Journal of the American Heart Association

ORIGINAL RESEARCH

Avocado Consumption and Risk of Cardiovascular Disease in US Adults

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BACKGROUND: Epidemiologic studies on the relationship between avocado intake and long-term cardiovascular disease (CVD) risk are lacking.

METHODS AND RESULTS: This study included 68 786 women from the NHS (Nurses' Health Study) and 41 701 men from the HPFS (Health Professionals Follow-up Study; 1986–2016) who were free of cancer, coronary heart disease, and stroke at baseline. Diet was assessed using validated food frequency questionnaires at baseline and then every 4 years. Cox proportional hazards regressions were used to estimate hazard ratios and 95% CIs. A total of 14 274 incident cases of CVD (9185 coronary heart disease events and 5290 strokes) were documented over 30 years of follow-up. After adjusting for lifestyle and other dietary factors, compared with nonconsumers, those with analysis-specific higher avocado intake (≥2 servings/week) had a 16% lower risk of CVD (pooled hazard ratio, 0.84; 95% CI, 0.75–0.95) and a 21% lower risk of coronary heart disease (pooled hazard ratio, 0.79; 95% CI, 0.68–0.91). No significant associations were observed for stroke. Per each half serving/day increase in avocado intake, the pooled hazard ratio for CVD was 0.80 (95% CI, 0.71–0.91). Replacing half a serving/day of margarine, butter, egg, yogurt, cheese, or processed meats with the equivalent amount of avocado was associated with a 16% to 22% lower risk of CVD.

CONCLUSIONS: Higher avocado intake was associated with lower risk of CVD and coronary heart disease in 2 large prospective cohorts of US men and women. The replacement of certain fat-containing foods with avocado could lead to lower risk of CVD.

Key Words: avocado ■ coronary heart disease ■ dietary intake ■ *Persea americana* ■ stroke ■ unsaturated fat

Cardiovascular disease (CVD), which includes coronary heart disease (CHD) and stroke, is the leading cause of death in the United States.[1] However, CVD can be largely prevented by a healthy lifestyle including a healthy diet.[2,3] The American Heart Association/American College of Cardiology recommends a heart-healthy diet limited to 5% to 6% of calories from saturated fatty acid (SFA) and underscores the replacement of SFA and trans-fat with monounsaturated fats (MUFA) and polyunsaturated fats,[4] for the prevention of CVD.

Avocados are a nutrient-dense fruit, containing dietary fiber, potassium, magnesium, MUFA, and polyunsaturated fatty acids, as well as phytonutrients and bioactive compounds, which have been independently associated with cardiovascular health.[5–7] The most commonly consumed variety in the United States (Hass avocado) contains ≈13 g of oleic acid in a medium-sized fruit (136 g), comparable to the amount of oleic acid in 1.5oz (42 g) of almonds or 2 tablespoons (26 g) of olive oil.[5] Specifically, half an avocado provides up to 20% of the daily recommended fiber, 10% of potassium, 5% of magnesium, and 15% of folate, as well as 7.5 g of MUFA and 1.5 g of polyunsaturated fatty acid.[5,8] As such, avocados can be a nutrient-dense component of a healthful dietary pattern. National

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Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.024014

For Sources of Funding and Disclosures, see page 13.

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

CLINICAL PERSPECTIVE

What Is New?

- Clinical trials have studied avocado-induced changes in the cardiovascular risk factors; however, these studies have been limited to intermediate risk factors as end points.
- In 2 large US cohorts of men and women, higher intake of avocado (≥2 servings/week) was associated with lower risk of cardiovascular disease and coronary heart disease.
- The replacement of margarine, butter, egg, yogurt, cheese, or processed meats with avocado was also associated with a lower risk of cardiovascular disease.

What Are the Clinical Implications?

- Our findings support the existing evidence on the intake of plant-based healthy fats and their positive impact on diet quality and their role in cardiovascular disease prevention in the general population.

Nonstandard Abbreviations and Acronyms

FFQ	food frequency questionnaire
HPFS	Health Professionals Follow-up Study
MUFA	monounsaturated fatty acid
NHS	Nurses' Health Study
PREDIMED	Prevencion con Dieta Mediterranea (Primary Prevention of Cardiovascular Disease with a Mediterranean Diet)
SFA	saturated fatty acid
TC	total cholesterol

population data have indicated that after accounting for lifestyle and sociodemographic factors including socioeconomic status, avocado consumers tend to have higher high-density lipoprotein (HDL) cholesterol levels; a lower risk of metabolic syndrome; and lower weight, body mass index (BMI), and waist circumference, compared with avocado nonconsumers.[6]

Although avocado-induced changes in the CVD risk profile of individuals have been investigated, clinical trials are limited to intermediate risk factors as end points.[9–17] These studies have involved a varied daily dose of avocado (0.5–2 avocados) and primarily evaluated serum lipids. Compared with low-fat, cholesterol-lowering diets, avocado-containing diets showed unchanged HDL cholesterol levels, while triglyceride, low-density lipoprotein (LDL) cholesterol, and total cholesterol (TC) levels were comparable or reduced.[9–14,17] However, these trials used avocados as a source of MUFA in dietary interventions that replaced macronutrients to determine the impact of dietary fat intake on serum lipids.

A recently published systematic review and meta-analysis[18] encourages the examination of avocado intake in well-conducted prospective observational studies to examine the association between avocado consumption and clinical CVD end points. In this study, we aimed to examine the association between avocado consumption with total CVD, CHD, and stroke, in 2 large US prospective cohort studies, the NHS (Nurses' Health Study) and the HPFS (Health Professionals Follow-up Study). We also conducted substitution analyses to estimate the risk of total CVD, CHD, and stroke when different fat-containing food sources were replaced by avocado.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Population

The HPFS[19] is an ongoing prospective cohort study established in 1986 consisting of 51 529 US male health professionals aged 40 to 75 years from all 50 US states. The NHS[20] is a prospective cohort study that began in 1976 and consists of 121 700 registered female nurses aged 30 to 55 years from 11 US states. Participants from both cohorts responded to validated questionnaires inquiring about lifestyle, medical history, and other health information at baseline and every 2 years thereafter to update personal information on lifestyle behaviors, risk factors, and diagnoses of chronic diseases.[20,21] A detailed description of the 2 cohorts has been previously reported.[22] Baseline for both cohorts was 1986, when avocado consumption was first included as part of the food frequency questionnaires (FFQs) and detailed information about diet and lifestyle was assessed with subsequent biennial questionnaires.

We excluded men and women who had a baseline history of heart disease, stroke, or cancer because the diagnoses of these conditions might have changed diet. We also excluded participants with missing information on avocado intake, and those who were out of the predefined limits of energy intake levels (<800 or >4200 kcal/day for men and <500 or >3500 kcal/day for women). After exclusions, a total of 62 225 women and 41 701 men remained for analysis. The protocol was approved by the institutional review board

of Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health. All participants gave informed consent.

Ascertainment of CVD

The primary outcome measure was incident cases of total CVD defined as the composite of fatal CHD and nonfatal myocardial infarction and fatal and nonfatal stroke. Secondary outcomes included incident cases of: total CHD, defined as fatal CHD and nonfatal myocardial infarction; and total stroke, defined as fatal and nonfatal ischemic, hemorrhagic, and unknown subtypes of stroke. When a participant reported an incident event on each biennial questionnaire, permission was requested to examine medical records, reviewed by study investigators blinded to the participant's risk factor status. For each event, the month and year of diagnosis was recorded as the diagnosis date. Nonfatal events were confirmed through review of medical records. Myocardial infarction was defined according to the World Health Organization criteria and cardiac-specific troponin or other cardiac enzyme levels.[23] When medical records were unavailable, interviews or letters confirmed CHD events that were designated as "probable." Strokes were confirmed if data in the medical records fulfilled the National Survey of Stroke criteria requiring evidence of a neurological deficit with sudden or rapid onset that persisted for >24 hours or until death.[24] Strokes were classified as ischemic stroke (thrombotic or embolic occlusion of a cerebral artery), hemorrhagic stroke (subarachnoid and intraparenchymal hemorrhage), or stroke of probable or unknown subtype (subtype data not available). Death ascertainment was performed by searching the National Death Index,[25] by family members' response to follow-up questionnaires, or by reports from participants' professional organizations. We requested access to medical records, autopsy reports, and death certificates to confirm all suspected deaths caused by myocardial infarction. Fatal myocardial infarction was confirmed by medical records or autopsy reports. Death certificates alone were not considered sufficient to confirm myocardial infarction as the cause of death unless family members or medical records indicated that the participant was diagnosed with coronary artery disease before death but after admission into the study. We included all confirmed and probable cases in our report because results were similar after probable cases were excluded. Follow-up for deaths was >98% complete.

Assessment of Avocado Consumption

Dietary intake was assessed using a validated semiquantitative FFQ with over 130 items administered every 4 years. The reproducibility and validity of these FFQs have been described in detail elsewhere.[26,27] Participants were asked how often, on average, they consumed each food of a standard portion size in the past year. The frequency responses ranged from never or less than once per month to ≥6 times per day. Avocado intake was calculated from 1 questionnaire item that specifically asked about avocado amount and frequency. Avocado intake was collapsed into 4 categories: (1) never or less than once per month, (2) 1 to 3 times per month, (3) once per week; and (4) ≥2 times per week. We also analyzed avocado intake as a continuous variable by including half a serving of avocado (one-fourth of an avocado), which is equivalent to 40 g, in the multivariable models. Total margarine was calculated on the basis of the reported frequency of stick, tub, or soft margarine and the amount of margarine added from baking and frying at home. Butter intake was also calculated on the basis of the frequency that butter was added to foods and used for frying, sautéing, and baking. Olive oil intake was calculated from the frequency of consumption of 3 questionnaire items (olive oil salad dressing; olive oil added to food or bread; and olive oil used for baking and frying at home). Other plant oils (eg, corn, safflower, soybean, canola) amounts were estimated from the participant's reported oil brand and type of fat used for cooking at home, including frying, sautéing, baking, and salad dressing. Intakes of dairy, mayonnaise, eggs, yogurt, cheese, processed meats, and nuts, and nutrients were calculated on the basis of the US Department of Agriculture and Harvard University Food Composition Database[28] and our biochemical analyses.

Assessment of Covariates

Baseline history of hypertension, hypercholesterolemia, and type 2 diabetes were determined by self-report of a physician diagnosis. Updated biennial information on lifestyle and CVD risk factors was assessed including age, body weight, smoking status, physical activity, aspirin and other medication use, multivitamin use, menopausal status, postmenopausal hormone therapy and oral contraceptives use, and newly diagnosed chronic disease (self-reported physician diagnosed). Height was ascertained for women in 1976 and for men in 1986. Height and body weight were used to calculate BMI (kg/m^2). Alcohol intake was updated on the FFQs every 4 years. Demographic information was also collected via mailed questionnaires, in 1986 for men and in 1992 for women. This included the participants' ancestry ("Your ancestry: Southern European/Mediterranean; Scandinavian; Other Caucasian; African-American; Hispanic; Asian; Native-American; Other"). Since the data on race and ethnicity in our cohorts were collected more than 30 years ago, they are not consistent with the current standard classifications.

Statistical Analysis

Person-years of follow-up for each participant were calculated from the return of the baseline questionnaire to the date of diagnosis of CVD, death, or end of follow-up (June 30, 2016, for the NHS, and January 31, 2016, for HPFS), whichever came first. Multivariable Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% CIs of developing CVD according to avocado intake. Model 1 was adjusted for age. Multivariable model 2 was adjusted for age; race (White or other [Black, American-Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander]), ancestry (Southern European/Mediterranean, other Caucasian/Scandinavian, other); alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, and ≥15.0 g/day); smoking status (never, former, current smoker [1–14 cigarettes per day, 15–24 cigarettes per day, or ≥25 cigarettes per day]); physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, ≥27.0 metabolic equivalents–h/week); family history of diabetes (yes, no); family history of myocardial infarction (yes, no); family history of cancer (yes, no); baseline diabetes (yes, no); baseline hypertension or antihypertensive medication use (yes, no); baseline hypercholesterolemia or cholesterol-lowering medication use (yes, no); multivitamin use (yes, no); aspirin use (yes, no); postmenopausal status and menopausal hormone use (premenopausal, postmenopausal [no, past, or current hormone use]; women only); total energy intake (kcal/day); and BMI (kg/m^2, continuous). Multivariable model 3 was additionally adjusted for trans-fat and quintiles of red and processed meat, fruits and vegetables other than avocado, nuts, soda (caloric and low or noncaloric), whole grains, eggs, tortilla (whole and chips; tertiles in NHS), breads, and cheese intakes. Race was dichotomized for the statistical analysis since >90% of our population is White and having multiple categories would affect the degrees of freedom of the model.

Spearman correlations were used to assess the correlation between avocado and other types of fats.

We used the simple update approach for dietary variables, including the covariates, wherein the most recently reported diet is assessed against incident disease by the end of the subsequent interval (eg, whether intake reported in 1988 was associated with CVD in 1992). Thereby, the information closest to the time of the event was used in the primary analyses. This analysis took into account a substantial increase in avocado intake among our cohort participants over the past 3 decades. With the exception of fixed covariates, which includes family history of disease, baseline medical conditions, and race, ethnicity, and ancestry, we used the same method to update the rest of the covariates. This method considered changes in covariate lifestyle behaviors at follow-up (biennially, every 4 years for alcohol), applied to smoking status, alcohol intake, physical activity, multivitamin and aspirin use, and postmenopausal status and menopausal hormone use. Because participants may alter dietary patterns after the diagnosis of major illness, we stopped updating dietary variables when participants reported a diagnosis of coronary artery bypass, angina, or cancer, although follow-up continued until CVD end point occurrence, death, or the end of the study period.[29] Missing values during follow-up were replaced by using the carry-forward method.

Prespecified subgroup analyses were performed according to baseline age (<60 compared with ≥60 years), BMI (<25 compared with ≥25 kg/m^2), family history of myocardial infarction (yes compared with no), ancestry (Southern European/Mediterranean, and other Caucasian compared with other [including Hispanic]), and above and below the median for each of the following: alternative healthy eating index score, total fruit intake, total vegetable intake, green vegetable intake, and lettuce intake. Significance was assessed by the Wald test on cross-product terms on the basis of avocado intake and the stratification variables. The proportion of participants with Hispanic ancestry in the study population is low, which precluded us from looking specifically into this subgroup that may have a higher intake of avocados.

We also estimated the risk of total CVD when substituting half a serving of avocado (40 g, one-fourth of an avocado) for the equivalent amount (40 g) of other types of fat-containing foods: margarine, butter, mayonnaise (regular and light), eggs, yogurt (plain, sweetened, and artificially sweetened), cheese (cottage or ricotta, cream, and all other cheeses including hard—regular and low-fat or light), processed meats (beef or pork hot dogs, bacon, salami, bologna, sausages, kielbasa, other similar deli-type processed sandwich meats), olive oil, other plant oils (corn, safflower, soybean, and canola oils), nuts (peanuts, walnuts, and other nuts), and dairy foods (milk, cheese, yogurt) with total CVD by including both variables in the same multivariable model previously described and mutually adjusted for other types of fat-containing food sources. These foods were considered since avocado could often be used as an alternative in the same manner (ie, ingredient, spread, dressing, topping). We used the difference between regression coefficients and in variances and covariances to derive the HRs and 95% CIs of the substitution analyses.

Sensitivity analyses were conducted to test the robustness of the results. First, to test whether the results were affected by selectively stopping updating diet, diet was continuously updated until the end of follow-up. Second, models were mutually adjusted for other

types of fat-containing food sources (ie, margarine, butter, mayonnaise, eggs, yogurt, cheese, processed meats, olive oil, other plant oils, dairy foods). Third, sensitivity analyses excluding BMI from the models were conducted. Fourth, to test whether the results were altered by socioeconomic status, models were adjusted for median household income and education. Fifth, instead of using the simple update approach of diet, the average of the 2 most recent measures of diet were used. Finally, in place of the simple update method, the cumulative average of all the FFQs that asked about avocado intake was used. For this particular research question, we considered the simple update approach as the most suitable method since avocado intake in the cohorts was almost negligible during the first few FFQs. Bonferroni corrections to account for multiple testing were conducted at α=0.025 (alpha corrected for 2 secondary outcomes) and α=0.005 (alpha corrected for 11 tests in the substitution analyses).

Tests for linear trend were conducted by assigning the median value to each category of intake and modeling this value as a continuous variable. HRs from multivariate models in each cohort were pooled by using a fixed-effect inverse-variance meta-analysis. Proportional hazards assumptions were assessed, and no variables violated the assumption. All *P* values were 2-sided, and an α level of <0.05 was considered statistically significant. Data were analyzed with the SAS package, version 9.4 (SAS Institute, Cary, NC).

RESULTS

During 30 years of follow-up (median follow-up duration was 13.3 and 14.2 years for men and women, respectively), there were a total of 14 274 total CVD cases documented, 6661 in the HPFS and 7613 in the NHS. Mean intake of avocado increased from an average of 17.2 g/week (0.2 servings/week) in 1986 to 32.3 g/week (0.4 servings/week) in 2014 for HPFS, and from 9.2 g/day (0.1 servings/week) in 1986 to 16.3 g/week (0.2 servings/week) in 2010 for NHS, while the intake of margarine, mayonnaise, dairy foods, and other plant oils decreased (Table S1). The Spearman correlations between avocado and other fat-containing foods are presented in Table S2. Characteristics of participants according to frequency of avocado intake at baseline 1986 are shown in Table 1. Men and women with a higher intake of avocado also tended to have a higher total energy intake and better diet quality, characterized by a higher intake of fruits and vegetables, whole grains, nuts, dairy products such as yogurt and cheese, and alternative healthy eating index score. The mean intake of avocado in the highest baseline category (≥2 servings/day) was about 40 g/day (Table 1).

After adjusting for major diet and lifestyle factors, compared with nonconsumers, those with an analysis-specific higher avocado intake (≥2 servings/week) had a 16% lower risk of CVD (pooled HR, 0.84; 95% CI, 0.75–0.95; *P* trend=0.0007) (Table 2). When BMI was excluded from the models, the results were unchanged (pooled HR, 0.84; 95% CI, 0.75–0.95; *P* trend=0.0005) (Table S3). When the models for avocado were mutually adjusted for other types of fat-containing food sources, the pooled HR for CVD was 0.89 (95% CI, 0.80–0.98; *P* trend=0.02) (Table S4). Per each half a serving/day (one-fourth avocado) increase in avocado intake, the pooled HR for CVD was 0.80 (95% CI, 0.71 to 0.91; *P* trend=0.0007). Comparing extreme categories of avocado intake after adjusting for potential confounders, the pooled HRs were 0.79 (95% CI, 0.68–0.91; *P* trend<0.001) for CHD and 0.94 (95% CI, 0.78–1.14; *P* trend=0.78) for stroke (Table 2). The pooled estimate for the overall HR of ischemic stroke was 0.93 (95% CI, 0.69–1.25; *P* trend=0.62) per each half a serving/day increase in avocado consumption (Table S5).

We found significant inverse associations in most of the prespecified subgroup analyses (Table 3). No significant interactions were observed for any of the variables analyzed. Prespecified subgroup analyses for CHD and stroke are presented in Table S6. Substituting half a serving/day of avocado for the equivalent amount of margarine was estimated to be associated with 16% lower risk of CVD (HR, 0.84; 95% CI, 0.75–0.95; *P*=0.004) (Figure). The respective HR estimate for butter was 0.78 (95% CI, 0.63–0.96; *P*=0.02). For mayonnaise, the HR was 0.92 (95% CI, 0.80–1.07; *P*=0.29). Substituting half a serving/day of avocado for the equivalent amount of egg and cheese was estimated to be associated with 18% (HR, 0.82; 95% CI, 0.73–0.93; *P*=0.001) and 13% (HR, 0.87; 95% CI, 0.77 to 0.98; *P*=0.02) lower risk of CVD. A lower risk of CVD was observed when substituting avocado for processed meats and yogurt, while substituting half a serving/day of avocado for the equivalent amount of olive oil, nuts, and other plant oils was not statistically significant. Replacing half a serving/day of mayonnaise, margarine, butter, egg, yogurt, cheese, or processed meats with the equivalent amount of avocado was associated with 19% to 31% lower risk of CHD (Figure). We did not observe significant associations when substituting avocado for any of the prespecified foods and stroke, with the exception of all other plant oils (safflower, corn, soybean, and canola oils). Replacing half a serving/day of all other plant oils with the equivalent amount of avocado was associated with a 45% higher risk of stroke. Cohort-specific substitution analyses are presented in Figure S1.

In the sensitivity analysis to test whether the results were affected by selectively stop updating diet, diet was continuously updated until the end of follow-up. The associations for half a serving/day increase in

Table 1. Baseline* Characteristics of Participants According to Categories of Avocado Intake

	Health Professionals Follow-up Study				Nurses' Health Study			
	Never or <1 per month n=29 483	1–3 per month n=9323	1 per week n=1991	≥2 per week n=904	Never or <1 per month n=57 401	1–3 per month n=8669	1 per week n=1955	≥2 per week n=761
Avocado, g/d	0.0±0.0	5.0±0.0	10.7±0.0	38.8±18.8	0.0±0.0	5.0±0.0	10.7±0.0	37.6±13.3
Age, y	52.8±9.4	52.7±9.5	53.4±9.8	55.8±10.0	52.3±7.1	53.2±7.2	53.8±6.8	54.7±6.9
BMI, kg/m^2	25.6±3.3	25.3±3.3	25.1±3.4	25.0±3.4	25.5±4.9	24.4±4.3	24.2±4.3	24.6±4.7
Physical activity, MET-h/wk	20.5±28.4	22.4±30.5	23.7±32.1	24.3±27.0	13.6±20.2	16.1±21.2	16.8±19.9	18.2±28.5
Family history of myocardial infarction (%)	32.6	29.8	28.7	30.5	39.0	37.2	37.1	36.7
Race, White	95.2	94.4	95.0	93.2	98.1	96.4	96.9	96.4
Ancestry (%)								
Southern European or Mediterranean	24.1	21.9	23.6	24.5	16.9	15.5	14.7	16.0
Other Caucasian or Scandinavian	67.1	68.5	67.8	65.3	60.7	65.9	65.5	60.7
All other ancestry including Hispanic	8.8	9.6	8.6	10.2	22.3	18.6	19.7	23.4
Hispanic only	0.3	0.9	1.1	0.8	0.5	1.8	3.2	4.0
Current smoker (%)	10.0	9.7	7.7	6.8	21.3	19.7	19.5	18.8
Hypertension (%)	22.3	20.6	19.1	22.1	16.0	14.4	15.1	16.0
Hypercholesterolemia (%)	10.7	10.0	9.0	9.9	7.5	7.6	6.9	6.7
Multivitamin supplement use (%)	40.3	44.4	47.8	46.9	41.6	47.1	47.6	43.7
Aspirin use (%)	26.7	27.0	24.5	23.9	67.8	68.4	66.6	64.4
Current menopausal hormone use (%)	-	-	-	-	13.3	20.5	22.2	20.7
Total energy intake, kcal/d	1970±617	2031±615	2143±634	2236±668	1750±524	1819±531	1915±536	1997±553
Alcohol, g/d	10.6±15.1	13.3±16.4	14.5±16.5	13±15.8	5.7±10.2	8.7±12.5	8.8±12.3	8.9±14.1
Red and processed meat, servings/d	1.2±0.9	1.1±0.8	1.1±0.9	1.1±0.9	1.0±0.7	1.0±0.7	1.0±0.7	1.0±0.7
Processed meat, servings/d	0.4±0.4	0.4±0.4	0.3±0.4	0.3±0.4	0.3±0.3	0.3±0.3	0.3±0.3	0.3±0.3
Eggs, servings/d	0.3±0.4	0.4±0.4	0.4±0.4	0.4±0.5	0.3±0.3	0.3±0.3	0.3±0.3	0.3±0.3
Nuts, servings/d	0.5±0.6	0.5±0.6	0.6±0.7	0.7±0.7	0.1±0.3	0.2±0.3	0.2±0.3	0.3±0.4
Whole grains, servings/d	1.6±1.5	1.6±1.4	1.7±1.4	1.9±1.6	1.5±1.3	1.7±1.4	1.8±1.4	1.8±1.3
Non–whole grain breads, servings/d	0.8±1.0	0.6±0.8	0.6±0.8	0.6±0.8	0.8±0.9	0.6±0.7	0.6±0.7	0.6±0.7
Tortilla, servings/d	0.1±0.1	0.1±0.2	0.1±0.2	0.1±0.2	0.0±0.1	0.1±0.2	0.1±0.2	0.1±0.2

(*Continued*)

Table 1. Continued

	Health Professionals Follow-up Study				Nurses' Health Study			
	Never or <1 per month n=29 483	1–3 per month n=9323	1 per week n=1991	≥2 per week n=904	Never or <1 per month n=57 401	1–3 per month n=8669	1 per week n=1955	≥2 per week n=761
Chips and crackers, servings/d	0.4±0.6	0.4±0.5	0.4±0.5	0.4±0.5	0.4±0.7	0.4±0.6	0.4±0.5	0.4±0.6
Fruits, servings/d	2.2±1.6	2.3±1.6	2.7±1.7	3.1±2.4	2.4±1.5	2.5±1.6	2.9±1.8	3.1±2.0
Vegetables, servings/d	2.9±1.6	3.3±1.8	3.6±1.8	4.1±2.1	2.7±1.1	3.0±1.2	3.2±1.2	3.3±1.2
Soda†, servings/d	0.8±1.1	0.7±0.9	0.7±0.9	0.7±0.9	0.7±0.9	0.6±0.8	0.6±0.9	0.6±0.8
Dairy foods, g/d	14.3±9.2	14.6±9.1	15.5±9.9	15.8±10.2	15.0±8.6	15.1±8.7	15.7±8.5	16.6±10.2
Margarine, g/d	10.7±15.1	10.0±14.1	9.9±14.2	10.2±15.2	15.1±17.4	13.8±16.4	14.3±16.5	12.7±15.7
Butter, g/d	1.7±3.7	2.0±3.8	2.3±4.2	2.2±3.9	1.8±3.8	2.0±3.8	2.0±3.7	2.8±4.8
Mayonnaise, g/d	4.8±6.7	5.4±6.6	5.8±6.7	6.0±8.2	5.5±6.3	6.0±6.2	6.8±7.0	6.6±7.7
Yogurt‡, g/d	19.1±51.3	22.7±46.9	28.2±54.2	36.1±89.7	27.8±58.0	35.2±59.9	39.2±60.7	39.5±66.6
Total cheese, g/d	20.8±22.1	22.7±22.8	25.1±24.2	28.4±36.0	25.9±24.5	28.0±24.9	29.2±25.3	29.2±25.3
AHEI	46.7±11.2	49.5±10.8	51.3±10.8	53.8±10.5	46.7±11.0	50.5±10.9	51.6±10.9	53.2±11.1

Values are mean±SD or %, and are standardized to the age distribution of the study population. HPFS, n=41 701; NHS, n=68 786. AHEI indicates alternative healthy index; BMI, body mass index; and MET, metabolic equivalent task.

*Baseline is 1986.

†Includes sweetened and artificially sweetened soda.

‡Includes plain, sweetened, and artificially sweetened yogurt.

Table 2. Risk of Cardiovascular Events According to Avocado Intake* in 2 Large US Cohorts

		HR (95% CI)				
	Never or <1 per month	1–3 per month	1 per week	≥2 per week	*P* value for trend	HR (95% CI) for half serving (one-fourth avocado) increase in avocado Intake per day
Total CVD†						
Health Professionals Follow-up Study						
No. cases/person-years	5076/702 080	1117/176 523	282/49 201	186/27 947		
Age-adjusted model 1	1.00	0.95 (0.89–1.01)	0.83 (0.74–0.94)	0.82 (0.71–0.95)	0.0004	0.75 (0.64–0.88)
Multivariable model 2	1.00	1.00 (0.93–1.07)	0.88 (0.76–1.04)	0.88 (0.76–1.03)	0.06	0.86 (0.73–1.01)
Multivariable model 3	1.00	0.93 (0.87–0.99)	0.84 (0.75–0.95)	0.82 (0.71–0.95)	0.0005	0.75 (0.63–0.88)
Nurses' Health Study I						
No. cases/person-years	6407/1 473 683	831/212 466	257/60 263	118/28 780		
Age-adjusted model 1	1.00	0.93 (0.86–1.00)	0.93 (0.82–1.05)	0.79 (0.66–0.95)	0.002	0.74 (0.61–0.89)
Multivariable model 2	1.00	1.02 (0.95–1.10)	1.05 (0.93–1.19)	0.91 (0.76–1.10)	0.67	0.96 (0.80–1.16)
Multivariable model 3	1.00	0.98 (0.91–1.06)	1.01 (0.89–1.15)	0.88 (0.73–1.06)	0.24	0.89 (0.73–1.08)
Pooled						
Age-adjusted model 1	1.00	0.94 (0.89–0.98)	0.88 (0.81–0.96)	0.81 (0.72–0.91)	<0.0001	0.74 (0.66–0.84)
Multivariable model 2	1.00	1.01 (0.96–1.06)	0.98 (0.90–1.07)	0.90 (0.80–1.00)	0.09	0.90 (0.80–1.02)
Multivariable model 3	1.00	0.95 (0.90–1.00)	0.92 (0.84–1.01)	0.84 (0.75–0.95)	0.0007	0.80 (0.71–0.91)
CHD‡						
Health Professionals Follow-up Study						
No. cases/person-years	3872/703 191	843/176 758	203/49 258	135/27 993		
Age-adjusted model 1	1.00	0.93 (0.86–1.00)	0.79 (0.68–0.91)	0.78 (0.66–0.93)	0.0001	0.69 (0.57–0.83)
Multivariable model 2	1.00	0.99 (0.92–1.07)	0.88 (0.76–1.02)	0.85 (0.71–1.01)	0.03	0.81 (0.67–0.97)
Multivariable model 3	1.00	0.92 (0.85–0.99)	0.81 (0.70–0.93)	0.79 (0.66–0.94)	0.0004	0.70 (0.58–0.85)
Nurses' Health Study I						
No. cases/person-years	3530/1 475 581	436/212 727	114/60 357	52/28 818		
Age-adjusted model 1	1.00	0.88 (0.80–0.97)	0.76 (0.63–0.91)	0.65 (0.49–0.86)	<0.0001	0.53 (0.40–0.70)
Multivariable model 2	1.00	1.02 (0.92–1.13)	0.91 (0.75–1.09)	0.80 (0.60–1.05)	0.09	0.79 (0.60–1.04)
Multivariable model 3	1.00	0.97 (0.88–1.08)	0.88 (0.72–1.06)	0.79 (0.60–1.04)	0.04	0.74 (0.55–0.98)
Pooled						
Age-adjusted model 1	1.00	0.91 (0.86–0.97)	0.78 (0.69–0.87)	0.74 (0.64–0.86)	<0.0001	0.63 (0.54–0.74)
Multivariable model 2	1.00	1.00 (0.94–1.06)	0.89 (0.79–1.00)	0.83 (0.72–0.96)	0.005	0.80 (0.69–0.94)
Multivariable model 3	1.00	0.94 (0.88–1.00)	0.83 (0.74–0.93)	0.79 (0.68–0.91)	<0.0001	0.71 (0.61–0.84)

(*Continued*)

Table 2. Continued

		HR (95% CI)				
	Never or <1 per month	1–3 per month	1 per week	≥2 per week	*P* value for trend	HR (95% CI) for half serving (one-fourth avocado) increase in avocado Intake per day
Stroke[§]						
Health Professionals Follow-up Study						
No. cases/person-years	1204/704 059	274/176 971	79/49 317	51/27 999		
Age-adjusted model 1	1.00	0.99 (0.87–1.13)	0.99 (0.78–1.24)	0.96 (0.72–1.27)	0.73	0.95 (0.70–1.29)
Multivariable model 2	1.00	1.01 (0.89–1.16)	1.03 (0.82–1.30)	1.00 (0.75–1.32)	0.94	1.01 (0.75–1.37)
Multivariable model 3	1.00	0.96 (0.84–1.10)	0.95 (0.76–1.21)	0.91 (0.69–1.22)	0.45	0.89 (0.64–1.22)
Nurses' Health Study I						
No. cases/person-years	3046/1 475 539	421/212 662	147/60 321	68/28 802		
Age-adjusted model 1	1.00	0.99 (0.89–1.10)	1.11 (0.94–1.31)	0.94 (0.74–1.19)	0.93	0.99 (0.77–1.26)
Multivariable model 2	1.00	1.04 (0.93–1.15)	1.18 (1.00–1.40)	1.02 (0.80–1.30)	0.34	1.13 (0.88–1.44)
Multivariable model 3	1.00	1.00 (0.90–1.11)	1.13 (0.96–1.34)	0.97 (0.76–1.24)	0.81	1.03 (0.80–1.33)
Pooled						
Age-adjusted model 1	1.00	0.99 (0.91–1.07)	1.06 (0.93–1.22)	0.94 (0.79–1.13)	0.78	0.97 (0.80–1.18)
Multivariable model 2	1.00	1.03 (0.95–1.11)	1.13 (0.98–1.29)	1.01 (0.84–1.21)	0.43	1.08 (0.89–1.31)
Multivariable model 3	1.00	0.98 (0.90–1.07)	1.07 (0.93–1.23)	0.94 (0.78–1.14)	0.78	0.97 (0.80–1.19)

Model 2 was adjusted for: age (years); race (Whiteor other [Black, American-Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander]); ancestry (Southern European/Mediterranean, other Caucasian/Scandinavian, other); alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, and ≥15.0 g/day); smoking status (never, former, current smoker [1–14 cigarettes per day, 15–24 cigarettes per day; or ≥25 cigarettes per day]); physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, ≥27.0 metabolic equivalent task–h/week); family history of diabetes (yes, no); family history of myocardial infarction (yes, no); family history of cancer (yes, no); baseline diabetes (yes, no); baseline hypertension or antihypertensive medication use (yes, no); baseline hypercholesterolemia or cholesterol-lowering medication use (yes, no); multivitamin use (yes, no); aspirin use (yes, no); in women, postmenopausal status and menopausal hormone use (premenopausal, postmenopausal [no, past, or current hormone use]); total energy intake (kcal/day); and body mass index (kg/m^2). Model 3 was additionally adjusted for red and processed meat, fruits and vegetables (excluding avocado), nuts, soda (caloric and noncaloric), whole grains, eggs, tortilla (whole and chips), breads, cheese intakes (in quintiles; tortilla in tertiles in NHS), and trans-fat.

Results were pooled with the use of the fixed-effects model. CHD indicates coronary heart disease; CVD, cardiovascular disease; and HR, hazard ratio.

*1 serving avocado=one-half avocado; half serving=one-fourth avocado.

[†]CVD: fatal and nonfatal myocardial infarction plus fatal and nonfatal stroke.

[‡]CHD: fatal and nonfatal myocardial infarction.

[§]Fatal and nonfatal stroke.

Table 3. Subgroup Analyses for Risk of Cardiovascular Disease According to Avocado Intake*

	Pooled adjusted HR (95% CI)	*P* value for Interaction
Sex		
Women, n=7613†	0.89 (0.73–1.08)	0.17
Men, n=6661	0.75 (0.63–0.88)	
Age, y		
<65, n=3496	0.94 (0.71–1.25)	0.19
≥65, n=10 778	0.79 (0.69–0.91)	
BMI, kg/m^2		
<25, n=7352	0.80 (0.68–0.94)	0.86
≥25, n=6922	0.83 (0.68–1.01)	
Ancestry		
Mediterranean and other Caucasian, n=12 728	0.81 (0.71–0.92)	0.14
All other, including Hispanic, n=1546	0.68 (0.43–1.07)	
Family history of myocardial infarction		
No, n=8242	0.75 (0.64–0.88)	0.37
Yes, n=6032	0.91 (0.75–1.11)	
AHEI		
Below median, n=7547	0.86 (0.69–1.06)	0.32
Above median, n=6727	0.80 (0.69–0.94)	
Total fruit intake		
Below median, n=6471	0.78 (0.63–0.98)	0.77
Above median, n=7803	0.84 (0.72–0.97)	
Total vegetable intake		
Below median, n=6783	0.72 (0.57–0.92)	0.43
Above median, n=7491	0.86 (0.74–1.00)	
Green vegetable intake		
Below median, n=7639	0.77 (0.63–0.95)	0.52
Above median, n=6635	0.84 (0.72–0.99)	
Lettuce vegetable intake		
Below median, n=7581	0.80 (0.65–0.97)	0.73
Above median, n=6693	0.82 (0.70–0.97)	

HRs for half a serving/day (one-fourth avocado) increase in avocado intake in each subgroup category.

Multivariable model was adjusted for the following: age (y); race (Whitevs other [Black, American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander]); ancestry (Southern European/Mediterranean, other Caucasian/Scandinavian, other); alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, and ≥15.0 g/day); smoking status (never, former, current smoker [1–14 cigarettes per day, 15–24 cigarettes per day; or ≥2 cigarettes per day]); physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, ≥27.0 metabolic equivalent task–h/week); family history of diabetes (yes, no); family history of myocardial infarction (yes, no); family history of cancer (yes, no); baseline diabetes (yes, no); baseline hypertension or antihypertensive medication use (yes, no); baseline hypercholesterolemia or cholesterol-lowering medication use (yes, no); multivitamin use (yes, no); aspirin use (yes, no); postmenopausal status and menopausal hormone use (premenopausal, postmenopausal [no, past, or current hormone use], in women only); total energy intake (kcal/day);body mass index (kg/m^2, continuous); red and processed meat, fruits and vegetables (excluding avocado), nuts, soda (caloric and low or noncaloric), whole grains, eggs, tortilla (whole and chips), breads, cheese intakes (all in quintiles; tortilla in tertiles in NHS); and trans-fat, except the stratified factor. AHEI indicates alternative healthy eating index score; and BMI, body mass index.

*1 serving avocado=½ avocado; ½ serving=¼ avocado.

†n= number of cases per subgroup.

avocado intake were attenuated (Table S7). The pooled HR for CVD was 0.93 (95% CI, 0.82–1.05; *P* trend=0.24). However, the CHD results remained consistent (pooled HR, 0.85; 95% CI, 0.73–0.99; *P* trend=0.03). When using the average intake of the last 2 dietary measurements, the respective HR estimate was 0.75 (95% CI, 0.66–0.86; *P* trend=<0.0001) (Table S8). Findings persisted after we excluded BMI from the models (Table S3) as well as after we adjusted for socioeconomic status (data not shown). Compared with nonconsumers, those with higher avocado intake (≥2 servings/week) had a 13% lower risk of CVD (pooled HR, 0.87; 95% CI, 0.77–0.98; *P* trend=0.02) and a 29% lower risk of CHD (pooled HR, 0.81; 95% CI, 0.70–0.94; *P* trend=0.006). The associations for half a serving/day increase in avocado intake and

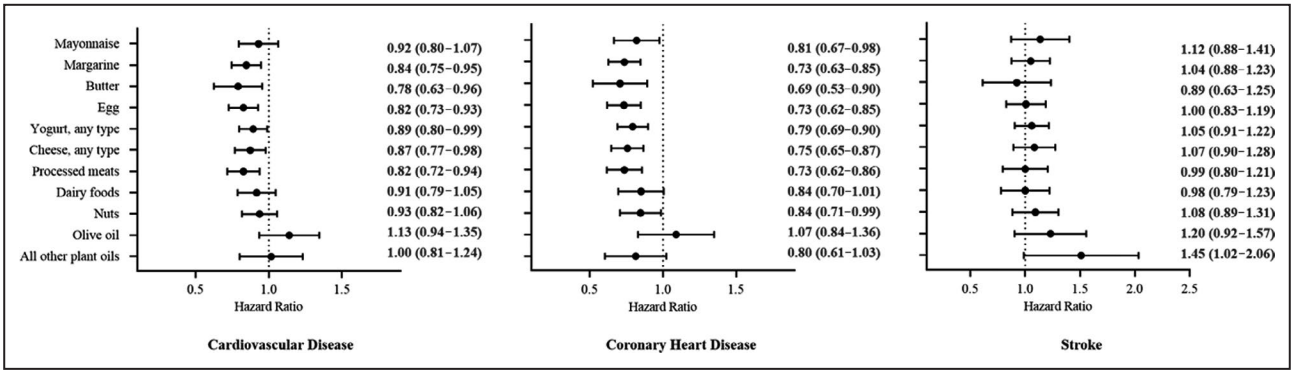

Figure. Hazard ratios for cardiovascular events associated with substitution of half a serving of avocado for equivalent amounts of other fat-containing food sources in two large US cohorts.

Pooled hazard ratios for cardiovascular disease, coronary heart disease, and stroke associated with substitution of half a serving/day (one-fourth avocado) of avocado for equivalent amounts of other fat-containing foods. Multivariate-adjusted models were adjusted for the following: age (years); race (White) or other [Black, American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander]; ancestry (Southern European/Mediterranean, other Caucasian/Scandinavian, all other); alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, and ≥15.0 g/day); smoking status (never, former, current smoker [1–14 cigarettes per day, 15–24 cigarettes per day; or ≥2 cigarettes per day); physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, ≥27.0 metabolic equivalent task–h/week); family history of diabetes (yes, no); family history of myocardial infarction (yes, no); family history of cancer (yes, no); baseline diabetes (yes, no); baseline hypertension or antihypertensive medication use (yes, no); baseline hypercholesterolemia or cholesterol-lowering medication use (yes, no); multivitamin use (yes, no); aspirin use (yes, no); postmenopausal status and menopausal hormone use (premenopausal, postmenopausal [no, past, or current hormone use]), only in women; total energy intake (kcal/day); body mass index (kg/m^2, continuous), red and processed meat, fruits and vegetables (excluding avocado), nuts, soda (caloric and low or noncaloric), whole grains, eggs, tortilla (whole and chips), breads, cheese intakes (all in quintiles; tortillas in tertiles in Nurses' Health Study); trans-fat, and mutually adjusted for other types of fat-containing foods. Results were pooled with the use of the fixed-effects model. Horizontal lines represent 95% CIs.

substitution analysis were also consistent after adjusting for these variables. After adjusting for MUFA intake, results were consistent. The pooled HR for CVD was 0.85 (95% CI, 0.75–0.95; *P* trend=0.001) (Table S9). The cumulative average method results are shown in Table S10. We did not observe significant associations between avocado intake and incident total CVD, CHD, or stroke.

When we adjusted for multiple testing using the Bonferroni correction, the main results and conclusions did not change, as the *P* values for the pooled analyses were <0.001. In the substitution analysis, results changed for the replacement of avocado for butter and yogurt (*P*>0.005).

DISCUSSION

In 2 large prospective cohorts of men and women followed for 30 years, we found inverse associations between avocado consumption and the incidence of CVD and CHD events after adjusting for cardiovascular risk factors and other dietary variables. Compared with nonconsumers, those with higher consumption of avocados had 16% lower risk of CVD and 21% lower risk of CHD, but no association for stroke. Findings were consistent across all subgroups. Additionally, compared with margarine, butter, egg, yogurt, cheese, and processed meats, avocados were associated with lower risk of CVD and CHD, whereas when compared with olive oil, nuts, and other plant oils combined, avocados were not associated with CVD and CHD. To our knowledge, the present study is the first large prospective study to examine and generate evidence on the longitudinal association between avocado consumption and CVD events. Results also suggest that substitution of certain fat-containing food sources (ie, margarine, cheese, processed meats) with healthy unsaturated fats such as avocado, may lead to lower CVD and CHD risk. On the other hand, the substitution of other healthy dietary fats such as olive oil, nuts, and other plants oils for avocado yielded nonsignificant results, suggesting that they can all be considered as healthy sources of fat for the prevention of CVD. Although we observed a significantly higher risk of stroke when substituting all other plant oils (safflower, corn, soybean, and canola oils) for avocado, this result may be attributable to chance because of the several different replacement foods and outcomes we have examined.

Existing published literature is inconclusive regarding the association between avocado intake and incidence of cardiovascular risk factors and CVD and other chronic diseases.[18,30] While clinical trial evidence on the effects of avocados on the cardiovascular risk profile of adults exist, these intervention studies have reported inconsistent effects on serum lipids in participants with and without cardiometabolic disease.[9–16]

This has been further determined by 2, to-date, thorough systematic reviews and meta-analyses[18,30] of existing trials examining the effects of avocado intake on heart disease risk factors and plasma lipoproteins. The first review (2016; n=10 studies [8 crossover and 2 parallel trials, 1–12 weeks in duration, 229 participants] in meta-analysis),[30] concluded that avocado-substituted diets (substitution of SFA with MUFA-rich avocados versus adding to the free diet) decrease TC, LDL cholesterol, and triglyceride levels, as well as found that HDL cholesterol levels decreased nonsignificantly in healthy adults with a normal BMI. In this review, half of the studies included Hass-type avocados,[9,10,12,14,17] 3 studies replaced MUFA content with avocado and other dietary MUFA sources such as olive oil and almonds,[12,31,32] and the remaining 7 used avocado as the only source of MUFA.[9–11,13–15,17] All 10 studies examined the substitution of dietary fats for avocados with no particular control diet. However, the most recent review (2018, n=10 studies [8 crossover and 2 parallel trials, 3–24 weeks in duration, 249 participants] in meta-analysis, 1 not included in the previous analyses and 1 new trial since 2016)[18] observed no difference in serum TC, LDL cholesterol, and triglyceride concentrations with avocado intake, but did find an increase in serum HDL cholesterol levels, yet with significant heterogeneity. The quantitative analysis included 7 trials that compared avocado intake with a control diet with no avocado intake.[9,12–15,17,33] It also excluded trials with <3 weeks of follow-up, whereas the 2016 review included 2 studies with <3 weeks of follow-up[10,14] in their quantitative analysis.

Although the latter systematic review and meta-analysis seem to provide a more comprehensive assessment of avocado intake and cardiometabolic factors, with a set of abundant sensitivity analyses, it is important to highlight that both reviews showed significant heterogeneity across eligible studies, differed in their inclusion criteria with only 5 shared studies, and were unable to examine risk of CVD events because no studies have reported incident clinical outcomes of CVD, including CHD events or stroke. However, high-quality randomized controlled trials that have demonstrated a favorable outcome on lipid profiles should be highlighted, as many of the studies included in the meta-analyses have had a small sample size[9,11,13,14,16] participants had existing cardiometabolic diseases[9–12,14,15] and differed in dietary intervention design and feeding period length.[10,13,16] A high-grade crossover, controlled feeding trial in adults with overweight/obesity, reported that compared with baseline, the avocado-containing diet (moderate fat [34% fat] diet with 6%–7% of energy from MUFA from 1 avocado per day in substitution for SFA, ≈136 g with pulp), lowered LDL cholesterol, TC, LDL particle, non-HDL cholesterol, and TC/HDL cholesterol and LDL/HDL cholesterol ratios significantly more than the moderate-fat diet (34% fat; 6%–7% of energy from MUFA from high oleic oils to match the fatty acid content of avocado in substitution for SFA).[17] This trial also examined circulating oxidized LDL, an independent risk factor for CVD,[34] and found that compared with baseline, only the avocado-containing diet significantly decreased plasma oxidized LDL.[35] Furthermore, the reduction in oxidized LDL by this diet was significantly greater than that by the other 2 study diets, moderate-fat and low-fat diets.

Despite the conflicting clinical literature among avocado-enriched trials on cardiometabolic factors and a lack of prospective analyses between avocado intake and risk of CVD for comparison with our results, the current study's findings provide novel, necessary, and robust evidence that higher intake of avocados is associated with a lower risk of CVD and CHD in healthy US adults. These results are particularly noteworthy since the consumption of avocado has risen steeply in the United States in the past 20 years.[36,37]

In lieu of comparable studies, we can evaluate our results against that of olive oil, another MUFA-rich food that has been extensively studied and shares phytonutrients and the main component, oleic acid, with avocados. Findings from the PREDIMED (Primary Prevention of Cardiovascular Disease with a Mediterranean Diet) trial, determined that a Mediterranean diet supplemented with extra virgin olive oil reduced the risk of cardiovascular events by 31% (95% CI, 0.53–0.91) in a population at high cardiovascular risk.[38] Additionally, observational studies have shown that olive oil consumption is inversely associated with cardiovascular events in both Mediterranean[39,40] and US populations.[41] In the NHS and HPFS cohorts, compared with nonconsumers, those with higher olive oil intake (>0.5 tablespoon/day or >7 g/day) had a 14% lower risk of CVD (pooled HR, 0.86; 95% CI, 0.79–0.94) and an 18% lower risk of CHD (pooled HR, 0.82; 95% CI, 0.73–0.91). This evidence provides support for our findings. Further replications of our analysis in other cohorts that have collected data on avocado intake and prospectively assessed CVD end points are warranted.

Diet is a key element in improving the cardiometabolic profile, thus decreasing the risk of CVD.[4] Favorable bioactive food compounds include MUFAs and polyunsaturated fatty acids, soluble fiber, vegetable proteins, phytosterols, and polyphenols,[42] all present in avocados. Moreover, replacement of fats high in SFAs or trans-fat with unsaturated fatty acids can be beneficial for CVD prevention,[4] as indicated by leading medical entities. Thereby, our substitution analysis, estimating the risk of CVD and CHD by substituting specific types of fat-containing food sources with avocado, is consistent and supported by this evidence. The replacement of fat-containing foods (some with SFA) with the same amount of avocado was associated with a lower risk of

CVD and CHD, while the substitution for olive oil and other plant oils yielded nonsignificant results. This is an important finding for public health recommendations, emphasizing the consumption of avocado and other unsaturated fats to follow a healthy dietary pattern and reduce the risk of CVD.[43] Furthermore, 2 current analyses found a lower risk of CHD and CVD mortality when plant-sourced MUFAs substitute animal-sourced MUFAs as well as SFAs.[44,45]

There are potential biological mechanisms by which avocados offer cardioprotective benefits through modulating cardiovascular risk factors. The primary MUFA present in avocados is oleic acid, and it is suggested that it helps in improving endothelial dysfunction, hypertension, inflammation, and insulin sensitivity.[46,47] Additionally, plant sterols, plant analogs of cholesterol, are moderately high in avocados (136 g fruit without skin and seed=≈104 mg beta-sitosterol),[48] and could have favorable effects on lipid profiles. Moreover, higher fiber intake via avocado consumption can lead to a better lipid profile.[49]

Interestingly, we found an association between avocado consumption and CHD but not with stroke, including ischemic stroke. Although no evidence exists on the effect of avocados on CHD and stroke prevention, our findings were unexpected since we know that following a healthful diet, such as the Mediterranean dietary pattern, is one of the key lifestyle components that support primordial prevention of cardiovascular events.[50] The PREDIMED trial showed that a Mediterranean diet supplemented with extra virgin olive oil significantly reduced the risk of stroke by 35% (HR, 0.65; 95% CI, 0.44–0.95).[38] However, PREDIMED investigators did not find a significant reduction in myocardial infarction risk (HR, 0.82; 95% CI, 0.52–1.30) after a median follow-up of 4.8 years. Similarly, it has been determined that greater adherence to healthy eating patterns, including the Mediterranean diet, was associated with lower risk of total CVD, CHD, and stroke.[51] Moreover, a recent study examining the long-term association between olive oil, another MUFA-containing food, and CVD risk in the NHS and HPFS cohorts reported no significant associations for total or ischemic stroke.[41] Our stroke findings, including the substitution analysis findings, as well as those of olive oil in the NHS and HPFS cohorts, could be explained by chance or the lack of statistical power. It is also possible that the bioactive compound effects of avocado differ by variety and level of ripeness,[52] which we did not ask in the biennial questionnaires, affecting their contribution to disease outcomes.

The strengths of this study include a prospective population-based design, a large sample size, a long follow-up, repeated and validated measurements of diet and lifestyle data, and a well-defined clinical event outcome. Limitations need to be considered in our study. First, because dietary information was self-reported, our assessment of absolute intake of avocado will have some degree of measurement error. However, the use of repeated measurements reduces random measurement error caused by within-person variation. Misclassification is a possibility, yet because of the study's prospective design, misclassification and measurement error was most likely nondifferential, attenuating the association towards the null. Third, because of the observational design, a causal association cannot be established and residual confounding cannot be completely ruled out even though the analyses were extensively adjusted for potential confounders. Fourth, our study population consisted of primarily non-Hispanic White nurses and health professionals, thereby limiting the generalizability of our results to other populations. Still, there is no known reason to expect that the underlying biological mechanisms may be different in other ethnic groups or that socioeconomic status would affect the results since the sensitivity analysis included adjusting the models for socioeconomic status. Finally, because of the large number of statistical tests conducted, it is possible that some were by chance, but the primary outcome results remained unchanged after correcting for multiple testing.

CONCLUSIONS

In conclusion, in this large study of US men and women, higher intake of avocados was associated with significantly lower risk of total CVD and CHD. No significant associations were observed for total or ischemic stroke. In substitution analyses, we observed that replacing margarine, butter, egg, total yogurt, total cheese, and processed meats with avocado was associated with a lower incidence of CVD events. Our study provides further evidence that the intake of plant-sourced unsaturated fats can improve diet quality and is an important component in CVD prevention in the general population. Further studies are needed to assess the impact and effectiveness of avocado intake in reducing incident CVD and CVD risk factors.

ARTICLE INFORMATION

Received September 17, 2021; accepted February 7, 2022.

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Acknowledgments

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

Sources of Funding

The research reported in this manuscript were supported by National Institutes of Health grants UM1 CA186107, U01 CA167552, HL60712, P30DK046200, R01 HL034594, R01 HL088521, and R01 HL35464. Additionally, this work was supported by grant T32 DK007703-26 from the National Institute of Diabetes and Digestive and Kidney Diseases and the Harvard Chan Yerby Fellowship at Harvard T.H. Chan School of Public Health.

Disclosures

Dr Pacheco collaborated in the Hass Avocado Board–funded trial Effects of Avocado Intake on the Nutritional Status of Families during 2016 to 2019 as a graduate student researcher, but the present study was not supported or endorsed by the Hass Avocado Board. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S10
Figure S1

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Supplemental Material

Table S1. Mean consumption[*] of avocado and other fats in the Health Professionals Follow-Up Study (1986-2014) and Nurse's Health Study (1986-2010).

Avocado			Margarine			Mayonnaise		
Year	HPFS Mean ± SD	NHS Mean ± SD	Year	HPFS Mean ± SD	NHS Mean ± SD	Year	HPFS Mean ± SD	NHS Mean ± SD
1986	17.5 ± 46.2	9.1 ± 32.2	1986	72.1 ± 103.6	103.6 ± 121.1	1986	35.7 ± 46.9	39.2 ± 44.1
1990	--	--	1990	76.3 ± 10.6.4	100.8 ± 119.0	1990	31.5 ± 44.1	37.1 ± 46.2
1994	16.1 ± 45.5	8.4 ± 32.2	1994	69.3 ± 101.5	83.3 ± 109.9	1994	34.3 ± 50.4	37.8 ± 48.3
1998	16.8 ± 51.1	8.4 ± 32.9	1998	59.5 ± 94.5	71.4 ± 105.0	1998	34.3 ± 48.3	35.7 ± 46.2
2002	20.3 ± 62.3	--	2002	47.6 ± 88.2	63.7 ± 100.8	2002	31.5 ± 48.3	34.3 ± 45.5
2006	24.5 ± 63.7	14.0 ± 47.6	2006	44.1 ± 84.7	58.8 ± 96.6	2006	30.8 ± 48.3	32.9 ± 44.1
2010	27.3 ± 74.2	16.1 ± 51.1	2010	40.6 ± 81.2	35.7 ± 84.0	2010	29.4 ± 47.6	32.2 ± 42.0
2014	32.2 ± 81.2	--	2014	39.2 ± 80.5	--	2014	30.1 ± 49.0	--
Butter			**Olive Oil**			**Other Plant Oils**		
Year	HPFS Mean ± SD	NHS Mean ± SD	Year	HPFS Mean ± SD	NHS Mean ± SD	Year	HPFS Mean ± SD	NHS Mean ± SD
1986	12.6 ± 25.9	13.3 ± 26.6	1986	0.0 ± 2.8	0.0 ± 1.4	1986	39.9 ± 31.5	38.5 ± 28.7
1990	10.5 ± 23.8	9.1 ± 22.4	1990	7.0 ± 16.1	7.7 ± 16.8	1990	32.9 ± 29.4	32.9 ± 29.4
1994	10.5 ± 23.8	11.2 ± 23.1	1994	14.7 ± 33.6	17.5 ± 37.8	1994	29.4 ± 30.1	23.8 ± 25.9
1998	12.6 ± 25.2	12.6 ± 25.2	1998	14.0 ± 30.8	24.5 ± 48.3	1998	25.9 ± 28.0	23.8 ± 26.6
2002	14.0 ± 26.6	14.0 ± 25.9	2002	23.1 ± 46.9	28.0 ± 52.5	2002	25.9 ± 27.3	28.7 ± 20.3
2006	13.3 ± 25.9	14.0 ± 25.2	2006	27.3 ± 53.9	27.3 ± 53.9	2006	25.2 ± 28.0	23.1 ± 24.5
2010	12.6 ± 24.5	14.7 ± 25.2	2010	28.0 ± 51.8	27.3 ± 53.2	2010	25.2 ± 28.0	24.5 ± 24.5
2014	13.3 ± 24.5	--	2014	28.7 ± 53.2	--	2014	25.2 ± 28.0	--
Dairy Foods			**Nuts**			**Cheese**		
Year	HPFS Mean ± SD	NHS Mean ± SD	Year	HPFS Mean ± SD	NHS Mean ± SD	Year	HPFS Mean ± SD	NHS Mean ± SD
1986	101.5 ± 63.7	105.0 ± 58.8	1986	49.0 ± 79.8	29.4 ± 55.3	1986	149.1 ± 155.4	184.8 ± 170.1
1990	84.7 ± 58.8	86.8 ± 51.8	1990	43.3 ± 73.5	23.1 ± 47.6	1990	131.6 ± 144.2	149.8 ± 148.4
1994	77.7 ± 58.1	74.2 ± 51.8	1994	41.3 ± 72.8	21.0 ± 45.5	1994	127.4 ± 144.2	136.5 ± 139.3
1998	74.2 ± 56.7	75.6 ± 53.2	1998	45.5 ± 80.5	24.5 ± 52.5	1998	133.7 ± 155.4	144.2 ± 149.1
2002	79.8 ± 61.6	78.4 ± 55.3	2002	58.1 ± 101.5	37.1 ± 74.2	2002	131.6 ± 162.4	141.4 ± 157.5
2006	82.6 ± 62.3	80.5 ± 56.7	2006	64.4 ± 106.4	51.8 ± 95.2	2006	137.9 ± 169.4	149.1 ± 161.0
2010	84.0 ± 63.0	80.5 ± 56.7	2010	71.4 ± 119.0	50.4 ± 93.8	2010	133.7 ± 162.4	144.2 ± 154.7
2014	86.1 ± 64.4	--	2014	74.9 ± 123.2	72.1 ± 124.6	2014	136.5 ± 165.9	--
Egg			**Yogurt[†]**			**Processed meats**		
Year	HPFS Mean ± SD	NHS Mean ± SD	Year	HPFS Mean ± SD	NHS Mean ± SD	Year	HPFS Mean ± SD	NHS Mean ± SD
1986	116.9 ± 145.6	105.7 ± 99.4	1986	146.3 ± 381.5	208.6 ± 415.8	1986	76.3 ± 86.1	63.0 ± 48.3
1990	88.9 ± 123.2	72.8 ± 84.7	1990	143.5 ± 369.6	218.4 ± 425.6	1990	64.4 ± 80.5	49.7 ± 58.8
1994	82.6 ± 118.3	67.9 ± 81.2	1994	147.7 ± 375.9	257.6 ± 487.9	1994	59.5 ± 77.7	44.1 ± 56.7

1998	94.5 ± 133.0	83.3 ± 98.7	1998	180.6 ± 437.5	298.9 ± 543.2	1998	59.5 ± 76.3	59.5 ± 77.0
2002	101.5 ± 147.0	90.3 ± 107.8	2002	174.3 ± 441.7	277.2 ± 527.1	2002	62.3 ± 84.0	58.1 ± 76.3
2006	103.6 ± 149.8	91.0 ± 104.3	2006	196.7 ± 484.4	319.9 ± 557.2	2006	63.7 ± 85.4	57.4 ± 74.9
2010	102.9 ± 145.6	93.1 ± 107.1	2010	233.1 ± 552.3	388.5 ± 633.5	2010	62.3 ± 84.0	52.5 ± 67.9
2014	112.0 ± 156.8	--	2014	259.0 ± 599.2	--	2014	65.1 ± 87.5	--

* Consumption in grams/week for all foods listed.

† Includes plain, sweetened, and artificially sweetened yogurt.

Table S2. Spearman correlations between avocado intake and other types of fat at the mid-point of follow-up (1998).

	Avocado	Margarine	Butter	Mayonnaise	Olive Oil	Other plant oils	Dairy foods	Cheese	Egg	Yogurt*	Processed Meats	Nuts
	Health Professionals Follow-up Study†											
Avocado	1.0	-0.04	0.09	0.09	0.10	0.08	0.06	0.08	0.08	0.10	0.01	0.11
Margarine	-0.04	1.0	-0.14	0.20	-0.11	0.18	0.10	0.14	0.10	-0.06	0.18	0.05
Butter	0.09	-0.14	1.0	0.10	0.12	0.08	0.42	0.13	0.22	0.002	0.21	0.08
Mayonnaise	0.09	0.20	0.10	1.0	0.04	0.55	0.17	0.19	0.17	-0.004	0.22	0.10
Olive Oil	0.10	-0.11	0.12	0.04	1.0	-0.17	-0.002	0.02	-0.02	0.12	-0.11	0.16
Other plant oils	0.08	0.18	0.08	0.55	-0.17	1.0	0.23	0.15	0.18	-0.08	0.27	0.13
Dairy foods	0.06	0.10	0.42	0.17	-0.002	0.23	1.0	0.52	0.28	0.05	0.35	0.11
Cheese	0.08	0.14	0.13	0.19	0.02	0.15	0.52	1.0	0.22	0.10	0.22	0.11
Egg	0.08	0.10	0.22	0.17	-0.02	0.18	0.28	0.22	1.0	-0.03	0.40	0.05
Yogurt*	0.10	-0.06	0.002	-0.004	0.12	-0.08	0.05	0.10	-0.03	1.0	-0.15	0.06
Processed meats	0.01	0.18	0.21	0.22	-0.11	0.27	0.35	0.22	0.40	-0.15	1.0	0.06
Nuts	0.11	0.05	0.08	0.10	0.16	0.13	0.11	0.11	0.05	0.06	0.06	1.0
	Nurses' Health Study‡											
Avocado	1.0	0.03	-0.03	0.01	-0.10	0.11	0.07	0.04	0.06	0.06	-0.03	0.14
Margarine	0.03	1.0	-0.28	0.14	-0.12	0.15	0.02	0.09	0.09	-0.06	0.13	0.02
Butter	-0.03	-0.28	1.0	0.08	0.19	0.10	0.44	0.07	0.15	-0.01	0.16	0.06
Mayonnaise	0.01	0.14	0.08	1.0	0.08	0.51	0.16	0.17	0.18	0.02	0.18	0.10
Olive Oil	-0.10	-0.12	0.19	0.08	1.0	-0.16	-0.02	0.03	-0.001	0.18	-0.10	0.16
Other plant oils	0.11	0.15	0.10	0.51	-0.16	1.0	0.29	0.14	0.19	-0.11	0.27	0.13
Dairy foods	0.07	0.02	0.44	0.16	-0.02	0.29	1.0	0.49	0.26	0.08	0.32	0.12
Cheese	0.04	0.09	0.07	0.17	0.03	0.14	0.49	1.0	0.21	0.14	0.16	0.12
Egg	0.06	0.09	0.15	0.18	-0.001	0.19	0.26	0.21	1.0	-0.09	0.33	0.05
Yogurt*	0.06	-0.06	-0.01	0.02	0.18	-0.11	0.08	0.14	-0.09	1.0	-0.15	0.09
Processed meats	-0.03	0.13	0.16	0.18	-0.10	0.27	0.32	0.16	0.33	-0.15	1.0	0.05
Nuts	0.14	0.02	0.06	0.10	0.16	0.13	0.12	0.12	0.05	0.09	0.05	1.0

* Includes plain, sweetened, and artificially sweetened yogurt.

† All correlations = 0.02, p-value <0.001; all correlations ≥ 0.03, p-value <0.0001.

‡ All correlations = 0.01, p-value <0.001; all correlations ≥ 0.02, p-value <0.0001.

Table S3. Risk of Cardiovascular Events According to Categories of Avocado Intake* without adjusting for BMI in Two Large US Cohorts.

	HR (95% CI)					
	Never or less than 1 per month	1-3 per month	1 per week	≥2 per week	P value for trend	HR (95% CI) for 1/2 serving (1/4 avocado)-Increase in Avocado Intake per day
CVD†						
Health Professionals Follow-Up Study						
No. cases/person-years	5,076/702,080	1,117/176,523	282/49,201	186/27,947		
Multivariable Model 3	1.00	0.93 (0.87, 0.99)	0.84 (0.75, 0.95)	0.82 (0.71, 0.95)	0.0005	0.75 (0.63, 0.88)
Multivariable Model 3 without BMI	1.00	0.92 (0.86, 0.99)	0.84 (0.74, 0.95)	0.82 (0.71, 0.95)	0.0004	0.74 (0.63, 0.87)
Nurses' Health Study I						
No. cases/person-years	6,407/1,473,683	831/212,466	257/60,263	118/28,780		
Multivariable Model 3	1.00	0.98 (0.91, 1.06)	1.01 (0.89, 1.15)	0.88 (0.73, 1.06)	0.24	0.89 (0.73, 1.08)
Multivariable Model 3 without BMI	1.00	0.98 (0.91, 1.05)	1.01 (0.89, 1.15)	0.88 (0.73, 1.06)	0.22	0.89 (0.73, 1.07)
Pooled						
Multivariable Model 3	1.00	0.95 (0.90, 1.00)	0.92 (0.84, 1.01)	0.84 (0.75, 0.95)	0.0007	0.80 (0.71, 0.91)
Multivariable Model 3 without BMI	1.00	0.95 (0.90, 1.00)	0.92 (0.84, 1.00)	0.84 (0.75, 0.95)	0.0005	0.80 (0.71, 0.91)
CHD‡						
Health Professionals Follow-Up Study						
No. cases/person-years	3,872/703,191	843/176,758	203/49,258	135/27,993		
Multivariable Model 3	1.00	0.92 (0.85, 0.99)	0.81 (0.70, 0.93)	0.79 (0.66, 0.94)	0.0004	0.70 (0.58, 0.85)
Multivariable Model 3 without BMI	1.00	0.91 (0.85, 0.99)	0.80 (0.70, 0.93)	0.79 (0.66, 0.94)	0.0003	0.70 (0.57, 0.85)
Nurses' Health Study I						
No. cases/person-years	3,530/1,475,581	436/212,727	114/60,357	52/28,818		
Multivariable Model 3	1.00	0.97 (0.88, 1.08)	0.88 (0.72, 1.06)	0.79 (0.60, 1.04)	0.04	0.74 (0.55, 0.98)
Multivariable Model 3 without BMI	1.00	0.97 (0.87, 1.07)	0.87 (0.72, 1.05)	0.78 (0.59, 1.03)	0.03	0.73 (0.55, 0.97)
Pooled						
Multivariable Model 3	1.00	0.94 (0.88, 1.00)	0.83 (0.74, 0.93)	0.79 (0.68, 0.91)	<0.0001	0.71 (0.61, 0.84)
Multivariable Model 3 without BMI	1.00	0.93 (0.88, 0.99)	0.83 (0.74, 0.93)	0.79 (0.68, 0.91)	<0.0001	0.71 (0.60, 0.83)
Stroke§						
Health Professionals Follow-Up Study						
No. cases/person-years	1,204/704,059	274/176,971	79/49,317	51/27,999		
Multivariable Model 3	1.00	0.96 (0.84, 1.10)	0.95 (0.76, 1.21)	0.91 (0.69, 1.22)	0.45	0.89 (0.64, 1.22)
Multivariable Model 3 without BMI	1.00	0.96 (0.83, 1.10)	0.95 (0.75, 1.20)	0.91 (0.68, 1.21)	0.43	0.88 (0.64, 1.21)
Nurses' Health Study I						
No. cases/person-years	3,046/1,475,539	421/212,662	147/60,321	68/28,802		
Multivariable Model 3	1.00	1.00 (0.90, 1.11)	1.13 (0.96, 1.34)	0.97 (0.76, 1.24)	0.81	1.03 (0.80, 1.33)
Multivariable Model 3 without BMI	1.00	1.00 (0.90, 1.11)	1.13 (0.96, 1.34)	0.97 (0.76, 1.24)	0.81	1.03 (0.80, 1.33)
Pooled						
Multivariable Model 3	1.00	0.98 (0.90, 1.07)	1.07 (0.93, 1.23)	0.94 (0.78, 1.14)	0.78	0.97 (0.80, 1.19)
Multivariable Model 3 without BMI	1.00	0.98 (0.90, 1.07)	1.07 (0.93, 1.22)	0.94 (0.78, 1.14)	0.76	0.97 (0.79, 1.18)

[*] 1 serving avocado = ½ avocado; ½ serving = ¼ avocado. [†] CVD = cardiovascular disease: Fatal and nonfatal myocardial infarction plus fatal and nonfatal stroke. [‡] CHD = coronary heart disease: Fatal and nonfatal myocardial infarction. [§] Fatal and nonfatal stroke.

BMI, body mass index.

Model 3 was adjusted for: age (years); race (White or other [Black, American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander]); ancestry (Southern European/Mediterranean, other Caucasian/Scandinavian, other); alcohol intake (0, 0.1 to 4.9, 5.0 to 9.9, 10.0 to 14.9, and ≥15.0 g/day); smoking status (never, former, current smoker 1 to 14 cigarettes per day, 15 to 24 cigarettes per day; or ≥25 cigarettes per day); physical activity (<3.0, 3.0 to 8.9, 9.0 to 17.9, 18.0 to 26.9, ≥27.0 MET–h/week); family history of diabetes (yes, no); family history of myocardial infarction (yes, no); family history of cancer (yes, no); baseline diabetes mellitus (yes, no); baseline hypertension or antihypertensive medication use (yes, no); baseline hypercholesterolemia or cholesterol-lowering medication use (yes, no); multivitamin use (yes, no); aspirin use (yes, no); in women, postmenopausal status and menopausal hormone use (premenopausal, postmenopausal [no, past, or current hormone use]); total energy intake (kcal/day); and body mass index (kg/m^2, continuous), and red and processed meat, fruits and vegetables (excluding avocado), nuts, soda (caloric and low or noncaloric), whole grains, eggs, tortilla (whole and chips), breads, cheese intakes (all in quintiles; tortilla in tertiles in NHS), and trans-fat.

Table S4. Risk of Cardiovascular Events According to Avocado Intake[*] Mutually Adjusting for Other Fats[†] in Two Large US Cohorts.

	P value for trend	HR (95% CI) for 1/2 serving (1/4 avocado)-Increase in Avocado Intake per day
CVD[‡]		
Health Professionals Follow-Up Study		
Multivariable Model 3	0.0005	0.75 (0.63, 0.88)
Multivariable Model 3, mutually-adjusted for other fat-containing foods[†]	0.01	0.85 (0.74, 0.97)
Nurses' Health Study I		
Multivariable Model 3	0.24	0.89 (0.73, 1.08)
Multivariable Model 3, mutually-adjusted for other fat-containing foods[†]	0.60	0.96 (0.81, 1.13)
Pooled		
Multivariable Model 3	0.0007	0.80 (0.71, 0.91)
Multivariable Model 3, mutually-adjusted for other fat-containing foods[†]	0.02	0.89 (0.80, 0.98)
CHD[§]		
Health Professionals Follow-Up Study		
Multivariable Model 3	0.0004	0.70 (0.58, 0.85)
Multivariable Model 3, mutually-adjusted for other fat-containing foods[†]	0.002	0.78 (0.66, 0.91)
Nurses' Health Study I		
Multivariable Model 3	0.04	0.74 (0.55, 0.98)
Multivariable Model 3, mutually-adjusted for other fat-containing foods[†]	0.13	0.82 (0.63, 1.06)
Pooled		
Multivariable Model 3	<0.0001	0.71 (0.61, 0.84)
Multivariable Model 3, mutually-adjusted for other fat-containing foods[†]	0.0007	0.79 (0.69, 0.90)
Stroke[‖]		
Health Professionals Follow-Up Study		
Multivariable Model 3	0.45	0.89 (0.64, 1.22)
Multivariable Model 3, mutually-adjusted for other fat-containing foods[†]	0.80	1.03 (0.84, 1.25)
Nurses' Health Study I		
Multivariable Model 3	0.81	1.03 (0.80, 1.33)
Multivariable Model 3, mutually-adjusted for other fat-containing foods[†]	0.54	1.07 (0.86, 1.33)
Pooled		
Multivariable Model 3	0.78	0.97 (0.80, 1.19)
Multivariable Model 3, mutually-adjusted for other fat-containing foods[†]	0.55	1.05 (0.90, 1.21)

[*] 1 serving avocado = ½ avocado; ½ serving = ¼ avocado. [†] Mutually-adjusted for other fat-containing foods includes the following variables: margarine, mayonnaise, olive oil, all other plant oils, and dairy foods. [‡] CVD = cardiovascular disease: Fatal and nonfatal myocardial infarction plus fatal and nonfatal stroke. [§] CHD = coronary heart disease: Fatal and nonfatal myocardial infarction. [‖] Fatal and nonfatal stroke.

Model 3 was adjusted for: age (years); race (White or other [Black, American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander]); ancestry (Southern European/Mediterranean, other Caucasian/Scandinavian, other); alcohol intake (0, 0.1 to 4.9, 5.0 to 9.9, 10.0 to 14.9, and ≥15.0 g/day); smoking status (never, former, current smoker 1 to 14 cigarettes per day, 15 to 24 cigarettes per day; or ≥25 cigarettes per day); physical activity (<3.0, 3.0 to 8.9, 9.0 to 17.9, 18.0 to 26.9, ≥27.0 MET–h/week); family history of diabetes (yes, no); family history of myocardial infarction (yes, no); family history of cancer (yes, no); baseline diabetes mellitus (yes, no); baseline hypertension or antihypertensive medication use (yes, no); baseline hypercholesterolemia or cholesterol-lowering medication use (yes, no); multivitamin use (yes, no); aspirin use (yes, no); in women, postmenopausal status and menopausal hormone use (premenopausal, postmenopausal [no, past, or current hormone use]); total energy intake (kcal/day); body mass index (kg/m^2, continuous), red and processed meat, fruits and vegetables (excluding avocado), nuts, soda (caloric and low or noncaloric), whole grains, eggs, tortilla (whole and chips), breads, cheese intakes (all in quintiles; tortilla in tertiles in NHS), and trans-fat.

Table S5. Risk of Stroke Sub-type According to Simple Update Categories of Avocado Intake* in Two Large US Cohorts.

	HR (95% CI)					
	Never or less than 1 per month	1-3 per month	1 per week	≥2 per week	P value for trend	HR (95% CI) for 1/2 serving (1/4 avocado)-Increase in Avocado Intake per day
Ischemic stroke†						
Health Professionals Follow-Up Study						
No. cases/person-years	628/704,059	147/176,971	44/49,317	29/27,999		
Age-adjusted Model 1	1.00	1.01 (0.84, 1.21)	1.01 (0.74, 1.37)	1.08 (0.74, 1.58)	0.69	1.09 (0.72, 1.64)
Multivariable Model 2	1.00	1.01 (0.84, 1.21)	1.01 (0.74, 1.38)	1.10 (0.76, 1.61)	0.63	1.11 (0.73, 1.68)
Multivariable Model 3	1.00	0.96 (0.80, 1.16)	0.95 (0.69, 1.31)	1.00 (0.68, 1.47)	0.91	0.98 (0.63, 1.50)
Nurses' Health Study I						
No. cases/person-years	1,385/1,475,539	187/212,662	58/60,321	24/28,802		
Age-adjusted Model 1	1.00	0.97 (0.83, 1.13)	1.02 (0.78, 1.33)	0.84 (0.56, 1.26)	0.43	0.85 (0.57, 1.27)
Multivariable Model 2	1.00	1.00 (0.86, 1.17)	1.07 (0.82, 1.39)	0.90 (0.60, 1.35)	0.81	0.95 (0.63, 1.43)
Multivariable Model 3	1.00	0.97 (0.83, 1.14)	1.03 (0.79, 1.35)	0.87 (0.58, 1.31)	0.56	0.88 (0.58, 1.34)
Pooled						
Age-adjusted Model 1	1.00	0.99 (0.88, 1.11)	1.02 (0.83, 1.24)	0.96 (0.73, 1.27)	0.78	0.96 (0.72, 1.28)
Multivariable Model 2	1.00	1.00 (0.89, 1.13)	1.05 (0.85, 1.28)	1.00 (0.76, 1.32)	0.87	1.03 (0.77, 1.37)
Multivariable Model 3	1.00	0.97 (0.85, 1.09)	1.00 (0.81, 1.23)	0.94 (0.71, 1.24)	0.62	0.93 (0.69, 1.25)
Hemorrhagic stroke‡						
Health Professionals Follow-Up Study						
No. cases/person-years	187/704,059	40/176,971	12/49,317	7/27,999		
Age-adjusted Model 1	1.00	0.93 (0.66, 1.32)	0.96 (0.53, 1.73)	0.88 (0.41, 1.89)	0.69	0.85 (0.37, 1.93)
Multivariable Model 2	1.00	0.96 (0.68, 1.36)	1.02 (0.56, 1.84)	0.93 (0.43, 1.98)	0.84	0.92 (0.41, 2.09)
Multivariable Model 3	1.00	0.89 (0.63, 1.28)	0.91 (0.50, 1.67)	0.83 (0.38, 1.79)	0.54	0.77 (0.33, 1.81)
Nurses' Health Study I						
No. cases/person-years	385/1,475,539	58/212,662	18/60,321	9/28,802		
Age-adjusted Model 1	1.00	1.09 (0.82, 1.43)	1.16 (0.72, 1.87)	1.18 (0.61, 2.28)	0.43	1.31 (0.67, 2.57)
Multivariable Model 2	1.00	1.12 (0.84, 1.48)	1.20 (0.75, 1.94)	1.21 (0.62, 2.35)	0.35	1.38 (0.70, 2.72)
Multivariable Model 3	1.00	1.00 (0.75, 1.34)	1.07 (0.66, 1.74)	1.06 (0.54, 2.09)	0.80	1.10 (0.54, 2.24)
Pooled						
Age-adjusted Model 1	1.00	1.02 (0.83, 1.27)	1.08 (0.75, 1.56)	1.04 (0.63, 1.71)	0.72	1.10 (0.65, 1.85)
Multivariable Model 2	1.00	1.05 (0.85, 1.31)	1.13 (0.78, 1.63)	1.08 (0.65, 1.78)	0.55	1.17 (0.70, 1.98)
Multivariable Model 3	1.00	0.96 (0.76, 1.20)	1.01 (0.69, 1.47)	0.95 (0.57, 1.58)	0.85	0.95 (0.55, 1.64)

* 1 serving avocado = ½ avocado; ½ serving = ¼ avocado. † Thrombotic or embolic occlusion of a cerebral artery. ‡ Subarachnoid and intraparenchymal hemorrhage.

Model 2 was adjusted for: age (years); race (White or other [Black, American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander]); ancestry (Southern European/ Mediterranean, other Caucasian/Scandinavian, other); alcohol intake (0, 0.1 to 4.9, 5.0 to 9.9, 10.0 to 14.9, and ≥15.0 g/day); smoking status (never, former, current smoker 1 to 14 cigarettes per day, 15 to 24 cigarettes per day; or ≥25 cigarettes per day); physical activity (<3.0, 3.0 to 8.9, 9.0 to 17.9, 18.0 to 26.9, ≥27.0 MET–h/week); family history of diabetes (yes, no); family history of myocardial infarction (yes, no); family history of cancer (yes, no); baseline diabetes mellitus (yes, no); baseline hypertension or antihypertensive medication use (yes, no); baseline hypercholesterolemia or cholesterol-lowering medication use (yes, no); multivitamin use (yes, no); aspirin use (yes, no); in women, postmenopausal status and menopausal hormone use (premenopausal, postmenopausal [no, past, or current hormone use]); total energy intake (kcal/day); and BMI kg/m^2. Model 3 was additionally

adjusted for red and processed meat, fruits and vegetables (excluding avocado), nuts, soda (caloric and low or noncaloric), whole grains, eggs, tortilla (whole and chips), breads, cheese intakes (in quintiles; tortilla in tertiles in NHS), and trans-fat. Results were pooled with the use of the fixed-effects model.

Table S6. Subgroup Analyses for Risk of Coronary Heart Disease and Stroke According to Avocado Intake*.

CHD†			Stroke‡		
	Pooled Adjusted HR (95% CI)	**p Value for Interaction**		**Pooled Adjusted HR (95% CI)**	**p Value for Interaction**
Sex			**Sex**		
Women, n=4,132§	0.74 (0.55, 0.98)	0.78	Women, n=3,682§	1.03 (0.80, 1.33)	0.46
Men, n=5,053	0.70 (0.58, 0.85)		Men, n=1,608	0.89 (0.64, 1.22)	
Age, years			**Age, years**		
<65, n=2,484	0.92 (0.66, 1.30)	0.08	<65, n=1,073	1.04 (0.62, 1.74)	0.77
≥65, n=6,701	0.69 (0.57, 0.82)		≥65, n=4,217	0.97 (0.78, 1.21)	
BMI, kg/m^2			**BMI, kg/m^2**		
<25, n=4,744	0.76 (0.62, 0.94)	0.55	<25, n=2,685	0.87 (0.66, 1.13)	0.19
≥25, n=4,441	0.67 (0.52, 0.87)		≥25, n=2,605	1.14 (0.85, 1.54)	
Ancestry			**Ancestry**		
Mediterranean and Other Caucasian, n=8,287	0.74 (0.63, 0.87)	0.03	Mediterranean and Other Caucasian, n=4,597	0.95 (0.77, 1.17)	0.90
All Other, including Hispanic, n=898	0.37 (0.18, 0.76)		All Other, including Hispanic, n=693	1.15 (0.62, 2.11)	
Family history of myocardial infarction			**Family history of myocardial infarction**		
No, n=5,212	0.69 (0.56, 0.85)	0.73	No, n=3,111	0.85 (0.66, 1.11)	0.28
Yes, n=3,973	0.75 (0.59, 0.97)		Yes, n=2,179	1.20 (0.88, 1.64)	
AHEI			**AHEI**		
Below median, n=5,032	0.78 (0.60, 1.02)	0.24	Below median, n=2,632	1.04 (0.72, 1.50)	0.82
Above median, n=4,153	0.71 (0.58, 0.88)		Above median, n=2,658	0.96 (0.76, 1.22)	
Total fruit intake			**Total fruit intake**		
Below median, n=4,117	0.65 (0.49, 0.87)	0.53	Below median, n=2,445	1.00 (0.72, 1.40)	0.91
Above median, n=5,068	0.76 (0.63, 0.92)		Above median, n=2,845	0.98 (0.77, 1.26)	
Total vegetable intake			**Total vegetable intake**		
Below median, n=4,456	0.79 (0.60, 1.06)	0.39	Below median, n=2,414	0.67 (0.43, 1.02)	0.09
Above median, n=4,729	0.71 (0.58, 0.86)		Above median, n=2,876	1.15 (0.92, 1.44)	
Green vegetable intake			**Green vegetable intake**		
Below median, n=4,901	0.73 (0.56, 0.95)	0.57	Below median, n=2,857	0.85 (0.60, 1.19)	0.64
Above median, n=4,284	0.73 (0.60, 0.90)		Above median, n=2,433	1.05 (0.82, 1.35)	
Lettuce vegetable intake			**Lettuce vegetable intake**		
Below median, n=4,909	0.76 (0.59, 0.97)	0.38	Below median, n=2,781	0.86 (0.62, 1.19)	0.79
Above median, n=4,276	0.70 (0.56, 0.86)		Above median, n=2,509	1.07 (0.83, 1.39)	

* 1 serving avocado = ½ avocado; ½ serving = ¼ avocado. † CHD = coronary heart disease: Fatal and nonfatal myocardial infarction. ‡ Fatal and nonfatal stroke. § n= number of cases per subgroup. HRs for ½ a serving/day (1/4 avocado) increase in avocado intake in each subgroup category. Multivariable model was adjusted for the following: age (years); race (White or other [Black, American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander]); ancestry (Southern European/Mediterranean, other Caucasian/Scandinavian, other); alcohol intake (0, 0.1 to 4.9, 5.0 to 9.9, 10.0 to 14.9, and ≥15.0 g/day); smoking status (never, former, current smoker 1 to 14 cigarettes per day, 15 to 24 cigarettes per day; or ≥2 cigarettes per day); physical activity (<3.0, 3.0 to 8.9, 9.0 to 17.9, 18.0 to 26.9, ≥27.0 MET–h/week); family history of diabetes (yes, no); family history of myocardial infarction (yes, no); family history of cancer (yes, no); baseline diabetes mellitus (yes, no); baseline hypertension or antihypertensive medication use (yes, no); baseline hypercholesterolemia or cholesterol-lowering medication use (yes, no); multivitamin use (yes, no); aspirin use (yes, no); postmenopausal status and menopausal hormone use (premenopausal, postmenopausal [no, past, or current hormone use], in women only); total energy intake (kcal/day);body mass index (kg/m^2, continuous); red and processed meat, fruits and vegetables (excluding avocado), nuts, soda (caloric and low or noncaloric), whole grains, eggs, tortilla (whole and chips), breads, cheese intakes (all in quintiles; tortilla in tertiles in NHS); and trans-fat, except the stratified factor. AHEI = Alternative Healthy Eating Index score.

Table S7. Risk of Cardiovascular Events According to Categories of Avocado Intake* without Stop Updating Diet for Chronic Disease Diagnosis in Two Large US Cohorts.

	HR (95% CI)					
	Never or less than 1 per month	1-3 per month	1 per week	≥2 per week	P value for trend	HR (95% CI) for 1/2 serving (1/4 avocado)-Increase in Avocado Intake per day
CVD†						
Health Professionals Follow-Up Study						
No. cases/person-years	5,076/702,080	1,117/176,523	282/49,201	186/27,947		
Age-adjusted Model 1	1.00	0.91 (0.85, 0.98)	0.84 (0.74, 0.94)	0.81 (0.71, 0.94)	<0.0001	0.73 (0.63, 0.86)
Multivariable Model 2	1.00	0.97 (0.91, 1.04)	0.93 (0.83, 1.05)	0.89 (0.77, 1.02)	0.05	0.86 (0.74, 1.00)
Multivariable Model 3	1.00	0.96 (0.89, 1.03)	0.92 (0.82, 1.04)	0.89 (0.78, 1.03)	0.06	0.86 (0.73, 1.00)
Nurses' Health Study I						
No. cases/person-years	6,407/1,473,683	831/212,466	257/60,263	118/28,780		
Age-adjusted Model 1	1.00	0.89 (0.83, 0.96)	0.96 (0.85, 1.08)	0.89 (0.76, 1.05)	0.03	0.83 (0.70, 0.99)
Multivariable Model 2	1.00	0.99 (0.92, 1.07)	1.08 (0.96, 1.22)	1.03 (0.88, 1.21)	0.47	1.07 (0.90, 1.26)
Multivariable Model 3	1.00	0.97 (0.89, 1.04)	1.05 (0.93, 1.18)	1.01 (0.86, 1.18)	0.87	1.01 (0.85, 1.21)
Pooled						
Age-adjusted Model 1	1.00	0.89 (0.84, 0.94)	0.84 (0.76, 0.92)	0.80 (0.71, 0.90)	<0.0001	0.76 (0.67, 0.86)
Multivariable Model 2	1.00	0.97 (0.92, 1.02)	1.02 (0.93, 1.11)	0.88 (0.79, 0.98)	0.39	0.95 (0.84, 1.07)
Multivariable Model 3	1.00	0.96 (0.91, 1.02)	1.00 (0.91, 1.10)	0.94 (0.83, 1.05)	0.24	0.93 (0.82, 1.05)
CHD‡						
Health Professionals Follow-Up Study						
No. cases/person-years	3,872/703,191	843/176,758	203/49,258	135/27,993		
Age-adjusted Model 1	1.00	0.90 (0.83, 0.97)	0.83 (0.73, 0.95)	0.77 (0.66, 0.91)	<0.0001	0.69 (0.58, 0.83)
Multivariable Model 2	1.00	0.97 (0.90, 1.05)	0.95 (0.83, 1.08)	0.86 (0.73, 1.01)	0.04	0.83 (0.70, 0.99)
Multivariable Model 3	1.00	0.96 (0.88, 1.04)	0.94 (0.82, 1.08)	0.87 (0.74, 1.03)	0.06	0.84 (0.70, 1.01)
Nurses' Health Study I						
No. cases/person-years	3,530/1,475,581	436/212,727	114/60,357	52/28,818		
Age-adjusted Model 1	1.00	0.82 (0.74, 0.91)	0.85 (0.71, 1.01)	0.75 (0.59, 0.95)	0.004	0.63 (0.48, 0.81)
Multivariable Model 2	1.00	0.96 (0.86, 1.06)	1.00 (0.84, 1.19)	0.92 (0.72, 1.17)	0.44	0.91 (0.71, 1.16)
Multivariable Model 3	1.00	0.94 (0.84, 1.04)	0.98 (0.82, 1.17)	0.91 (0.71, 1.15)	0.31	0.87 (0.67, 1.13)
Pooled						
Age-adjusted Model 1	1.00	0.87 (0.82, 0.92)	0.84 (0.75, 0.93)	0.77 (0.67, 0.88)	<0.0001	0.67 (0.58, 0.77)
Multivariable Model 2	1.00	0.96 (0.91, 1.03)	0.97 (0.87, 1.07)	0.88 (0.77, 1.00)	0.04	0.86 (0.74, 0.99)
Multivariable Model 3	1.00	0.95 (0.89, 1.01)	0.96 (0.86, 1.07)	0.88 (0.77, 1.01)	0.03	0.85 (0.73, 0.99)
Stroke§						
Health Professionals Follow-Up Study						
No. cases/person-years	1,204/704,059	274/176,971	79/49,317	51/27,999		
Age-adjusted Model 1	1.00	0.97 (0.85, 1.11)	0.85 (0.67, 1.08)	0.94 (0.72, 1.23)	0.41	0.88 (0.65, 1.19)
Multivariable Model 2	1.00	0.99 (0.87, 1.14)	0.89 (0.70, 1.12)	0.99 (0.75, 1.29)	0.69	0.94 (0.70, 1.27)

Multivariable Model 3	1.00	0.97 (0.84, 1.12)	0.87 (0.68, 1.10)	0.96 (0.73, 1.25)	0.52	0.90 (0.66, 1.23)
Nurses' Health Study I						
No. cases/person-years	3,046/1,475,539	421/212,662	147/60,321	68/28,802		
Age-adjusted Model 1	1.00	0.99 (0.89, 1.10)	1.05 (0.89, 1.24)	1.05 (0.85, 1.30)	0.59	1.07 (0.85, 1.33)
Multivariable Model 2	1.00	1.04 (0.94, 1.16)	1.12 (0.95, 1.32)	1.14 (0.92, 1.40)	0.11	1.21 (0.96, 1.51)
Multivariable Model 3	1.00	1.01 (0.91, 1.12)	1.08 (0.91, 1.28)	1.09 (0.88, 1.36)	0.31	1.13 (0.89, 1.43)
Pooled						
Age-adjusted Model 1	1.00	0.98 (0.91, 1.07)	0.98 (0.86, 1.12)	1.01 (0.85, 1.19)	0.95	0.99 (0.83, 1.19)
Multivariable Model 2	1.00	1.02 (0.94, 1.11)	1.04 (0.90, 1.19)	1.07 (0.91, 1.27)	0.29	1.10 (0.92, 1.32)
Multivariable Model 3	1.00	0.99 (0.91, 1.08)	1.01 (0.88, 1.15)	1.04 (0.88, 1.23)	0.67	1.04 (0.86, 1.26)

[*] 1 serving avocado = ½ avocado; ½ serving = ¼ avocado. [†] CVD = cardiovascular disease: Fatal and nonfatal myocardial infarction plus fatal and nonfatal stroke. [‡] CHD = coronary heart disease: Fatal and nonfatal myocardial infarction. [§] Fatal and nonfatal stroke.

Model 2 was adjusted for: age (years); race (White or other [Black, American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander]); ancestry (Southern European/Mediterranean, other Caucasian/Scandinavian, other); alcohol intake (0, 0.1 to 4.9, 5.0 to 9.9, 10.0 to 14.9, and ≥15.0 g/day); smoking status (never, former, current smoker 1 to 14 cigarettes per day, 15 to 24 cigarettes per day; or ≥25 cigarettes per day); physical activity (<3.0, 3.0 to 8.9, 9.0 to 17.9, 18.0 to 26.9, ≥27.0 MET–h/week); family history of diabetes (yes, no); family history of myocardial infarction (yes, no); family history of cancer (yes, no); baseline diabetes mellitus (yes, no); baseline hypertension or antihypertensive medication use (yes, no); baseline hypercholesterolemia or cholesterol-lowering medication use (yes, no); multivitamin use (yes, no); aspirin use (yes, no); in women, postmenopausal status and menopausal hormone use (premenopausal, postmenopausal [no, past, or current hormone use]); total energy intake (kcal/day); and BMI kg/m^2. Model 3 was additionally adjusted for red and processed meat, fruits and vegetables (excluding avocado), nuts, soda (caloric and low or noncaloric), whole grains, eggs, tortilla (whole and chips), breads, cheese intakes (in quintiles; tortilla in tertiles in NHS), and trans-fat. Results were pooled with the use of the fixed-effects model.

Table S8. Risk of Cardiovascular Events According to Categories of the Average Intake* of the Last Two Dietary Measurements of Avocado in Two Large US Cohorts.

	HR (95% CI)					
	Never or less than 1 per month	1-3 times per month	1 per week	≥2 per week	P value for trend	HR (95% CI) for 1/2 serving (1/4 avocado)-Increase in Avocado Intake per day
CVD†						
Health Professionals Follow-Up Study						
No. cases/person-years	4,827/657,003	1,277/205,874	328/58,796	229/34,077		
Age-adjusted Model 1	1.00	0.92 (0.86, 0.97)	0.80 (0.72, 0.90)	0.82 (0.72, 0.94)	<0.0001	0.73 (0.63, 0.85)
Multivariable Model 2	1.00	0.98 (0.92, 1.04)	0.89 (0.80, 1.00)	0.90 (0.78, 1.02)	0.03	0.85 (0.73, 0.99)
Multivariable Model 3	1.00	0.93 (0.87, 0.99)	0.84 (0.75, 0.94)	0.84 (0.74, 0.97)	0.0008	0.77 (0.66, 0.90)
Nurses' Health Study I						
No. cases/person-years	6,245/1,429,788	974/251,487	252/57,717	142/36,200		
Age-adjusted Model 1	1.00	0.88 (0.82, 0.94)	0.95 (0.84, 1.08)	0.74 (0.63, 0.87)	<0.0001	0.64 (0.53, 0.78)
Multivariable Model 2	1.00	0.98 (0.91, 1.05)	1.08 (0.95, 1.22)	0.86 (0.72, 1.01)	0.12	0.86 (0.71, 1.04)
Multivariable Model 3	1.00	0.94 (0.88, 1.01)	1.03 (0.91, 1.17)	0.83 (0.70, 0.98)	0.02	0.79 (0.65, 0.97)
Pooled						
Age-adjusted Model 1	1.00	0.90 (0.86, 0.94)	0.87 (0.80, 0.94)	0.79 (0.71, 0.87)	<0.0001	0.70 (0.62, 0.78)
Multivariable Model 2	1.00	0.98 (0.93, 1.02)	0.97 (0.89, 1.06)	0.88 (0.79, 0.98)	0.009	0.85 (0.76, 0.96)
Multivariable Model 3	1.00	0.93 (0.89, 0.98)	0.92 (0.84, 1.00)	0.84 (0.75, 0.93)	<0.0001	0.75 (0.66, 0.86)
CHD‡						
Health Professionals Follow-Up Study						
No. cases/person-years	3,694/658,045	956/206,151	240/58,865	163/34,139		
Age-adjusted Model 1	1.00	0.90 (0.84, 0.96)	0.77 (0.68, 0.88)	0.77 (0.66, 0.90)	<0.0001	0.66 (0.55, 0.79)
Multivariable Model 2	1.00	0.97 (0.90, 1.04)	0.88 (0.77, 1.00)	0.85 (0.72, 0.99)	0.01	0.80 (0.67, 0.95)
Multivariable Model 3	1.00	0.92 (0.86, 0.99)	0.82 (0.72, 0.94)	0.80 (0.68, 0.94)	0.0004	0.72 (0.60, 0.87)
Nurses' Health Study I						
No. cases/person-years	3,448/1,431,618	505/251,810	113/57,811	66/36,244		
Age-adjusted Model 1	1.00	0.83 (0.76, 0.91)	0.78 (0.64, 0.94)	0.64 (0.50, 0.82)	<0.0001	0.48 (0.35, 0.64)
Multivariable Model 2	1.00	0.97 (0.88, 1.07)	0.93 (0.77, 1.13)	0.79 (0.62, 1.01)	0.04	0.74 (0.56, 0.98)
Multivariable Model 3	1.00	0.93 (0.85, 1.03)	0.90 (0.74, 1.08)	0.77 (0.60, 0.98)	0.01	0.69 (0.52, 0.93)
Pooled						
Age-adjusted Model 1	1.00	0.87 (0.82, 0.92)	0.77 (0.70, 0.86)	0.73 (0.64, 0.83)	<0.0001	0.61 (0.52, 0.71)
Multivariable Model 2	1.00	0.97 (0.92, 1.03)	0.89 (0.80, 1.00)	0.83 (0.73, 0.95)	0.001	0.78 (0.68, 0.91)
Multivariable Model 3	1.00	0.92 (0.87, 0.98)	0.85 (0.76, 0.94)	0.79 (0.69, 0.91)	<0.0001	0.71 (0.61, 0.83)
Stroke§						
Health Professionals Follow-Up Study						
No. cases/person-years	1,133/658,877	321/206,398	88/58,929	66/34,142		
Age-adjusted Model 1	1.00	0.98 (0.86, 1.11)	0.90 (0.73, 1.12)	0.99 (0.77, 1.27)	0.71	0.95 (0.72, 1.25)

Multivariable Model 2	1.00	1.00 (0.88, 1.13)	0.94 (0.76, 1.17)	1.04 (0.81, 1.33)	0.93	1.01 (0.77, 1.34)
Multivariable Model 3	1.00	0.95 (0.84, 1.08)	0.88 (0.71, 1.10)	0.96 (0.75, 1.25)	0.54	0.91 (0.68, 1.22)
Nurses' Health Study I						
No. cases/person-years	2,963/1,431,588	497/251,730	144/57,776	78/36,230		
Age-adjusted Model 1	1.00	0.95 (0.86, 1.04)	1.14 (0.96, 1.35)	0.84 (0.69, 1.05)	0.18	0.84 (0.64, 1.08)
Multivariable Model 2	1.00	1.00 (0.90, 1.10)	1.21 (1.02, 1.43)	0.91 (0.72, 1.14)	0.78	0.96 (0.74, 1.25)
Multivariable Model 3	1.00	0.96 (0.87, 1.06)	1.16 (0.97, 1.37)	0.86 (0.69, 1.09)	0.33	0.87 (0.67, 1.14)
Pooled						
Age-adjusted Model 1	1.00	0.96 (0.89, 1.03)	1.04 (0.91, 1.19)	0.90 (0.76, 1.07)	0.21	0.89 (0.73, 1.07)
Multivariable Model 2	1.00	1.00 (0.92, 1.08)	1.10 (0.96, 1.26)	0.96 (0.81, 1.14)	0.88	0.99 (0.82, 1.19)
Multivariable Model 3	1.00	0.96 (0.89, 1.04)	1.04 (0.91, 1.20)	0.91 (0.76, 1.08)	0.26	0.89 (0.73, 1.09)

[*] 1 serving avocado = ½ avocado; ½ serving = ¼ avocado. [†] CVD = cardiovascular disease: Fatal and nonfatal myocardial infarction plus fatal and nonfatal stroke. [‡] CHD = coronary heart disease: Fatal and nonfatal myocardial infarction. [§] Fatal and nonfatal stroke.

Model 2 was adjusted for: age (years); race (White or other [Black, American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander]); ancestry (Southern European/Mediterranean, other Caucasian/Scandinavian, other); alcohol intake (0, 0.1 to 4.9, 5.0 to 9.9, 10.0 to 14.9, and ≥15.0 g/day); smoking status (never, former, current smoker 1 to 14 cigarettes per day, 15 to 24 cigarettes per day; or ≥25 cigarettes per day); physical activity (<3.0, 3.0 to 8.9, 9.0 to 17.9, 18.0 to 26.9, ≥27.0 MET–h/week); family history of diabetes (yes, no); family history of myocardial infarction (yes, no); family history of cancer (yes, no); baseline diabetes mellitus (yes, no); baseline hypertension or antihypertensive medication use (yes, no); baseline hypercholesterolemia or cholesterol-lowering medication use (yes, no); multivitamin use (yes, no); aspirin use (yes, no); in women, postmenopausal status and menopausal hormone use (premenopausal, postmenopausal [no, past, or current hormone use]); total energy intake (kcal/day); and BMI kg/m^2. Model 3 was additionally adjusted for red and processed meat, fruits and vegetables (excluding avocado), nuts, soda (caloric or low or noncaloric), whole grains, eggs, tortilla (whole and chips), breads, cheese intakes (in quintiles; tortilla in tertiles in NHS), and trans-fat. Results were pooled with the use of the fixed-effects model.

Table S9. Risk of Cardiovascular Events According to Categories of the Average Intake* adjusting for MUFA intake in Two Large US Cohorts.

	HR (95% CI)					
	Never or less than 1 per month	1-3 times per month	1 per week	≥2 per week	P value for trend	HR (95% CI) for 1/2 serving (1/4 avocado)-Increase in Avocado Intake per day
CVD†						
Health Professionals Follow-Up Study						
No. cases/person-years	5,076/702,080	1,117/176,523	282/49,201	186/27,947		
Age-adjusted Model 1	1.00	0.95 (0.89, 1.01)	0.83 (0.74, 0.94)	0.82 (0.71, 0.95)	0.0004	0.75 (0.64, 0.88)
Multivariable Model 2	1.00	1.00 (0.93, 1.07)	0.92 (0.81, 1.04)	0.88 (0.76, 1.03)	0.06	0.86 (0.73, 1.01)
Multivariable Model 3	1.00	0.92 (0.86, 0.99)	0.84 (0.74, 0.95)	0.81 (0.69, 0.94)	0.0003	0.73 (0.62, 0.87)
Nurses' Health Study I						
No. cases/person-years	6,407/1,473,683	831/212,466	257/60,263	118/28,780		
Age-adjusted Model 1	1.00	0.93 (0.86, 1.00)	0.93 (0.82, 1.05)	0.79 (0.66, 0.95)	0.002	0.74 (0.61, 0.89)
Multivariable Model 2	1.00	1.02 (0.95, 1.10)	1.05 (0.93, 1.19)	0.91 (0.76, 1.10)	0.67	0.96 (0.80, 1.16)
Multivariable Model 3	1.00	0.99 (0.92, 1.07)	1.03 (0.91, 1.17)	0.92 (0.76, 1.10)	0.48	0.93 (0.77, 1.13)
Pooled						
Age-adjusted Model 1	1.00	0.94 (0.89, 0.98)	0.88 (0.81, 0.96)	0.81 (0.72, 0.91)	<0.0001	0.74 (0.66, 0.84)
Multivariable Model 2	1.00	1.01 (0.96, 1.06)	0.98 (0.90, 1.07)	0.90 (0.80, 1.00)	0.09	0.90 (0.80, 1.02)
Multivariable Model 3	1.00	0.95 (0.91, 1.00)	0.93 (0.85, 1.01)	0.85 (0.75, 0.95)	0.001	0.81 (0.71, 0.92)
CHD‡						
Health Professionals Follow-Up Study						
No. cases/person-years	3,872/703,245	843/176,760	203/49,258	135/27,995		
Age-adjusted Model 1	1.00	0.93 (0.86, 1.00)	0.79 (0.68, 0.91)	0.78 (0.66, 0.93)	0.0001	0.69 (0.57, 0.83)
Multivariable Model 2	1.00	0.99 (0.92, 1.07)	0.88 (0.76, 1.02)	0.85 (0.71, 1.01)	0.03	0.81 (0.67, 0.97)
Multivariable Model 3	1.00	0.92 (0.85, 0.99)	0.81 (0.70, 0.93)	0.78 (0.65, 0.93)	0.0002	0.69 (0.57, 0.84)
Nurses' Health Study I						
No. cases/person-years	3,530/1,475,581	436/212,727	114/60,357	52/28,818		
Age-adjusted Model 1	1.00	0.88 (0.80, 0.97)	0.76 (0.63, 0.91)	0.65 (0.49, 0.86)	<0.0001	0.53 (0.40, 0.70)
Multivariable Model 2	1.00	1.02 (0.92, 1.13)	0.91 (0.75, 1.09)	0.80 (0.60, 1.05)	0.09	0.79 (0.60, 1.03)
Multivariable Model 3	1.00	0.98 (0.88, 1.09)	0.89 (0.73, 1.07)	0.81 (0.61, 1.06)	0.07	0.76 (0.57, 1.02)
Pooled						
Age-adjusted Model 1	1.00	0.91 (0.86, 0.97)	0.78 (0.69, 0.87)	0.74 (0.64, 0.86)	<0.0001	0.63 (0.54, 0.74)
Multivariable Model 2	1.00	1.00 (0.94, 1.06)	0.89 (0.79, 1.00)	0.83 (0.72, 0.96)	0.005	0.80 (0.69, 0.94)
Multivariable Model 3	1.00	0.94 (0.88, 1.00)	0.83 (0.74, 0.94)	0.79 (0.68, 0.91)	<0.0001	0.71 (0.61, 0.84)
Stroke§						
Health Professionals Follow-Up Study						
No. cases/person-years	1,204/704,059	274/176,971	79/49,317	51/27,999		
Age-adjusted Model 1	1.00	0.99 (0.87, 1.13)	0.99 (0.78, 1.24)	0.96 (0.72, 1.27)	0.73	0.95 (0.70, 1.29)
Multivariable Model 2	1.00	1.01 (0.89, 1.16)	1.03 (0.82, 1.30)	1.00 90.75, 1.32)	0.94	1.01 (0.75, 1.37)
Multivariable Model 3	1.00	0.96 (0.83, 1.10)	0.95 (0.75, 1.20)	0.90 (0.67, 1.20)	0.38	0.87 (0.63, 1.19)

Nurses' Health Study I	3,046/1,475,539	421/212,662	147/60,321	68/28,802		
No. cases/person-years						
Age-adjusted Model 1	1.00	0.99 (0.89, 1.10)	1.11 (0.94, 1.31)	0.94 (0.74, 1.19)	0.93	0.99 (0.77, 1.26)
Multivariable Model 2	1.00	1.04 (0.93, 1.15)	1.18 (1.00, 1.40)	1.02 (0.80, 1.30)	0.34	1.13 (0.88, 1.44)
Multivariable Model 3	1.00	1.02 (0.91, 1.13)	1.16 (0.98, 1.38)	1.02 (0.80, 1.31)	0.45	1.11 (0.85, 1.43)
Pooled						
Age-adjusted Model 1	1.00	0.99 (0.91, 1.07)	1.06 (0.93, 1.22)	0.94 (0.79, 1.13)	0.78	0.97 (0.80, 1.18)
Multivariable Model 2	1.00	1.03 (0.95, 1.11)	1.13 (0.98, 1.29)	1.01 (0.84, 1.21)	0.43	1.08 (0.89, 1.31)
Multivariable Model 3	1.00	0.99 (0.91, 1.08)	1.08 (0.94, 1.24)	0.97 (0.80, 1.17)	0.97	1.00 (0.82, 1.23)

[*] 1 serving avocado = ½ avocado; ½ serving = ¼ avocado. [†] CVD = cardiovascular disease: Fatal and nonfatal myocardial infarction plus fatal and nonfatal stroke. [‡] CHD = coronary heart disease: Fatal and nonfatal myocardial infarction. [§] Fatal and nonfatal stroke.

Model 2 was adjusted for: age (years); race (White or other [Black, American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander]); ancestry (Southern European/Mediterranean, other Caucasian/Scandinavian, other); alcohol intake (0, 0.1 to 4.9, 5.0 to 9.9, 10.0 to 14.9, and ≥15.0 g/day); smoking status (never, former, current smoker 1 to 14 cigarettes per day, 15 to 24 cigarettes per day; or ≥25 cigarettes per day); physical activity (<3.0, 3.0 to 8.9, 9.0 to 17.9, 18.0 to 26.9, ≥27.0 MET–h/week); family history of diabetes (yes, no); family history of myocardial infarction (yes, no); family history of cancer (yes, no); baseline diabetes mellitus (yes, no); baseline hypertension or antihypertensive medication use (yes, no); baseline hypercholesterolemia or cholesterol-lowering medication use (yes, no); multivitamin use (yes, no); aspirin use (yes, no); in women, postmenopausal status and menopausal hormone use (premenopausal, postmenopausal [no, past, or current hormone use]); total energy intake (kcal/day); and BMI kg/m^2. Model 3 was additionally adjusted for red and processed meat, fruits and vegetables (excluding avocado), nuts, soda (caloric and low or noncaloric), whole grains, eggs, tortilla (whole and chips), breads, cheese intakes (in quintiles; tortilla in tertiles in NHS); trans-fat; and monounsaturated fat. Results were pooled with the use of the fixed-effects model.

Table S10. Risk of Cardiovascular Events According to Cumulative Average Intake* of Avocado in Two Large US Cohorts.

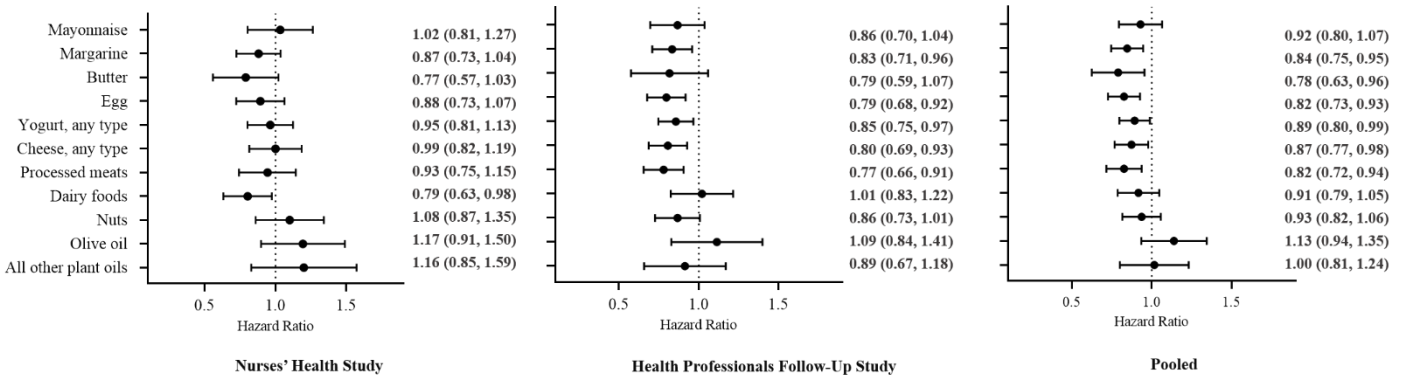
	HR (95% CI)					
	Never or less than 1 per month	1-3 times per month	1 per week	≥2 per week	P value for trend	HR (95% CI) for 1/2 serving (1/4 avocado)-Increase in Avocado Intake per day
CVD†						
Health Professionals Follow-Up Study						
No. cases/person-years	4,426/607,620	1,636/253,769	378/65,362	221/28,998		
Age-adjusted Model 1	1.00	0.89 (0.84, 0.95)	0.78 (0.70, 0.86)	0.88 (0.76, 1.00)	<0.0001	0.63 (0.50, 0.79)
Multivariable Model 2	1.00	0.96 (0.90, 1.01)	0.85 (0.77, 0.95)	0.94 (0.82, 1.08)	0.03	0.79 (0.63, 0.98)
Multivariable Model 3	1.00	1.00 (0.94, 1.06)	0.90 (0.81, 1.00)	1.00 (0.87, 1.15)	0.51	0.93 (0.74, 1.16)
Nurses' Health Study I						
No. cases/person-years	5,921/1,377,071	1,259/298,057	279/63,575	154/36,490		
Age-adjusted Model 1	1.00	0.89 (0.84, 0.95)	0.91 (0.80, 1.02)	0.77 (0.65, 0.90)	<0.0001	0.58 (0.45, 0.74)
Multivariable Model 2	1.00	1.00 (0.93, 1.06)	1.03 (0.91, 1.16)	0.87 (0.74, 1.02)	0.19	0.85 (0.66, 1.08)
Multivariable Model 3	1.00	0.94 (0.80, 1.10)	0.97 (0.80, 1.17)	0.82 (0.66, 1.03)	0.14	0.77 (0.54, 1.09)
Pooled						
Age-adjusted Model 1	1.00	0.89 (0.86, 0.93)	0.83 (0.77, 0.90)	0.83 (0.75, 0.92)	<0.0001	0.60 (0.51, 0.71)
Multivariable Model 2	1.00	0.97 (0.93, 1.02)	0.93 (0.85, 1.00)	0.91 (0.82, 1.01)	0.01	0.81 (0.69, 0.96)
Multivariable Model 3	1.00	0.99 (0.94, 1.05)	0.91 (0.83, 1.00)	0.95 (0.84, 1.07)	0.18	0.88 (0.73, 1.06)
CHD‡						
Health Professionals Follow-Up Study						
No. cases/person-years	3,394/608,581	1,224/254,122	272/65,450	163/29,046		
Age-adjusted Model 1	1.00	0.88 (0.82, 0.94)	0.73 (0.65, 0.83)	0.85 (0.72, 0.99)	<0.0001	0.66 (0.43, 0.73)
Multivariable Model 2	1.00	0.95 (0.89, 1.01)	0.82 (0.72, 0.93)	0.91 (0.78, 1.07)	0.02	0.73 (0.56, 0.94)
Multivariable Model 3	1.00	0.99 (0.93, 1.06)	0.87 (0.76, 0.98)	0.97 (0.83, 1.14)	0.27	0.86 (0.66, 1.12)
Nurses' Health Study I						
No. cases/person-years	3,290/1,378,803	640/298,471	134/63,673	68/36,536		
Age-adjusted Model 1	1.00	0.83 (0.76, 0.90)	0.80 (0.67, 0.95)	0.63 (0.49, 0.80)	<0.0001	0.36 (0.25, 0.52)
Multivariable Model 2	1.00	0.97 (0.89, 1.06)	0.96 (0.81, 1.14)	0.75 (0.59, 0.96)	0.02	0.66 (0.46, 0.94)
Multivariable Model 3	1.00	0.91 (0.74, 1.13)	0.86 (0.66, 1.08)	0.68 (0.50, 0.93)	0.02	0.54 (0.32, 0.91)
Pooled						
Age-adjusted Model 1	1.00	0.86 (0.82, 0.90)	0.75 (0.68, 0.83)	0.77 (0.68, 0.88)	<0.0001	0.48 (0.39, 0.60)
Multivariable Model 2	1.00	0.96 (0.91, 1.01)	0.86 (0.78, 0.96)	0.86 (0.75, 0.98)	0.001	0.70 (0.57, 0.87)
Multivariable Model 3	1.00	0.98 (0.92, 1.05)	0.86 (0.77, 0.97)	0.90 (0.78, 1.04)	0.04	0.79 (0.62, 0.99)
Stroke§						
Health Professionals Follow-Up Study						
No. cases/person-years	1,032/609,381	412/254,394	106/65,511	58/29,060		
Age-adjusted Model 1	1.00	0.95 (0.85, 1.07)	0.92 (0.75, 1.13)	0.98 (0.75, 1.27)	0.56	0.88 (0.57, 1.36)
Multivariable Model 2	1.00	0.98 (0.87, 1.10)	0.95 (0.78, 1.17)	1.03 (0.79, 1.34)	0.95	0.99 (0.64, 1.52)
Multivariable Model 3	1.00	1.02 (0.90, 1.14)	1.00 (0.82, 1.23)	1.10 (0.84, 1.44)	0.52	1.16 (0.75, 1.79)

Nurses' Health Study I						
No. cases/person-years	2,7941,378,805	64/298,357	149/63,642	90/36,519		
Age-adjusted Model 1	1.00	0.96 (0.88, 1.05)	1.01 (0.86, 1.20)	0.93 (0.75, 1.15)	0.45	0.88 (0.64, 1.22)
Multivariable Model 2	1.00	1.02 (0.93, 1.11)	1.08 (0.91, 1.27)	0.99 (0.80, 1.23)	0.74	1.06 (0.76, 1.47)
Multivariable Model 3	1.00	1.06 (0.84, 1.33)	1.16 (0.88, 1.51)	1.07 (0.79, 1.45)	0.84	1.05 (0.66, 1.68)
Pooled						
Age-adjusted Model 1	1.00	0.96 (0.90, 1.03)	0.97 (0.86, 1.11)	0.95 (0.80, 1.12)	0.34	0.88 (0.68, 1.14)
Multivariable Model 2	1.00	1.00 (0.93, 1.07)	1.03 (0.90, 1.17)	1.01 (0.85, 1.19)	0.82	1.03 (0.79, 1.34)
Multivariable Model 3	1.00	1.02 (0.92, 1.14)	1.06 (0.90, 1.24)	1.09 (0.89, 1.33)	0.54	1.11 (0.80, 1.52)

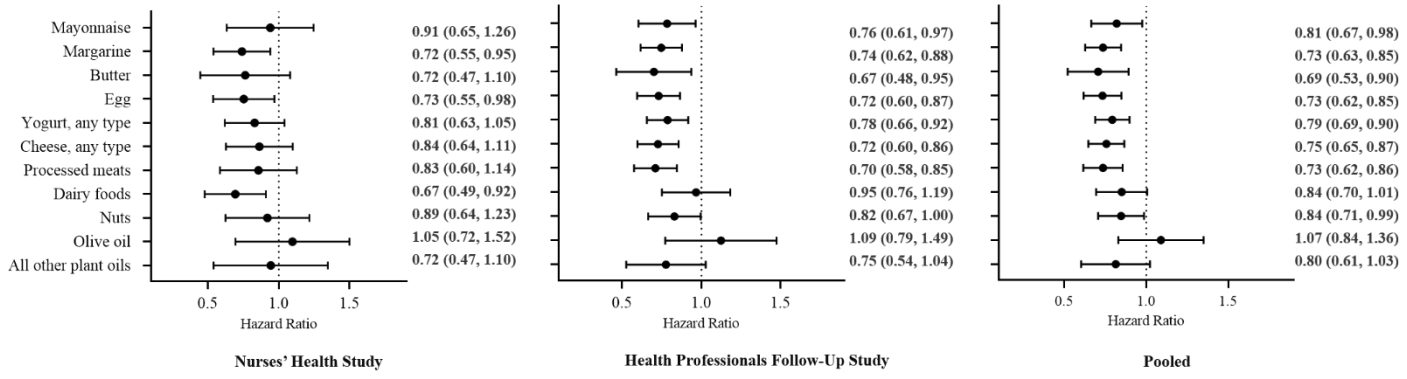
[*] 1 serving avocado = ½ avocado; ½ serving = ¼ avocado. [†] CVD = cardiovascular disease: Fatal and nonfatal myocardial infarction plus fatal and nonfatal stroke. [‡] CHD = coronary heart disease: Fatal and nonfatal myocardial infarction. [§] Fatal and nonfatal stroke.

Model 2 was adjusted for: age (years); race (White or other [Black, American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander]); ancestry (Southern European/Mediterranean, other Caucasian/Scandinavian, other); alcohol intake (0, 0.1 to 4.9, 5.0 to 9.9, 10.0 to 14.9, and ≥15.0 g/day); smoking status (never, former, current smoker 1 to 14 cigarettes per day, 15 to 24 cigarettes per day; or ≥25 cigarettes per day); physical activity (<3.0, 3.0 to 8.9, 9.0 to 17.9, 18.0 to 26.9, ≥27.0 MET–h/week); family history of diabetes (yes, no); family history of myocardial infarction (yes, no); family history of cancer (yes, no); baseline diabetes mellitus (yes, no); baseline hypertension or antihypertensive medication use (yes, no); baseline hypercholesterolemia or cholesterol-lowering medication use (yes, no); multivitamin use (yes, no); aspirin use (yes, no); in women, postmenopausal status and menopausal hormone use (premenopausal, postmenopausal [no, past, or current hormone use]); total energy intake (kcal/day); and BMI kg/m^2. Model 3 was additionally adjusted for red and processed meat, fruits and vegetables (excluding avocado), nuts, soda (caloric or low or noncaloric), whole grains, eggs, tortilla (whole and chips), breads, cheese intakes (in quintiles; tortilla in tertiles in NHS), and trans-fat. Results were pooled with the use of the fixed-effects model.

Cardiovascular Disease



Coronary Heart Disease



Stroke

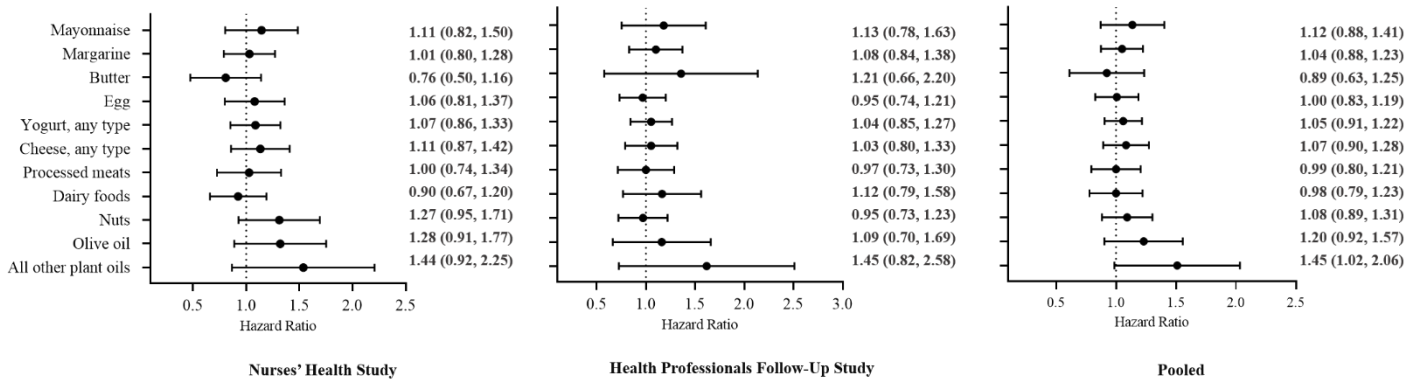


Figure S1. Hazard Ratios for Cardiovascular Events Associated with Substitution of Half A Serving of Avocado for Equivalent Amounts of Other Fat-Containing Food Sources in Two Large US Cohorts. Nurses' Health Study, Health Professional Follow-Up Study, and pooled hazard ratios (HRs) for cardiovascular disease, coronary heart disease, and stroke associated with substitution of ½ serving/day (1/4 avocado) of avocado for equivalent amounts of other fat-containing foods. Multivariate-adjusted models were adjusted for the following: age (years); race (White or other [Black, American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander]); ancestry (Southern European/Mediterranean, other Caucasian/Scandinavian, all other); alcohol intake (0, 0.1 to 4.9, 5.0 to 9.9, 10.0 to 14.9, and ≥15.0 g/day); smoking status (never, former, current smoker 1 to 14 cigarettes per day, 15 to 24 cigarettes per day; or ≥2 cigarettes per day); physical activity (<3.0, 3.0 to 8.9, 9.0 to 17.9, 18.0 to 26.9, ≥27.0 MET–h/week); family history of diabetes (yes, no); family history of myocardial infarction (yes, no); family history of cancer (yes, no); baseline diabetes mellitus (yes, no); baseline hypertension or antihypertensive medication use (yes, no); baseline hypercholesterolemia or cholesterol-lowering medication use (yes, no); multivitamin use (yes, no); aspirin use (yes, no); postmenopausal status and menopausal hormone use (premenopausal, postmenopausal [no, past, or current hormone use]), only in women; total energy intake (kcal/day); body mass index (kg/m2, continuous), red and processed meat, fruits and vegetables (excluding avocado), nuts, soda (caloric and low or noncaloric), whole grains, eggs, tortilla (whole and chips), breads, cheese intakes (all in quintiles; tortillas in tertiles in NHS); trans-fat, and mutually adjusted for other types of fat-containing foods. Results were pooled with the use of the fixed-effects model. Horizontal lines represent 95% confidence intervals (CIs).