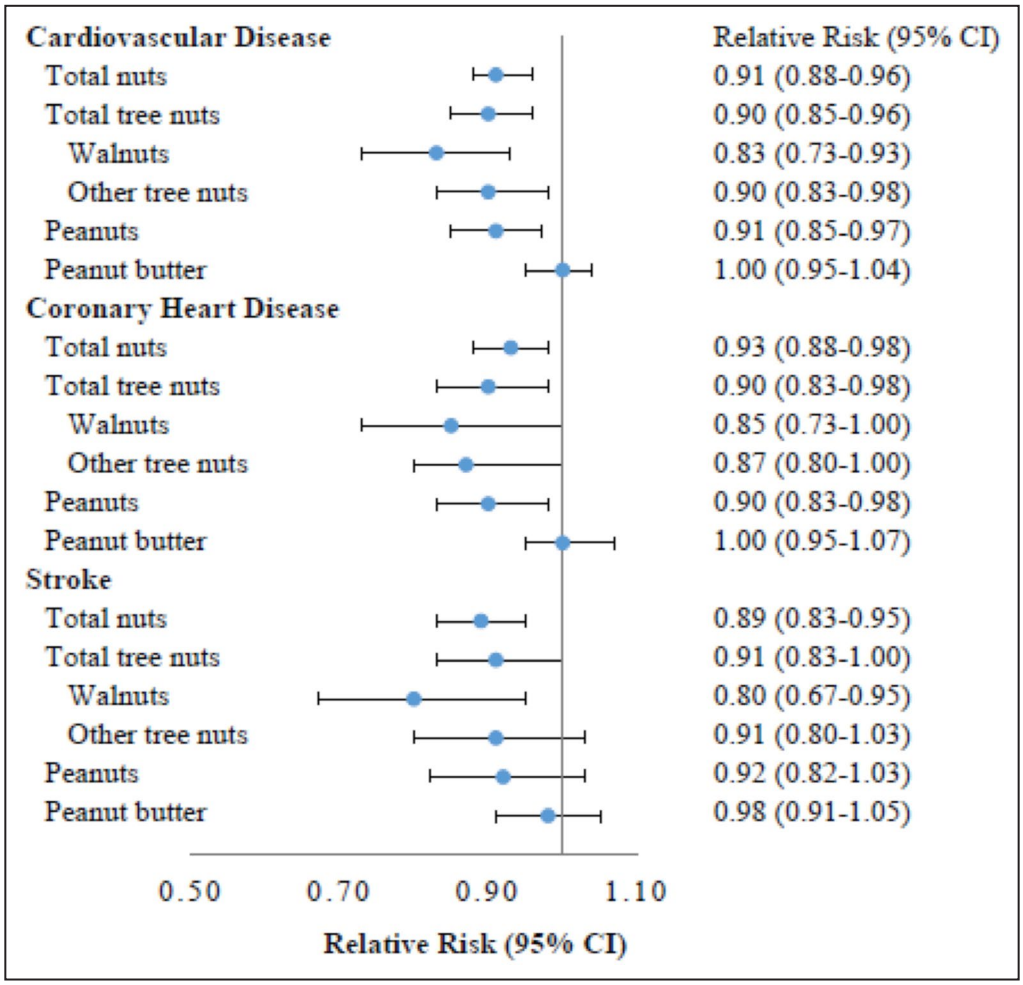

Figure 1. Risk for incident cardiovascular disease, per 0.5-serving/day increase in consumption of different types of nuts during follow-up.

Multivariate adjusted model was stratified by age, sex, and calendar year in 4-year intervals and adjusted for initial total nut intake, race (white or nonwhite), family history of myocardial infarction, initial and change in smoking status (never to never, never to current, past to past, current to past, current to current, missing indicator), menopausal status, postmenopausal hormone use (premenopausal, postmenopausal+current use, postmenopausal+past use, postmenopausal+never use, missing indicator, in NHS [Nurses' Health Study] and NHS II), number of teeth at baseline (0, 1–16, 17–24, 25–32, in NHS and HPFS [Health Professionals Follow-Up Study]) and updated teeth loss during follow-up (continuous, in NHS and HPFS), oral contraceptive use (never, current, past, missing indicator, in NHS II), initial (g/d: 0, 0.1–4.9, 5–14.9, 15–29.9, and ≥30) and change in alcohol intake (decrease, no change, or increase), initial (metabolic equivalent h/wk, quintiles) and change in physical activity level (metabolic equivalent h/wk: <–5, –5 to 4.9, ≥5), initial body mass index (<21.0, 21.0–24.9, 25.0–29.9, 30.0–31.9, and >32.0 kg/m^2), initial (quintiles) and changes in energy intakes (kcal/d: <–250, –250 to 250, or ≥250), initial (calculated without the alcohol component and nuts, quintile) and change in Alternate Healthy Eating Index score (<–2, –2 to 5, or ≥5) over each 4-year period, and initial history of hypercholesterolemia and high blood pressure at the start of each 4-year interval; model was further mutually adjusted for changes in total tree nuts, peanuts, and peanut butter; analysis of walnuts and other tree nuts was based on the subcohort data started from 1998 (NHS/HPFS) or 1999 (NHS II), and further mutually adjusted for changes in walnut, other tree nuts, peanuts, and peanut butter.

that a relatively large increment in nut consumption (from 0 to ≥0.5 servings/day) was associated with lower CVD risk when compared with consistent nonconsumers. Indeed, a consistent higher nut consumption (≥0.5 servings/day) was associated with even lower risks of CVD, CHD, and stroke, suggesting that long-term higher intake may play an important role in the prevention of CVD. These results support, among nonconsumers, relatively rapid changes in risk of CVD, CHD, and stroke after a large increase in nut consumption.

Results from the present study are in line with previous observational cohort findings.[6,21,22] In a

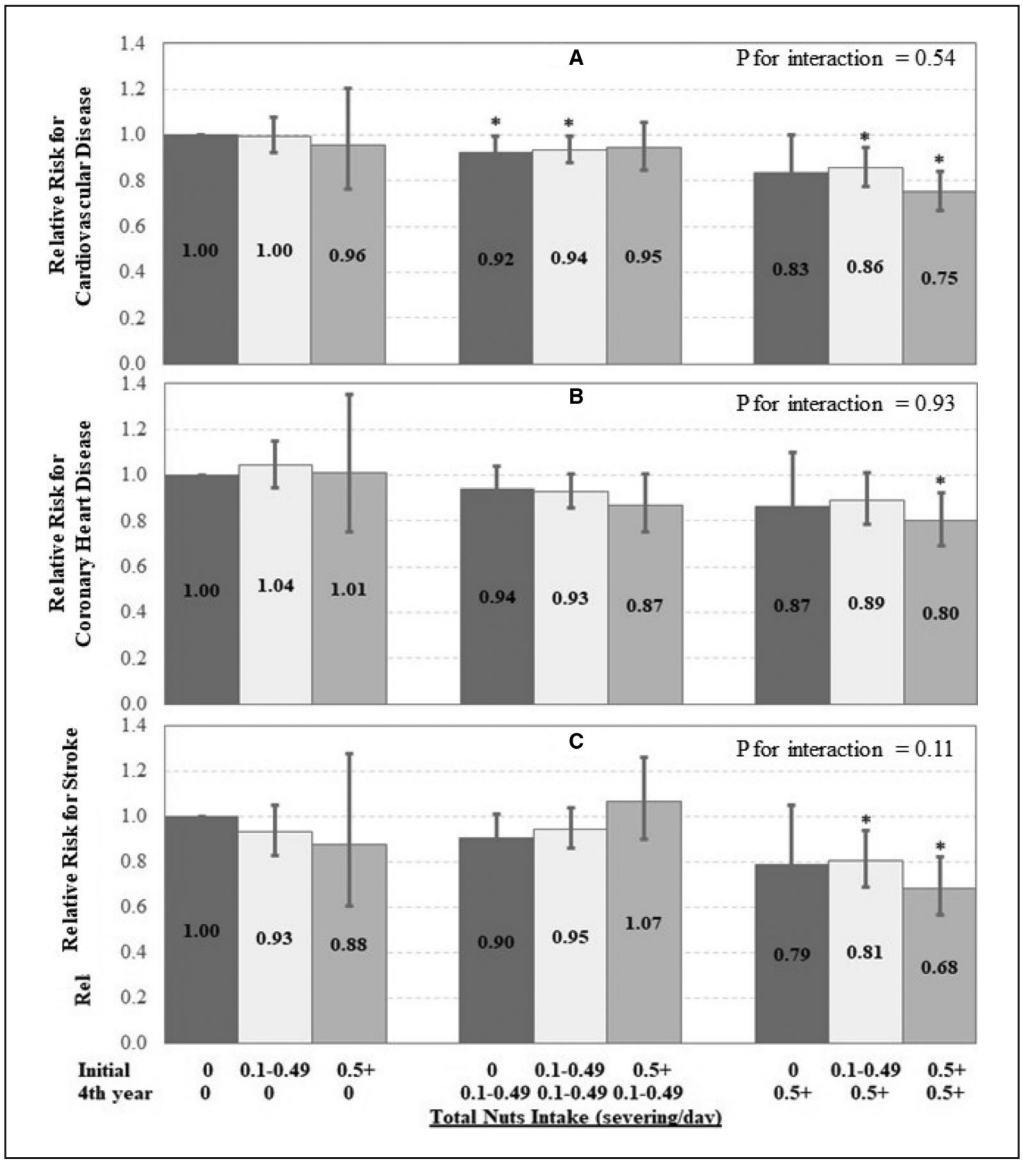

Figure 2. Risk for incident cardiovascular disease (CVD) (A), coronary heart disease (CHD) (B), and stroke (C) according to the joint categories of total consumption of nuts.
Multivariate adjusted model was stratified by age, sex, and calendar year in 4-year intervals and adjusted for initial total nut intake, race (white or nonwhite), family history of myocardial infarction, initial and change in smoking status (never to never, never to current, past to past, current to past, current to current, missing indicator), menopausal status, postmenopausal hormone use (premenopausal, postmenopausal+current use, postmenopausal+past use, postmenopausal+never use, missing indicator, in NHS [Nurses' Health Study] and NHS II), number of teeth at baseline (0, 1–16, 17–24, 25–32, in NHS and HPFS [Health Professionals Follow-Up Study]) and updated teeth loss during follow-up (continuous, in NHS and HPFS), oral contraceptive use (never, current, past, missing indicator, in NHS II), initial (g/d: 0, 0.1–4.9, 5–14.9, 15–29.9, and ≥30) and change in alcohol intake (decrease, no change, or increase), initial (metabolic equivalent h/wk, quintiles) and change in physical activity level (metabolic equivalent h/wk: <–5, –5 to 4.9, ≥5), initial body mass index (<21.0, 21.0–24.9, 25.0–29.9, 30.0–31.9, and >32.0 kg/m^2), initial (quintiles) and changes in energy intakes (kcal/d: <–250, –250 to 250, or ≥250), initial (calculated without the alcohol component and nuts, quintile) and change in Alternate Healthy Eating Index score (<–2, –2 to 5, or ≥5) over each 4-year period, and initial history of hypercholesterolemia and high blood pressure at the start of each 4-year interval. **P* for interaction between the initial year and the fourth year nut consumption over each 4-year period.

dose-response meta-analysis of 12 prospective studies, each 1-serving/day increment in nut consumption was associated with lower risk of CVD (RR, 0.79; 95% CI, 0.70–0.88) and CHD (RR, 0.71; 95% CI, 0.63–0.80).[6] In another dose-response meta-analysis including 5 prospective cohorts and 1 randomized clinical trial,

consumption of 4 servings of nuts per week (0.6 servings/day) was associated with a 24% (RR, 0.76; 95% CI, 0.69–0.84) lower risk of fatal ischemic heart disease.[23] The magnitude of inverse associations with CVD risk was similar between specific types of nuts. Our findings provide further support for previous epidemiological findings.

We observed that an increase in total nut consumption and consumption of walnuts by ≥0.5 servings/day was inversely associated with risk for stroke, and consumption of other types of nuts was also inversely associated with risk for stroke, but these associations were not statistically significant. Evidence for an association of nut consumption, especially individual types of nuts, with risk of stroke is inconsistent. Two prospective cohorts, the SMHS (Shanghai Men's Health Study)[24] and the NLCS (Netherlands Cohort Study),[25] reported inverse associations between peanut consumption and risk for stroke. In the PREDIMED study, participants who consumed 30 g of mixed nuts per day (including 15 g of walnuts) had a significant lower risk of stroke compared with those who were in the control group.[26] In a meta-analysis including 11 prospective cohorts, intake of nuts was not significantly associated with stroke risk (for 1 serving/day: RR, 0.93; 95% CI, 0.83–1.05).[6] There was evidence of a nonlinear J-shaped relationship between nut intake and stroke risk, with the most reduction in stroke risk observed at intakes up to 10 to 15 g/day (0.5 servings/day) and a slightly positive association with an intake of 30 g/day.[6] Further research on the dose-response association between nut consumption and stroke risk is warranted.

Cardiovascular and metabolic benefits of nut consumption have been supported by several lines of evidence. Nuts contain many healthful components, including unsaturated fatty acids, proteins, fiber, phytochemicals, antioxidant compounds, vitamins and minerals, and other bioactive compounds.[2] The mechanisms underlying the cardioprotective effects of nut consumption may be related to their benefits that have been observed on blood lipids, endothelium function,[27] systemic inflammation, oxidative stress, and insulin sensitivity.[28–31] In a pooled analysis of 25 controlled trials, daily nut consumption reduced total cholesterol concentration and low-density lipoprotein cholesterol concentration by 10.9 and 10.2 mg/dL, respectively; nut consumption also reduced triglycerides in subjects with higher baseline levels (>150 mg/dL).[32] A relatively large clinical trial (n=305) demonstrated a blood pressure–lowering effect of daily consumption of walnuts (30–60 g/d, depending on energy requirements) in elderly individuals,[33] which may partially explain the lower risk of stroke associated with walnut consumption reported herein. The potential mechanisms through which nuts may exert their health benefits also include improvements in circulating metabolites (eg, by reducing branch chain amino acid and acylcarnitines) and modifying the gut microbiome.[34–36]

Despite the relatively high energy density, intake of nuts was actually associated with less weight gain, lower risk of obesity, and lower risk of moderate weight gain in prospective studies.[37,38] Our results remained significant after we accounted for change in energy intake and weight that may accompany increases in nut consumption. Nuts are rich in fiber, which requires increased efforts and/or time of mastication, which can lead to a decreased rate of ingestion.[39] The high fiber content of nuts also can delay gastric emptying,[39] increase satiety,[5,40] suppress hunger, and promote fullness.[41] The deficit of metabolizable energy (>20%) with nut consumption (ie, almonds, walnuts) leads to inefficient energy absorption and increases in fecal fat excretion.[5] Of note, although peanut butter shares a similar nutrient profile with peanuts, the absence of effort in oral processing and other additives in peanut butter, such as sugar, may reduce its beneficial effects on cardiometabolic health.

In our analysis, increasing nuts while decreasing red meat or processed meats was associated with a significantly lower risk of both CHD and stroke. Furthermore, there may also be benefits of incorporating nuts in place of animal sources of protein (meats or other associated foods) with an impact beyond human health. Given the urgent need for a transforming global food system to provide health and environmental sustainability, experts recommend a global reduction in the consumption of animal-based foods and a doubling of the consumption of nuts and seeds.[42] Nuts are among the most environmentally sustainable foods to grow with the least carbon footprint.[43–45] Incorporating environmental-friendly plant-based protein at the expense of animal source protein that with high demands for agricultural resources could potentially improve the sustainability of our food system and reduce the public health burden through their cardioprotective effects.

The prospective design of the study, the long duration of follow-up, the high follow-up rate, the large sample size, and the repeated measures of dietary and lifestyle variables are strengths of the present study. Because of the large sample size and long follow-up period, we have the unique opportunity to investigate not only change in total consumption of nuts, but also intake of individual types of nuts. The repeated, validated measures of diet allowed assessment of within-person changes in dietary intake, reducing the possibility of reverse causation.[46] Last, analyses on substitutional associations provided direct estimate of disease associations for replacing less healthful food items with nuts. We also acknowledge several limitations. First, because nut consumption and other lifestyle factors were self-reported,

measurement errors are inevitable. The use of repeated measurements reduced random measurement errors caused by within-person variation and accommodated dietary changes over time. In addition, the errors are independent from the CVD case ascertainment and thus nondifferential and may be more likely to bias the association toward the null. In our study, information on how nuts were prepared was unspecified, and, thus, we were unable to examine the influence of preparation methods of nuts on risk of major cardiovascular events. The participants from our cohorts are health professionals, and most are whites, which may help reduce confounding by socioeconomic status, although such a relatively homogeneous socioeconomic/ethnic composition may also limit the generalization of our results. However, we do not expect the mechanisms to be different in other populations.

CONCLUSIONS

In conclusion, our results indicate that increasing total consumption of nuts and specific types of nuts (eg, tree nuts, walnuts, and peanuts) in 3 US prospective cohorts is associated with a lower risk of CVD. Our analysis provides further evidence that incorporating nuts into diet is beneficial for CVD risk, even among those who previously did not consume nuts. Our findings support the recommendation on including a variety of nuts as part of healthy dietary patterns is cardioprotective and provide theoretical evidence that replacing animal-based protein with plant-based protein can be helpful in the prevention of CVD.

ARTICLE INFORMATION

Received August 27, 2019; accepted February 12, 2020.

Affiliations

From the Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA (X.L., M.G.-F., J.-P.D.-C., D.K.T., S.N.B., W.C.W., Q.S., Y.L.); and Channing Division of Network Medicine (M.G.-F., S.N.B., W.C.W., Q.S.) and Division of Preventive Medicine (D.K.T., K.M.R.), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

Acknowledgments

We would like to thank the participants and staff of the NHS (Nurses' Health Study), NHS II, and the HPFS (Health Professionals Follow-Up Study) who contributed data for their valuable contributions.

Sources of Funding

This study was supported by research grants UM1 CA186107, UM1 CA176726, UM1 CA167552, HL035464, HL034594, HL088521, HL145386, and DK120870 from the National Institutes of Health. Dr Liu received other research support from The Peanut Institution. Dr Li was partly funded by the California Walnut Commission. Dr Drouin-Chartier is being supported by a Banting Postdoctoral Fellowship from the Canadian Institutes of Health Research (BPF-156628). Dr Guasch-Ferré is supported by the American Diabetes Association grant 1-18-PMF-029. The funders have no roles in study design, data collection and interpretation, and decision on manuscript publication.

Disclosures

Dr Drouin-Chartier received speaker and consulting honoraria from the Dairy Farmers of Canada in 2016 and 2018, outside the submitted work. Dr Li reported receiving research support from the California Walnut Commission. Dr Liu received other research support from The Peanut Institution. The remaining authors have no disclosures to report.

Supplementary Materials

Tables S1 to S2
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Multivariable adjusted relative risk (95% confidence intervals) for incident cardiovascular disease according to the joint categories of total nuts intake at the first and fourth year of each period in NHS, NHS II, and HPFS.

	Total nuts intake (serving/day)								
1st year intakes	**0**	**0.1-0.49**	**≥0.5**	**0**	**0.1-0.49**	**≥0.5**	**0**	**0.1-0.49**	**≥0.5**
4th year intakes	**0**	**0**	**0**	**0.1-0.49**	**0.1-0.49**	**0.1-0.49**	**≥0.5**	**≥0.5**	**≥0.5**
HPFS									
Person Years	61875	47484	3988	53113	187483	33991	6949	46258	44362
Cases	487	361	28	370	1205	245	47	295	254
Crude rate	787	760	702	697	643	721	676	638	573
Model 1	1.0 (ref.)	1.00 (0.88-1.15)	0.78 (0.53-1.15)	0.91 (0.79-1.04)	0.87 (0.78-0.97)	0.90 (0.77-1.05)	0.81 (0.60-1.09)	0.79 (0.68-0.91)	0.69 (0.59-0.81)
Model 2	1.0 (ref.)	1.03 (0.89-1.18)	0.82 (0.56-1.21)	0.94 (0.82-1.08)	0.92 (0.83-1.02)	0.97 (0.83-1.13)	0.86 (0.63-1.16)	0.86 (0.74-0.99)	0.77 (0.66-0.89)
Model 3	1.0 (ref.)	1.02 (0.89-1.17)	0.81 (0.55-1.19)	0.94 (0.82-1.07)	0.91 (0.81-1.01)	0.95 (0.81-1.1)	0.85 (0.63-1.15)	0.85 (0.73-0.99)	0.77 (0.65-0.90)
NHS									
Person Years	345186	164227	9989	176580	352732	46207	19123	73350	49085
Cases	1447	623	47	600	1134	150	65	231	136
Crude rate	419	379	471	340	321	325	340	315	277
Model 1	1.0 (ref.)	0.96 (0.88-1.06)	1.04 (0.78-1.40)	0.84 (0.76-0.92)	0.85 (0.78-0.92)	0.77 (0.65-0.91)	0.72 (0.56-0.93)	0.71 (0.62-0.82)	0.59 (0.49-0.70)
Model 2	1.0 (ref.)	1.03 (0.93-1.13)	1.14 (0.85-1.53)	0.91 (0.82-1.00)	0.97 (0.89-1.05)	0.91 (0.77-1.08)	0.83 (0.65-1.07)	0.86 (0.74-0.99)	0.74 (0.61-0.88)
Model 3	1.0 (ref.)	1.02 (0.93-1.12)	1.15 (0.86-1.54)	0.91 (0.82-1.00)	0.97 (0.89-1.05)	0.92 (0.77-1.09)	0.85 (0.66-1.09)	0.88 (0.76-1.01)	0.76 (0.63-0.92)
NHSII									
Person Years	311193	115799	5055	191070	299703	33812	22711	72669	41764
Cases	201	61	2	135	222	31	13	49	21
Crude rate	65	53	40	71	74	92	57	67	50
Model 1	1.0 (ref.)	0.74 (0.56-0.99)	0.39 (0.10-1.59)	0.93 (0.74-1.15)	0.85 (0.70-1.04)	0.84 (0.57-1.24)	0.62 (0.35-1.09)	0.65 (0.47-0.89)	0.42 (0.27-0.67)
Model 2	1.0 (ref.)	0.74 (0.56-0.99)	0.39 (0.10-1.59)	0.97 (0.77-1.20)	0.91 (0.74-1.11)	0.94 (0.63-1.39)	0.70 (0.39-1.23)	0.75 (0.54-1.04)	0.50 (0.32-0.80)
Model 3	1.0 (ref.)	0.74 (0.55-0.99)	0.40 (0.10-1.63)	0.96 (0.77-1.20)	0.92 (0.75-1.13)	0.98 (0.66-1.46)	0.73 (0.41-1.28)	0.79 (0.56-1.10)	0.58 (0.36-0.93)

Model 1 was stratified by age, sex, and calendar year in 4-year intervals;

Model 2 was stratified by age, sex, and calendar year in 4-year intervals, further adjusted for initial total nut intake, race (white, non-white), family history of MI, initial and change in smoking status (never to never, never to current, past to past, current to past, current to current, missing indicator), menopausal status and postmenopausal hormone use (premenopausal, postmenopausal + current use, postmenopausal + past use, postmenopausal + never use, missing indicator, in NHS and NHSII), number of tooth at baseline (0, 1-16, 17-24, 25-32, in NHS and HPFS) and updated teeth loss during follow-up (continuous, in NHS and HPFS), oral contraceptive use (never, current, past, missing indicator, in NHSII), initial (g/d, 0, 0.1-4.9, 5-14.9, 15-29.9 and ≥30) and change in alcohol intake (decrease, no-change or increase), initial (MET-h/week, quintiles) and change in physical activity level (MET-h/week, <-5, -5~4.9, ≥5). **Model 3** was model 2 further adjusted for initial BMI (<21.0, 21.0-24.9, 25.0-29.9, 30.0-31.9, >32.0 kg/m^2), initial history of hypercholesterolemia and high blood pressure at the start of each 4-year interval, initial (quintiles) and changes in energy intakes (kcal/day: <-250, -250~250, ≥250), initial (calculated without the alcohol component and nuts, quintile) and change in AHEI score (<-2, -2~5, ≥5) over each 4-year period

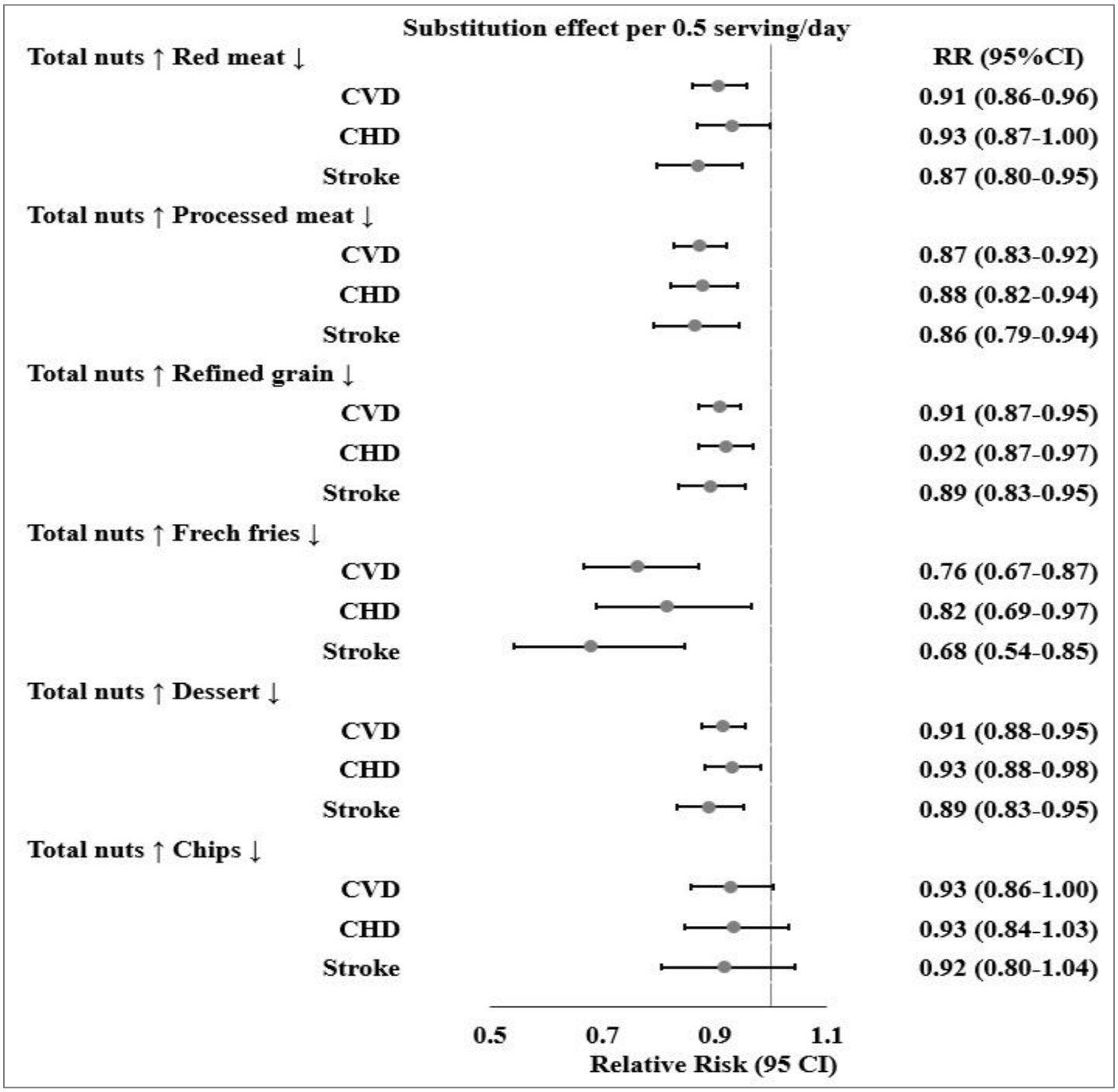
Table S2. Stratified analysis of the multivariable adjusted relative risk (RR, 95% confidence intervals) for incident cardiovascular disease associated with per 0.5 serving/day increase of total nuts based on pooled data of NHS, NHS II, and HPFS.

	CVD		CHD		Stroke	
Stratified variables	**Cases**	**RR (95%CI)**	**Cases**	**RR (95%CI)**	**Cases**	**RR (95%CI)**
Age (years)						
< 60	1634	0.90 (0.81-1.00)	1007	0.90 (0.79-1.03)	627	0.90 (0.76-1.07)
≥ 60	6826	0.92 (0.87-0.96)	3970	0.94 (0.89-0.99)	2856	0.88 (0.82-0.95)
P for interaction		0.35		0.24		0.99
Smoking status						
Never smoking	3550	0.94 (0.88-1.00)	2023	0.92 (0.85-1.00)	1527	0.96 (0.88-1.06)
Ever smoking	4840	0.89 (0.84-0.94)	2911	0.95 (0.88-1.02)	1929	0.81 (0.73-0.88)
P for interaction		0.15		0.74		0.008
Changes of alcohol intake						
No changes or decreased	5889	0.91 (0.87-0.96)	3422	0.93 (0.88-1.00)	2467	0.88 (0.81-0.95)
Increased	2571	0.92 (0.85-0.98)	1555	0.93 (0.85-1.02)	1016	0.89 (0.79-1.00)
P for interaction		0.71		0.81		0.78
Changes of physical activity						
No changes or decreased	4009	0.92 (0.86-0.97)	2444	0.91 (0.84-0.98)	1565	0.93 (0.84-1.02)
Increased	3154	0.96 (0.89-1.03)	1933	0.98 (0.90-1.07)	1221	0.92 (0.82-1.03)
P for interaction		0.34		0.33		0.77
Changes of energy intake						
No changes or decreased	4445	0.92 (0.86-0.99)	2622	0.93 (0.86-1.01)	1823	0.90 (0.82-1.00)
Increased	4015	0.91 (0.86-0.96)	2355	0.93 (0.86-0.99)	1660	0.88 (0.81-0.96)
P for interaction		0.53		0.71		0.59
Changes of AHEI score						
No changes or decreased	3793	0.89 (0.84-0.95)	2243	0.91 (0.84-0.99)	1550	0.86 (0.78-0.96)
Increased	4667	0.93 (0.88-0.98)	2734	0.95 (0.88-1.01)	1933	0.90 (0.83-0.98)
P for interaction		0.31		0.45		0.46
Changes of body weight						
No changes or decreased	4058	0.91 (0.86-0.97)	2393	0.91 (0.85-0.99)	1665	0.91 (0.83-1.00)
Increased	3446	0.91 (0.85-0.97)	1988	0.96 (0.88-1.05)	1458	0.84 (0.75-0.93)
P for interaction		0.98		0.64		0.57

Multivariate adjusted model was stratified by age, sex, and calendar year in 4-year intervals and adjusted for initial total nut intake, race (white, non-white), family history of MI, initial and change in smoking status (never to never, never to current, past to past, current to past, current to current, missing indicator), menopausal status, postmenopausal hormone use (premenopausal, postmenopausal + current use, postmenopausal + past use, postmenopausal + never use, missing indicator, in NHS and NHSII), number of tooth at baseline (0, 1-16, 17-24, 25-32, in NHS and HPFS) and updated teeth loss during follow-up (continuous, in NHS and HPFS), oral contraceptive use (never, current, past, missing indicator, in NHSII), initial (g/d, 0, 0.1-4.9, 5-14.9, 15-29.9 and ≥30) and change in alcohol intake (decrease, no-change or increase), initial (MET-h/week, quintiles) and change in physical activity level (MET-h/week, <-5, -5~4.9, ≥5), initial BMI (<21.0, 21.0-24.9, 25.0-29.9, 30.0-31.9, >32.0 kg/m^2), initial (quintiles) and changes in energy intakes (kcal/day: <-250, -250~250, ≥250), initial (calculated without the alcohol component and nuts, quintile) and change in AHEI score (<-2, -2~5, ≥5) over each 4-year period, and initial history of hypercholesterolemia and high blood pressure at the start of each 4-year interval, with the exclusion of stratified variable.

[*] *P* for interaction between the initial year and the fourth-year nut consumption over each 4-year period

Figure S1. Multivariable adjusted relative risk and 95% confidence intervals for incident cardiovascular disease associated with substitution of 0.5 serving of nuts with equal amount of other food items.



Multi-variates model stratified by age, sex, and calendar year in 4-year intervals, and adjusted initial total nut intake, race (white, non-white), family history of MI, initial and change in smoking status (never to never, never to current, past to past, current to past, current to current, missing indicator), menopausal status and postmenopausal hormone use (premenopausal, postmenopausal + current use, postmenopausal + past use, postmenopausal + never use, missing indicator, in NHS and NHSII), number of tooth at baseline (0, 1-16, 17-24, 25-32, in NHS and HPFS) and updated teeth loss during follow-up (continuous, in NHS and HPFS), oral contraceptive use (never, current, past, missing indicator, in NHSII), initial (g/d, 0, 0.1-4.9, 5-14.9, 15-29.9 and ≥30) and change in alcohol intake (decrease, no-change or increase), initial (MET-h/week, quintiles) and change in physical activity level (MET-h/week, <-5, -5~4.9, ≥5), initial BMI (<21.0, 21.0-24.9, 25.0-29.9, 30.0-31.9, >32.0 kg/m^2), initial history of hypercholesterolemia and high blood pressure at the start of each 4-year interval, initial energy intake (quintiles) as well as initial (continuous) and changes (continuous) in red meat, processed meat, whole grain, refined grain, French fries, dessert and chips.