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ORIGINAL INVESTIGATIONS

Healthful and Unhealthful Plant-Based Diets and the Risk of Coronary Heart Disease in U.S. Adults

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ABSTRACT

BACKGROUND Plant-based diets are recommended for coronary heart disease (CHD) prevention. However, not all plant foods are necessarily beneficial for health.

OBJECTIVES This study sought to examine associations between plant-based diet indices and CHD incidence.

METHODS We included 73,710 women in NHS (Nurses' Health Study) (1984 to 2012), 92,329 women in NHS2 (1991 to 2013), and 43,259 men in Health Professionals Follow-up Study (1986 to 2012), free of chronic diseases at baseline. We created an overall plant-based diet index (PDI) from repeated semiquantitative food-frequency questionnaire data, by assigning positive scores to plant foods and reverse scores to animal foods. We also created a healthful plant-based diet index (hPDI) where healthy plant foods (whole grains, fruits/vegetables, nuts/legumes, oils, tea/coffee) received positive scores, whereas less-healthy plant foods (juices/sweetened beverages, refined grains, potatoes/fries, sweets) and animal foods received reverse scores. To create an unhealthful PDI (uPDI), we gave positive scores to less-healthy plant foods and reverse scores to animal and healthy plant foods.

RESULTS Over 4,833,042 person-years of follow-up, we documented 8,631 incident CHD cases. In pooled multivariable analysis, higher adherence to PDI was independently inversely associated with CHD (hazard ratio [HR] comparing extreme deciles: 0.92; 95% confidence interval [CI]: 0.83 to 1.01; p trend = 0.003). This inverse association was stronger for hDPI (HR: 0.75; 95% CI: 0.68 to 0.83; p trend <0.001). Conversely, uPDI was positively associated with CHD (HR: 1.32; 95% CI: 1.20 to 1.46; p trend <0.001).

CONCLUSIONS Higher intake of a plant-based diet index rich in healthier plant foods is associated with substantially lower CHD risk, whereas a plant-based diet index that emphasizes less-healthy plant foods is associated with higher CHD risk. (J Am Coll Cardiol 2017;70:411–22) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CHD = coronary heart disease

CI = confidence interval

hPDI = healthful plant-based diet index

HR = hazard ratio

PDI = overall plant-based diet index

SSB = sugar-sweetened beverages

uPDI = unhealthful plant-based diet index

Plant-based diets have been associated with a lower risk of various diseases (1–3), including coronary heart disease (CHD) (4–9), the leading global cause of death (10). However, these studies suffer from key limitations. With the exception of a recent investigation (3), prior studies (4–9) have defined plant-based diets as "vegetarian" diets, which constitute a family of dietary patterns that exclude some or all animal foods. As recommendations based on incremental dietary changes are easier to adopt, it is important to understand how gradual reductions in animal food intake with concomitant increases in consumption of plant foods affect cardiovascular health. Additionally, in studies of vegetarian diets, all plant foods are treated equally, even though certain plant foods, such as refined grains and sugar-sweetened beverages (SSB) are associated with higher cardiometabolic risk (11–13).

SEE PAGE 423

To overcome these limitations, we have created 3 versions of plant-based diet indices using a graded approach: an overall plant-based diet index (PDI), which emphasizes consumption of all plant food while reducing animal food intake; a healthful plant-based diet index (hPDI), which emphasizes intake of healthy plant foods associated with improved health outcomes such as whole grains, fruits, and vegetables; and an unhealthful plant-based diet index (uPDI), which emphasizes consumption of less healthy plant foods known to be associated with a higher risk of several diseases (14). In 3 U.S. cohorts, we previously documented that the PDI was inversely associated with type 2 diabetes risk with a stronger inverse association for hPDI and a positive association for uPDI (14). In the present study, we examined the associations of these plant-based diet indices with CHD incidence in more than 200,000 male and female health professionals in the United States.

METHODS

STUDY POPULATION. The NHS (Nurses' Health Study) started in 1976 with 121,701 female registered nurses (ages 30 to 55 years), the NHS2 started in 1989 with 116,686 female registered nurses (ages 25 to 42 years), and the HPFS (Health Professionals Follow-Up Study) started in 1986 with 51,529 male health professionals (ages 40 to 75 years). Participants receive a follow-up questionnaire every 2 years on lifestyle, health behaviors, and medical history, with a response rate of ~90% at each cycle. Participants with CHD at baseline were excluded. Participants with cancer (except nonmelanoma skin cancer), stroke, and coronary artery surgery at baseline were also excluded, as diagnosis with these conditions can change diet. Lastly, individuals with implausible energy intake at baseline (<600 or >3,500 kcal/day for women and <800 or >4,200 kcal/day for men) were excluded. The final baseline sample included 73,710 women in NHS, 92,329 women in NHS2, and 43,259 men in HPFS (1984 for NHS, 1991 for NHS2, and 1986 for HPFS).

Study protocols for all cohorts were approved by the institutional review boards of Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health; completion of the self-administered questionnaire was considered to imply informed consent.

DIETARY ASSESSMENT AND THE PLANT-BASED DIET INDICES. Dietary data were collected using a semi-quantitative food frequency questionnaire every 2 to 4 years. Participants were asked how often, on average, they consumed a defined portion of ~130 food items over the previous year. There were 9 response categories ranging from "never or less than once/month" to "≥6 times/day." The reliability and validity of the questionnaires have been described previously (15–18).

Using this dietary data, we created 3 versions of a plant-based diet for each food frequency questionnaire cycle for each cohort: PDI; hPDI; and uPDI (14). We created 18 food groups based on nutrient and culinary similarities within the larger categories of healthy plant foods, less healthy plant foods, and animal foods (**Table 1**). Given that alcoholic beverages have different directions of association for various health outcomes, and margarine's fatty acid composition has changed over time from high trans to high unsaturated fats, we did not include these foods in the indices, but adjusted for them in the analysis. Food groups were ranked into quintiles and given positive or reverse scores. With positive scores, participants above the highest quintile of a food group received a score of 5, following on through to participants below the lowest quintile who received a score of 1. With reverse scores, this pattern of scoring was inversed. For creating PDI, plant food groups were given positive scores, and animal food groups were given reverse scores. For creating hPDI, positive scores were given to healthy plant food groups and reverse scores to less healthy plant food groups and animal food groups. Finally, for uPDI, positive scores were given to less healthy plant food groups and

TABLE 1 Examples of Food Items Constituting the 18 Food Groups (From the 1984 NHS FFQ)

		PDI	hPDI	uPDI
Plant Food Groups				
Healthy				
Whole grains	Whole grain breakfast cereal, other cooked breakfast cereal, cooked oatmeal, dark bread, brown rice, other grains, bran, wheat germ, popcorn	Positive scores	Positive scores	Reverse scores
Fruits	Raisins or grapes, prunes, bananas, cantaloupe, watermelon, fresh apples or pears, oranges, grapefruit, strawberries, blueberries, peaches or apricots or plums	Positive scores	Positive scores	Reverse scores
Vegetables	Tomatoes, tomato juice, tomato sauce, broccoli, cabbage, cauliflower, brussels sprouts, carrots, mixed vegetables, yellow or winter squash, eggplant or zucchini, yams or sweet potatoes, spinach cooked, spinach raw, kale or mustard or chard greens, iceberg or head lettuce, romaine or leaf lettuce, celery, mushrooms, beets, alfalfa sprouts, garlic, corn	Positive scores	Positive scores	Reverse scores
Nuts	Nuts, peanut butter	Positive scores	Positive scores	Reverse scores
Legumes	String beans, tofu or soybeans, beans or lentils, peas or lima beans	Positive scores	Positive scores	Reverse scores
Vegetable oils	Oil-based salad dressing, vegetable oil used for cooking	Positive scores	Positive scores	Reverse scores
Tea and coffee	Tea, coffee, decaffeinated coffee	Positive scores	Positive scores	Reverse scores
Less healthy				
Fruit juices	Apple cider (nonalcoholic) or juice, orange juice, grapefruit juice, other fruit juice	Positive scores	Reverse scores	Positive scores
Refined grains	Refined grain breakfast cereal, white bread, English muffins or bagels or rolls, muffins or biscuits, white rice, pancakes or waffles, crackers, pasta	Positive scores	Reverse scores	Positive scores
Potatoes	French fries, baked or mashed potatoes, potato or corn chips	Positive scores	Reverse scores	Positive scores
Sugar sweetened beverages	Colas with caffeine and sugar, colas without caffeine but with sugar, other carbonated beverages with sugar, noncarbonated fruit drinks with sugar	Positive scores	Reverse scores	Positive scores
Sweets and desserts	Chocolates, candy bars, candy without chocolate, cookies (home-baked and ready-made), brownies, doughnuts, cake (home-baked and ready-made), sweet roll (home-baked and ready-made), pie (home-baked and ready-made), jams or jellies or preserves or syrup or honey	Positive scores	Reverse scores	Positive scores
Animal Food Groups				
Animal fat	Butter added to food, butter or lard used for cooking	Reverse scores	Reverse scores	Reverse scores
Dairy	Skim low fat milk, whole milk, cream, sour cream, sherbet, ice cream, yogurt, cottage or ricotta cheese, cream cheese, other cheese	Reverse scores	Reverse scores	Reverse scores
Egg	Eggs	Reverse scores	Reverse scores	Reverse scores
Fish or seafood	Canned tuna, dark meat fish, other fish, shrimp or lobster or scallops	Reverse scores	Reverse scores	Reverse scores
Meat	Chicken or turkey with skin, chicken or turkey without skin, bacon, hot dogs, processed meats, liver, hamburger, beef or pork or lamb mixed dish, beef or pork or lamb main dish	Reverse scores	Reverse scores	Reverse scores
Miscellaneous animal-based foods	Pizza, chowder or cream soup, mayonnaise or other creamy salad dressing	Reverse scores	Reverse scores	Reverse scores

FFQ = food frequency questionnaire; hPDI = healthful plant-based diet index; NHS = Nurses' Health Study; PDI = overall plant-based diet index; uPDI = unhealthful plant-based diet index.

reverse scores to healthy plant food groups and animal food groups. The 18 food group scores were summed to obtain the indices. Higher intake of all indices reflected lower animal food intake (e.g., 5 to 6 vs. 3 servings/day comparing extreme PDI deciles).

OUTCOME ASCERTAINMENT. CHD was defined as nonfatal myocardial infarction and fatal CHD. Participants self-reporting newly diagnosed CHD on the biennial questionnaires were asked permission to access their medical records to confirm diagnosis, which was done through blinded review by study physicians. To confirm diagnosis of nonfatal myocardial infarction, we used the World Health Organization criteria (19) of the presence of typical symptoms plus either elevated enzymes or diagnostic electrocardiographic findings. Cases that required hospital admission and were confirmed by interview or letter but for which medical records were unobtainable were included in the analysis as "probable."

Reports from next of kin or postal authorities were used to identify deaths, in addition to searching the National Death Index. Classification of CHD as the cause of death was done by examining autopsy reports, hospital records, or death certificates, using International Classification of Diseases-8th and -9th Revisions (20). CHD deaths were considered confirmed if fatal CHD was established through

TABLE 2 HR (95% CI) for CHD According to Deciles of the PDI

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6
Nurses' Health Study						
Median	45.3	48.7	50.7	52.2	53.7	55.0
Cases/PY	354/187,576	345/182,392	342/188,258	295/175,859	352/200,856	272/183,715
Age-adjusted	1.00	0.96 (0.83–1.11)	0.92 (0.80–1.07)	0.83 (0.71–0.97)	0.86 (0.75–1.00)	0.71 (0.61–0.84)
Multivariable adjusted	1.00	1.02 (0.88–1.18)	1.04 (0.90–1.21)	0.97 (0.83–1.13)	1.01 (0.87–1.18)	0.88 (0.75–1.03)
Nurses' Health Study 2						
Median	45.0	48.5	50.7	52.3	53.8	55.0
Cases/PY	91/195,183	75/194,826	75/204,890	73/197,879	63/187,964	67/202,075
Age-adjusted	1.00	0.84 (0.62–1.15)	0.77 (0.57–1.05)	0.78 (0.58–1.07)	0.67 (0.48–0.92)	0.69 (0.51–0.95)
Multivariable adjusted	1.00	0.95 (0.70–1.29)	0.91 (0.67–1.24)	0.95 (0.69–1.29)	0.80 (0.58–1.12)	0.89 (0.64–1.23)
Health Professionals Follow-Up Study						
Median	45.0	48.0	50.4	52.0	54.0	55.3
Cases/PY	492/86,581	441/87,892	409/88,955	471/97,460	434/86,993	449/94,437
Age-adjusted	1.00	0.90 (0.79–1.02)	0.80 (0.70–0.91)	0.83 (0.73–0.94)	0.86 (0.75–0.97)	0.81 (0.71–0.92)
Multivariable adjusted	1.00	0.97 (0.85–1.10)	0.88 (0.77–1.01)	0.91 (0.80–1.04)	0.98 (0.86–1.12)	0.92 (0.81–1.05)
Pooled Results (Fixed-Effects Model)						
Age-adjusted	1.00	0.92 (0.84–1.01)	0.85 (0.78–0.94)	0.83 (0.76–0.91)	0.85 (0.78–0.93)	0.77 (0.70–0.84)
Multivariable adjusted	1.00	0.99 (0.91–1.09)	0.96 (0.87–1.05)	0.94 (0.86–1.04)	0.99 (0.90–1.08)	0.91 (0.83–1.00)

Multivariable adjusted model: adjusted for age (yrs); smoking status (never, past, current [1 to 14, 15 to 24, or ≥25 cigarettes/day]); physical activity (<3, 3 to 8.9, 9 to 17.9, 18 to 26.9, or ≥27 metabolic equivalent task h/week); alcohol intake (0, 0.1 to 4.9, 5 to 9.9, 10 to 14.9, or ≥15 g/day); multivitamin use (yes/no); aspirin use (yes/no); family history of CHD (yes/no); margarine intake (quintiles); energy intake (quintiles); baseline hypertension, hypercholesterolemia, and diabetes (yes/no); and updated body mass index (<21, 21 to 22.9, 23 to 24.9, 25 to 26.9, 27 to 29.9, 30 to 32.9, 33 to 34.9, 35 to 39.9, or ≥40 kg/m^2). Also adjusted for post-menopausal hormone use in NHS and NHS2 (pre-menopausal, post-menopausal current, past or never user), and for oral contraceptive use in NHS2 (never, past, or current user). *The p value when we assigned the median value to each decile and entered this as a continuous variable in the model. †The p value for Q-statistic for heterogeneity <0.05, indicating statistically significant heterogeneity in HR among the 3 studies. ‡I^2 statistic = 60% to 69%. §I^2 statistic = 80% to 89%.

CHD = coronary heart disease; CI = confidence interval(s); HR = hazard ratio(s); PY = person-years; other abbreviations as in Table 1.

Continued on the next page

medical records or autopsy reports or if CHD was listed as the cause of death on the death certificate with prior medical record of CHD. If CHD was listed as the cause of death on the death certificate, but medical records were unavailable and no prior knowledge of CHD existed, the CHD death was included in the analysis as "probable."

ASSESSMENT OF COVARIATES. We obtained updated information on participants' smoking status, multivitamin use, CHD family history, and physical activity through self-report on the biennial questionnaires. Among women, updated information was assessed on menopausal status, post-menopausal hormone use, and oral contraceptive use (NHS2 only). Self-reported data on height were collected at baseline, with updated information on weight assessed every 2 years through the questionnaires. We also collected updated information on self-reported diagnosis of diseases such as hypertension, hypercholesterolemia, and diabetes, and on medication use.

STATISTICAL ANALYSIS. We used Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CIs) evaluating, separately, the associations of deciles of each index with CHD. Person-time was calculated from questionnaire return date until CHD diagnosis, death, or end of follow-up (June 30, 2012, in NHS; June 30, 2013, in NHS2; and January 1, 2012, in HPFS). We used age (in years) as the time scale, with stratification by calendar time (in 2-year intervals). We adjusted for time-varying covariates including smoking status, alcohol intake, physical activity, CHD family history, multivitamin use, aspirin use, energy intake, margarine intake, body mass index (BMI), post-menopausal status and hormone use (women), and oral contraceptive use (NHS2). We additionally adjusted for baseline self-reported hypertension, hypercholesterolemia, and diabetes.

Indices were cumulatively averaged over follow-up to better capture long-term diet; for instance, for the 2001 to 2003 risk set, plant-based diet index scores in 1991, 1995, and 1999 were averaged to predict CHD risk. Because diagnosis of conditions such as type 2 diabetes, stroke, and cancer could change an individual's diet and potentially be associated with the underlying risk of CHD, we stopped updating diet on

TABLE 2 Continued

Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10-U	p Trend*
Nurses' Health Study					
56.5	58.0	60.0	63.5		
337/192,344	298/184,899	326/190,404	312/190,640		
0.82 (0.70–0.95)	0.74 (0.64–0.87)	0.78 (0.67–0.90)	0.70 (0.60–0.82)	0.81 (0.76–0.87)	<0.001
0.97 (0.83–1.13)	0.92 (0.79–1.09)	0.95 (0.81–1.12)	0.87 (0.74–1.03)	0.92 (0.85–0.98)	0.04
Nurses' Health Study 2					
56.8	58.5	60.7	64.0		
56/215,822	51/201,307	60/200,824	56/199,175		
0.54 (0.39–0.76)	0.51 (0.36–0.71)	0.59 (0.43–0.82)	0.54 (0.39–0.75)	0.69 (0.60–0.79)	<0.001
0.71 (0.50–1.01)	0.66 (0.46–0.95)	0.80 (0.56–1.13)	0.77 (0.54–1.11)	0.81 (0.70–0.95)	0.02
Health Professionals Follow-Up Study					
57.0	58.5	60.8	64.2		
369/80,989	435/89,147	397/92,546	463/92,145		
0.73 (0.64–0.84)	0.79 (0.69–0.90)	0.69 (0.60–0.79)	0.79 (0.70–0.90)	0.88 (0.84–0.92)	<0.001
0.85 (0.74–0.98)	0.91 (0.80–1.04)	0.82 (0.71–0.94)	0.95 (0.83–1.09)	0.96 (0.90–1.01)	0.10
Pooled Results (Fixed-Effects Model)					
0.76 (0.69–0.84)	0.75 (0.68–0.82)	0.71 (0.65–0.78)	0.75†‡ (0.68–0.82)	0.84†§ (0.81–0.87)	<0.001†§
0.90 (0.82–0.99)	0.90 (0.82–0.99)	0.87 (0.79–0.96)	0.92 (0.83–1.01)	0.93 (0.90–0.97)	0.003

diagnosis of these conditions. Values of other covariates were updated every 2 years to account for changes over time. A continuous variable for each index was created by assigning the median value to each decile and conducting tests for linear trend. To examine potential deviation from linearity, we fit restricted cubic splines to the fully adjusted model with the indices entered as continuous variables. The proportional hazards assumption was tested by including interaction terms between the indices, and age and calendar year. We examined potential effect modification by sex, BMI, physical activity, family history of CHD, and smoking status. We also evaluated the independent associations of the 3 food categories that constituted the diet indices (healthy plant foods, less healthy plant foods, animal foods) with CHD risk by entering all 3 simultaneously into the model in place of the diet indices. We also created a healthy omnivorous diet, by assigning positive scores to healthy plant foods and healthy animal foods (dairy products [except ice cream], egg, fish), and reverse scores to less healthy plant foods and less healthy animal foods (animal fat, ice cream, meat, miscellaneous animal-based foods). The analysis was carried out separately for each cohort and combined using a fixed-effects model; heterogeneity was examined using the Cochrane Q statistic (21) and the I^2 statistic (22). All analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina), and statistical significance was set at a 2-tailed p value of <0.05.

RESULTS

At baseline, the indices ranged from a median of 42 to 44 in the lowest decile, to 66 to 68 in the highest decile (Online Table 1). Participants with higher scores on PDI and hPDI were older, more active, leaner, and less likely to smoke than were participants with lower scores. Conversely, high consumers of uPDI were younger, less active, and more likely to smoke than were low consumers. The proportion of participants with a history of diabetes decreased with increasing deciles of PDI and uPDI, but increased with higher hPDI intake. Animal food intake ranged from 5 to 6 servings per day in the highest decile to 3 to 4 servings per day in the lowest decile of the indices.

Over 4,833,042 person-years of follow-up, 8,631 participants developed CHD (3,233 cases over 1,876,942 person-years in NHS; 667 cases over 1,999,945 person-years in NHS2; and 4,731 cases over 956,155 person-years in HPFS). In the pooled fully adjusted model, PDI was modestly inversely associated with CHD incidence (HR comparing extreme

TABLE 3 HR (95% CI) for CHD According to Deciles of the hPDI

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6
Nurses' Health Study						
Median	44.3	48.0	50.5	52.4	54.0	55.8
Cases/PY	359/188,352	323/186,140	327/190,716	327/187,664	313/183,877	322/191,819
Age-adjusted	1.00	0.85 (0.73–0.99)	0.80 (0.69–0.93)	0.78 (0.67–0.91)	0.74 (0.64–0.86)	0.71 (0.61–0.83)
Multivariable adjusted	1.00	0.91 (0.78–1.06)	0.90 (0.77–1.05)	0.88 (0.75–1.02)	0.87 (0.74–1.01)	0.83 (0.71–0.97)
Nurses' Health Study 2						
Median	44.0	48.0	50.5	52.3	54.0	55.8
Cases/PY	79/203,121	72/192,054	78/220,042	61/187,944	76/207,405	70/201,138
Age-adjusted	1.00	0.90 (0.66–1.24)	0.87 (0.64–1.19)	0.74 (0.53–1.03)	0.84 (0.61–1.15)	0.76 (0.55–1.05)
Multivariable adjusted	1.00	0.98 (0.71–1.35)	0.97 (0.71–1.34)	0.85 (0.60–1.19)	0.98 (0.71–1.35)	0.87 (0.62–1.21)
Health Professionals Follow-Up Study						
Median	43.0	47.2	50.0	52.0	53.8	55.5
Cases/PY	413/88,274	452/89,330	404/92,920	486/93,019	425/88,417	448/89,543
Age-adjusted	1.00	0.96 (0.84–1.10)	0.84 (0.73–0.96)	0.95 (0.83–1.08)	0.84 (0.74–0.97)	0.86 (0.75–0.98)
Multivariable adjusted	1.00	0.99 (0.87–1.14)	0.87 (0.76–1.00)	0.99 (0.86–1.13)	0.89 (0.78–1.03)	0.91 (0.79–1.04)
Pooled Results (Fixed-Effects Model)						
Age-adjusted	1.00	0.90 (0.82–0.99)	0.82 (0.74–0.90)	0.86 (0.78–0.94)	0.79 (0.72–0.87)	0.78 (0.71–0.85)
Multivariable adjusted	1.00	0.95 (0.86–1.04)	0.88 (0.80–0.97)	0.92 (0.84–1.01)	0.88 (0.80–0.97)	0.86 (0.78–0.95)

Multivariable adjusted model: adjusted for age (yrs); smoking status (never, past, current [1 to 14, 15 to 24, or ≥25 cigarettes/day]); physical activity (<3, 3 to 8.9, 9 to 17.9, 18 to 26.9, or ≥27 metabolic equivalent task h/week); alcohol intake (0, 0.1 to 4.9, 5 to 9.9, 10 to 14.9, or ≥15 g/day); multivitamin use (yes/no); aspirin use (yes/no); family history of CHD (yes/no); margarine intake (quintiles); energy intake (quintiles); baseline hypertension, hypercholesterolemia, and diabetes (yes/no); and updated body mass index (<21, 21 to 22.9, 23 to 24.9, 25 to 26.9, 27 to 29.9, 30 to 32.9, 33 to 34.9, 35 to 39.9, or ≥40 kg/m^2). Also adjusted for post-menopausal hormone use in NHS and NHS2 (pre-menopausal, post-menopausal current, past or never user), and for oral contraceptive use in NHS2 (never, past, or current user). *The p value when we assigned the median value to each decile and entered this as a continuous variable in the model. †The p value for Q-statistic for heterogeneity <0.05, indicating statistically significant heterogeneity in HR among the 3 studies. ‡I^2 statistic = 80% to 89%. §I^2 statistic = 70% to 79%.

Abbreviations as in Tables 1 and 2.

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deciles: 0.92; 95% CI: 0.83 to 1.01; HR per 10-U increase: 0.93; 95% CI: 0.90 to 0.97; p trend = 0.003) (Table 2). When we analyzed hPDI (Table 3) and uPDI (Table 4) separately, we found a stronger inverse association between hPDI and CHD incidence (HR comparing extreme deciles: 0.75; 95% CI: 0.68 to 0.83; HR per 10-U increase: 0.88; 95% CI: 0.85 to 0.91; p trend <0.001) and a positive association for uPDI (HR comparing extreme deciles: 1.32; 95% CI: 1.20 to 1.46; HR per 10-U increase: 1.10; 95% CI: 1.06 to 1.14; p trend <0.001). The association of uPDI with CHD was nonlinear (p for test of curvature = 0.01; p for nonlinear association <0.001) (**Central Illustration**, panel A, and Online Figure 1). We found no evidence of deviation from linearity for PDI and hPDI (p for test of curvature >0.20 for both; p for linearity = 0.001 for PDI, and <0.001 for hPDI). Further adjustment for ethnicity, marital status, recent physical exam, diet beverage intake, and indicators of socioeconomic status did not appreciably alter the results (pooled HR for extreme deciles of [PDI: 0.93; 95% CI: 0.84 to 1.03; p trend = 0.01; hPDI: 0.76; 95% CI: 0.69 to 0.84; p trend <0.001; uPDI: 1.30; 95% CI: 1.18 to 1.44; p trend <0.001]).

The associations of hPDI and uPDI with risk of CHD were consistently observed across strata defined by age, BMI, family history of CHD, and sex (Figure 1). Associations of both indices were significantly stronger among more active relative to less active participants (p interaction = 0.002 for both); the association of uPDI with CHD was slightly stronger among ever smokers compared with never smokers (p interaction = 0.04). There was no evidence of significant effect modification by calendar year in any of the cohorts for hPDI or uPDI (all p values for interaction >0.20).

When, in place of the indices, we entered variables for the 3 food categories together into the fully adjusted model, we found an inverse association for healthy plant foods, and positive associations for animal foods and less healthy plant foods (**Central Illustration**, panel B, Online Figure 1, and Online Table 2). To quantify the benefit of hPDI that was due to lower intake of red meat or SSB, we individually adjusted for these foods in the final model. The results were largely unchanged on red meat adjustment: (pooled HR for extreme deciles of PDI: 0.93; 95% CI: 0.84 to 1.03; p trend = 0.01;

TABLE 3 Continued

Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10-U	p Trend*
		Nurses' Health Study			
57.5	59.3	61.7	65.5		
306/188,145	330/187,373	322/184,367	304/188,490		
0.66 (0.57–0.77)	0.70 (0.60–0.81)	0.66 (0.57–0.77)	0.57 (0.49–0.67)	0.80 (0.75–0.84)	<0.001
0.76 (0.65–0.90)	0.83 (0.71–0.98)	0.78 (0.67–0.92)	0.68 (0.57–0.80)	0.86 (0.81–0.91)	<0.001
		Nurses' Health Study 2			
57.3	59.2	61.6	65.6		
60/196,640	65/199,695	62/192,381	44/199,524		
0.67 (0.47–0.93)	0.67 (0.48–0.93)	0.65 (0.47–0.91)	0.42 (0.29–0.61)	0.72 (0.64–0.81)	<0.001
0.78 (0.55–1.11)	0.80 (0.57–1.13)	0.77 (0.54–1.09)	0.53 (0.36–0.79)	0.79 (0.69–0.90)	0.001
		Health Professionals Follow-Up Study			
57.2	59.2	62.0	66.0		
425/89,922	431/85,604	424/91,479	452/88,635		
0.79 (0.69–0.90)	0.82 (0.72–0.94)	0.74 (0.65–0.85)	0.77 (0.67–0.88)	0.88 (0.84–0.92)	<0.001
0.84 (0.73–0.97)	0.89 (0.77–1.02)	0.80 (0.70–0.93)	0.84 (0.73–0.97)	0.90 (0.86–0.95)	<0.001
		Pooled Results (Fixed-Effects Model)			
0.72 (0.66–0.79)	0.75 (0.68–0.82)	0.70 (0.63–0.76)	0.66†‡ (0.60–0.73)	0.84†‡ (0.81–0.86)	<0.001†‡
0.80 (0.73–0.88)	0.85 (0.77–0.94)	0.79 (0.71–0.87)	0.75†§ (0.68–0.83)	0.88 (0.85–0.91)	<0.001

hPDI: 0.76; 95% CI: 0.68 to 0.84; p trend <0.001; uPDI: 1.32; 95% CI: 1.19 to 1.46; p trend <0.001) and changed in expected directions with SSB adjustment (pooled HR for extreme deciles of PDI: 0.90; 95% CI: 0.81 to 0.99; p trend = 0.001; hPDI: 0.79; 95% CI: 0.71 to 0.88; p trend <0.001; uPDI: 1.22; 95% CI: 1.10 to 1.36; p trend = 0.005). Given the previously observed inverse association between fish intake and CHD (23), we modified hPDI to score fish intake positively and found similar results (pooled HR for extreme deciles: 0.74; 95% CI: 0.67 to 0.81; p trend <0.001). The results were slightly attenuated when we modified hPDI to score healthy animal foods positively (dairy except ice cream, egg, and fish) (pooled HR comparing extreme deciles: 0.78; 95% CI: 0.71 to 0.86; HR per 10-U increase: 0.91; 95% CI: 0.89 to 0.94; p trend <0.001).

SENSITIVITY ANALYSES. The associations of PDI, hPDI, and uPDI with risk of CHD did not vary based on how we modeled diet. For example, we found similar results when we continuously updated the indices throughout follow-up, used baseline values of the indices, used the most recent index scores before CHD diagnosis, and stopped updating the indices once intermediate conditions such as hypertension and hypercholesterolemia developed (Online Table 3). When we created the plant-based diet indices with quintiles of energy-adjusted food groups (instead of with quintiles of unadjusted food groups as we had originally done), the association of PDI with CHD became slightly stronger, but that of uPDI with CHD was slightly attenuated (Online Table 4). Removing potential intermediates (BMI and aspirin use) from the model strengthened the association of PDI with CHD (pooled HR for extreme deciles of PDI: 0.86; 95% CI: 0.78 to 0.95; p trend <0.001; hPDI: 0.73; 95% CI: 0.66 to 0.81; p trend <0.001; uPDI: 1.27; 95% CI: 1.15 to 1.40; p trend <0.001). Adjustment for additional potential intermediates in the causal pathway, (updated history of hypertension, hypercholesterolemia, and diabetes instead of baseline history) slightly attenuated associations of hPDI and uPDI with CHD (pooled HR for extreme deciles of PDI: 0.92; 95% CI: 0.83 to 1.02; p trend = 0.003; hPDI: 0.80; 95% CI: 0.73 to 0.89; p trend <0.001; uPDI: 1.24; 95% CI: 1.12 to 1.37; p trend = 0.001; proportion of the association with hPDI explained by these intermediates ranged from 9.5% in NHS to 4.9% in HPFS, with all p < 0.01). Finally, the results did not change when we excluded participants who had diabetes at baseline (pooled HR for extreme deciles of PDI: 0.93; 95% CI: 0.84 to 1.03; p trend = 0.002; hPDI: 0.74; 95% CI: 0.66 to 0.82; p trend <0.001; uPDI: 1.35; 95% CI: 1.21

TABLE 4 HR (95% CI) for CHD According to Deciles of the uPDI

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6
Nurses' Health Study						
Median	43.5	47.6	50.0	52.0	53.7	55.5
Cases/PY	274/187,546	311/195,345	359/177,785	267/183,572	343/191,298	334/191,430
Age-adjusted	1.00	1.12 (0.95–1.32)	1.41 (1.20–1.65)	1.03 (0.87–1.22)	1.28 (1.10–1.51)	1.26 (1.07–1.47)
Multivariable adjusted	1.00	1.20 (1.02–1.41)	1.52 (1.30–1.78)	1.13 (0.96–1.34)	1.41 (1.20–1.66)	1.36 (1.16–1.61)
Nurses' Health Study 2						
Median	43.5	47.5	50.0	52.0	54.0	56.0
Cases/PY	52/205,047	77/197,734	65/198,432	71/214,560	58/196,690	71/205,961
Age-adjusted	1.00	1.57 (1.10–2.23)	1.35 (0.93–1.94)	1.49 (1.04–2.13)	1.26 (0.87–1.83)	1.52 (1.06–2.17)
Multivariable adjusted	1.00	1.67 (1.17–2.38)	1.45 (1.01–2.10)	1.56 (1.09–2.25)	1.29 (0.88–1.89)	1.59 (1.10–2.30)
Health Professionals Follow-Up Study						
Median	44.0	48.0	50.0	52.0	54.0	55.6
Cases/PY	456/90,508	454/90,758	415/86415	409/89,136	461/92,660	449/89,599
Age-adjusted	1.00	1.01 (0.89–1.15)	1.02 (0.89–1.16)	0.98 (0.86–1.12)	1.10 (0.97–1.26)	1.11 (0.97–1.26)
Multivariable adjusted	1.00	1.04 (0.92–1.19)	1.07 (0.94–1.22)	1.05 (0.91–1.20)	1.18 (1.04–1.35)	1.15 (1.01–1.32)
Pooled Results (Fixed-Effects Model)						
Age-adjusted	1.00	1.09 (0.99–1.20)	1.17†‡ (1.07–1.29)	1.05 (0.95–1.15)	1.17 (1.07–1.29)	1.18 (1.08–1.30)
Multivariable adjusted	1.00	1.14†‖ (1.04–1.25)	1.24†‡ (1.13–1.37)	1.12 (1.01–1.23)	1.26 (1.14–1.39)	1.25 (1.13–1.37)

Multivariable adjusted model: adjusted for age (yrs); smoking status (never, past, current [1 to 14, 15 to 24, or ≥25 cigarettes/day]); physical activity (<3, 3 to 8.9, 9 to 17.9, 18 to 26.9, or ≥27 metabolic equivalent task h/week); alcohol intake (0, 0.1 to 4.9, 5 to 9.9, 10 to 14.9, or ≥15 g/day); multivitamin use (yes/no); aspirin use (yes/no); family history of CHD (yes/no); margarine intake (quintiles); energy intake (quintiles); baseline hypertension, hypercholesterolemia, and diabetes (yes/no); and updated body mass index (<21, 21 to 22.9, 23 to 24.9, 25 to 26.9, 27 to 29.9, 30 to 32.9, 33 to 34.9, 35 to 39.9, or ≥40 kg/m^2). Also adjusted for post-menopausal hormone use in NHS and NHS2 (pre-menopausal, post-menopausal current, past or never user), and for oral contraceptive use in NHS2 (never, past, or current user). *The p value when we assigned the median value to each decile and entered this as a continuous variable in the model. †The p value for Q-statistic for heterogeneity <0.05, indicating statistically significant heterogeneity in HR among the 3 studies. ‡I^2 statistic = 80% to 89%. §I^2 statistic = 70% to 79%. ‖I^2 statistic = 60% to 69%.

Abbreviations as in Tables 1 and 2.

Continued on the next page

to 1.50; p trend <0.001) or when we pooled results across the cohorts using a random-effects model (pooled HR for extreme deciles of PDI: 0.92; 95% CI: 0.83 to 1.01; p trend = 0.01; hPDI: 0.71; 95% CI: 0.57 to 0.88; p trend <0.001; uPDI: 1.40; 95% CI: 1.13 to 1.73; p trend <0.001).

DISCUSSION

In 3 ongoing prospective cohort studies, higher adherence to PDI was modestly associated with lower CHD incidence (HR comparing extreme deciles: 0.92; 95% CI: 0.83 to 1.01). This inverse association was considerably stronger for adherence to a healthier version (hPDI) (HR: 0.75; 95% CI: 0.68 to 0.83), but positive for adherence to a less healthy version (uPDI) (HR: 1.32; 95% CI: 1.20 to 1.46) of a plant-based diet index. These associations remained robust to adjustment for multiple confounders and were consistently observed in various subgroups.

In a previous analysis (14), we found similar associations of these 3 indices with type 2 diabetes. Our current analysis extends the potentially protective association with hPDI to CHD. The mechanisms through which hPDI could reduce CHD risk are likely shared with the mechanisms for type 2 diabetes risk reduction (2,24–32). Specifically, greater adherence to hPDI would lead to diets high in dietary fiber, antioxidants, unsaturated fat, and micronutrient content, and low in saturated fat and heme iron content (Online Table 1), all of which could aid in weight loss/maintenance, enhance glycemic control and insulin regulation, improve lipid profile, reduce blood pressure, improve vascular health, decrease inflammation, and foster more favorable diet-gut microbiome interactions (e.g., through lowered levels of trimethylamine N-oxide), thereby lowering CHD risk. Greater adherence to uPDI, on the other hand, leads to diets with higher glycemic load and index; added sugar; and lower levels of dietary fiber, unsaturated fats, micronutrients, and antioxidants, which could result in higher CHD risk through the above-mentioned pathways. This is also illustrated in the fact that the associations of hPDI and uPDI with CHD incidence were slightly

TABLE 4 Continued

Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10-U	p Trend*
Nurses' Health Study					
57.3	59.3	62.0	66.0		
341/191,659	322/187,773	325/186,951	357/183,583		
1.32 (1.13–1.55)	1.26 (1.08–1.49)	1.30 (1.11–1.53)	1.49 (1.27–1.74)	1.14 (1.08–1.20)	<0.001
1.43 (1.21–1.68)	1.34 (1.13–1.58)	1.34 (1.13–1.58)	1.49 (1.26–1.76)	1.13 (1.06–1.19)	<0.001
Nurses' Health Study 2					
58.0	60.0	62.5	66.5		
61/192,014	80/194,172	60/204,436	72/190,899		
1.40 (0.97–2.03)	1.85 (1.30–2.62)	1.40 (0.96–2.03)	1.81 (1.26–2.58)	1.19 (1.06–1.32)	0.01
1.46 (0.99–2.14)	1.91 (1.32–2.75)	1.37 (0.93–2.03)	1.77 (1.21–2.59)	1.16 (1.03–1.31)	0.04
Health Professionals Follow-Up Study					
57.3	59.0	61.5	65.2		
447/94,149	416/87,472	410/87,604	443/88,847		
1.07 (0.94–1.22)	1.10 (0.96–1.25)	1.11 (0.97–1.27)	1.22 (1.07–1.40)	1.09 (1.04–1.14)	<0.001
1.10 (0.96–1.25)	1.14 (0.99–1.31)	1.14 (0.99–1.31)	1.21 (1.05–1.39)	1.08 (1.03–1.14)	0.003
Pooled Results (Fixed-Effects Model)					
1.20 (1.10–1.32)	1.19†§ (1.08–1.31)	1.19 (1.08–1.31)	1.35†‖ (1.22–1.48)	1.11 (1.08–1.15)	<0.001
1.25 (1.13–1.38)	1.23†§ (1.11–1.36)	1.21 (1.09–1.34)	1.32†§ (1.20–1.46)	1.10 (1.06–1.14)	<0.001

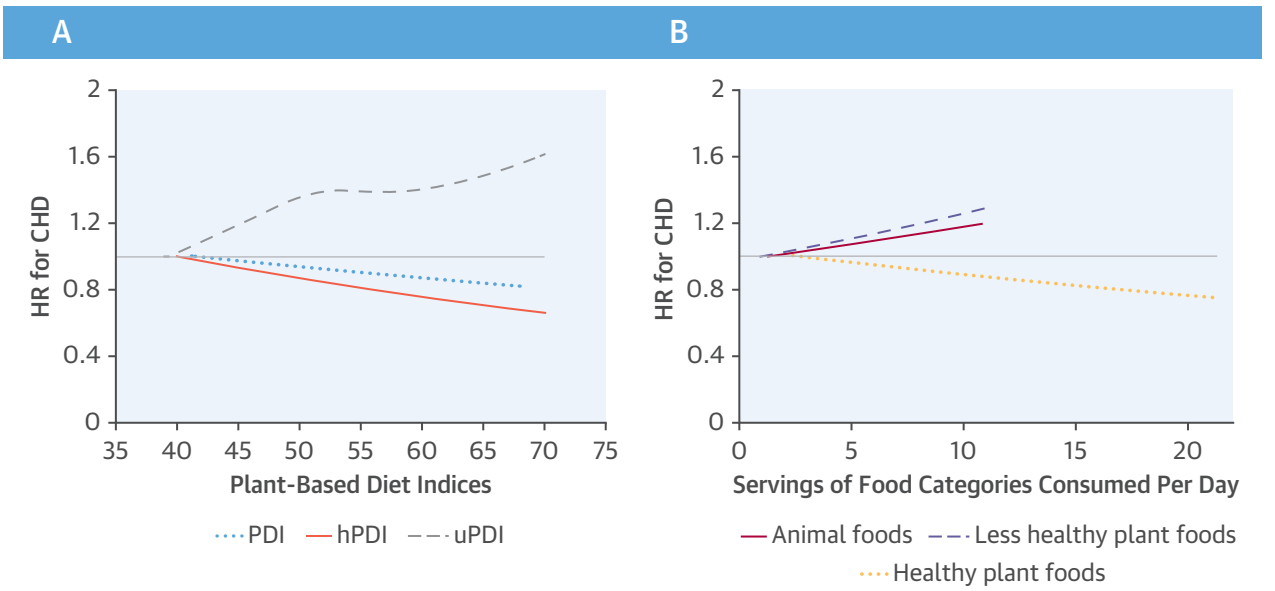
attenuated on adjustment for some of these pathways, specifically hypercholesterolemia, hypertension, and diabetes.

Prospective cohort studies examining the association of plant-based diets with CHD have focused on CHD mortality. Most of these studies have been carried out in Europe, with only 3 studies in the United States (Adventist Health Studies [7]). A pooled analysis of 5 of the above-mentioned cohorts found a 24% lower risk of CHD mortality (95% CI: 6% to 38%) comparing vegetarians with nonvegetarians (5). A recent meta-analysis found similar results with vegetarians experiencing a 29% lower risk of CHD mortality (95% CI: 13% to 43%) relative to nonvegetarians (6). The EPIC (European Prospective Investigation into Cancer and Nutrition)-Oxford study, 1 of the few studies to examine the association of a vegetarian diet with CHD incidence in addition to mortality, found a 32% lower 11-year CHD incidence (95% CI: 19% to 42%) among vegetarians relative to nonvegetarians (8).

These studies have defined plant-based diets dichotomously as being vegetarian or not. Our study adds to the evidence base by examining the association of gradations of adherence to PDI with CHD incidence. For instance, those in the lowest decile of PDI consumed 5 to 6 servings of animal foods per day, whereas those in the highest decile consumed 3 servings of animal foods per day. This approach has the advantage of being easily translatable, as we found that even a slightly lower intake of animal foods combined with higher intake of healthy plant foods is associated with lower CHD risk. One other study adopted this approach with respect to cardiovascular disease mortality and found similar results (3). However, these studies have examined plant-based diets at a single time point, making it difficult to fully capture the association of a time-varying exposure such as diet on the development of CHD, which has a long etiologic period. Our study adds to the existing reports by demonstrating the associations of long-term cumulative intake of a plant-based diet index with more than 20-year CHD incidence.

We also found that a healthier version of a plant-based diet index, which emphasizes plant foods known to be associated with improved health outcomes, is associated with substantially lower CHD risk. Contrarily, when intake of less healthy plant foods is emphasized, the opposite association was observed. When we examined associations of the 3 food categories with CHD risk, less healthy plant foods and animal foods were both associated with increased risk, with a potentially stronger association for less healthy plant foods. This highlights the wide variation in nutritional quality

CENTRAL ILLUSTRATION **Dose-Response Relationship of Plant-Based Diet Indices and Animal, Healthy Plant, and Less Healthy Plant Foods With CHD Incidence**



Satija, A. et al. J Am Coll Cardiol. 2017;70(4):411–22.

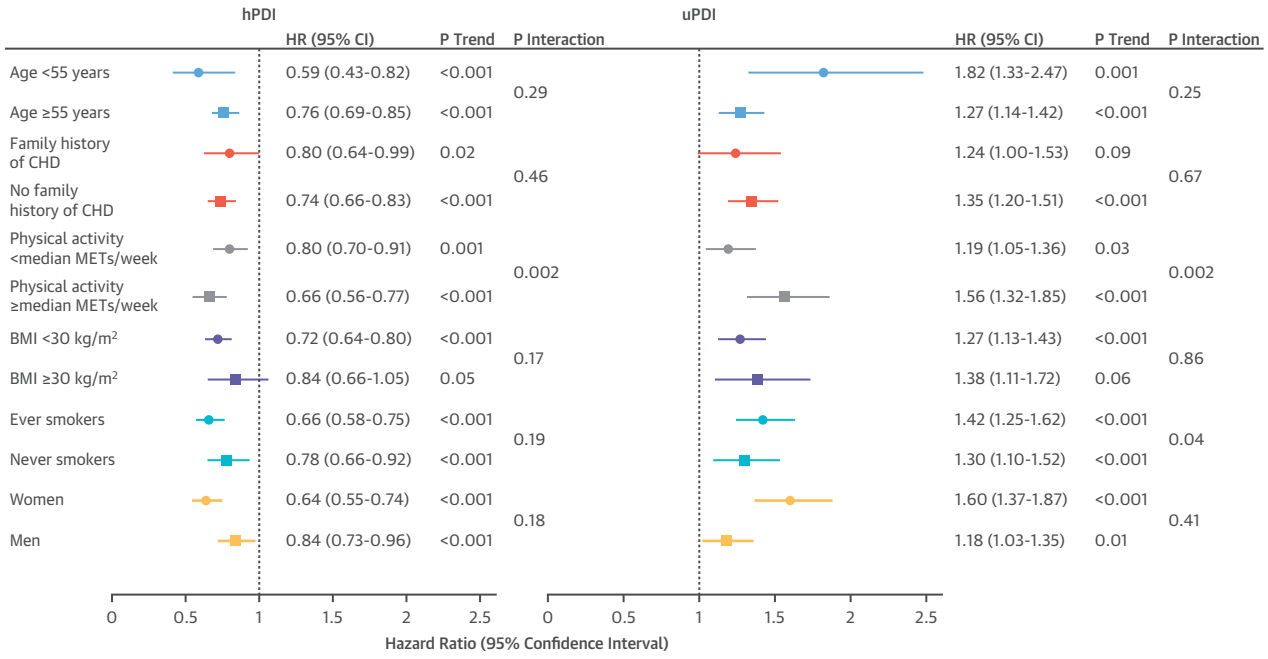
Analysis of the dose-response relationship of **(A)** the plant-based diet indices and **(B)** animal, healthy plant, and less healthy plant foods with CHD incidence was carried out after combining all 3 cohorts. Adjusted for age, smoking status, physical activity, alcohol intake, multivitamin use, aspirin use, family history of coronary heart disease (CHD), margarine intake, baseline hypertension, hypercholesterolemia, and diabetes, and updated body mass index. Also adjusted for post-menopausal hormone use in NHS (Nurses' Health Study) and NHS2 and for oral contraceptive use in NHS2. Energy intake was additionally adjusted when analyzing the plant-based diet indices. The 3 plant-based diet indices were examined in separate models. The 3 food categories (healthy and less healthy plant foods, and animal foods) were simultaneously included in the same model. For the unhealthful plant-based diet index (uPDI), p for test of curvature = 0.01 and p for nonlinear association is <0.001. The p values for test of curvature for overall plant-based diet index (PDI) = 0.25, for healthful plant-based diet index (hPDI) = 0.82, for animal foods = 0.58, for healthy plant foods = 0.99, and for less healthy plant foods = 0.74. The p values for linearity = 0.004 for animal foods, 0.001 for PDI, and <0.001 for hPDI, less healthy plant foods, and healthy plant foods. HR = hazard ratio.

of plant foods, making it crucial to consider the quality of plant foods consumed in plant-rich diets.

When we examined a diet that emphasized both healthy plant and healthy animal foods, the association with CHD was only slightly attenuated relative to that with hPDI. Thus, the moderate reductions in animal foods suggested here can be largely achieved by lowering intake of less healthy animal foods such as red and processed meats. The results of this study are in line with the recently released 2015 Dietary Guidelines for Americans (33), which recommends higher consumption of high-quality plant foods. Dietary recommendations based on the hPDI would also be environmentally sustainable, as plant-based food systems use fewer resources than food systems that are heavily reliant on animal foods (34).

STUDY LIMITATIONS. This is one of the largest prospective investigations of plant-based diet indices and incident CHD in the world, with periodic data on diet, lifestyle, and medical history collected over more than 2 decades. However, measurement error in diet assessment is likely, although evaluating cumulatively averaged intake reduces random errors (17) while allowing for the examination of long-term dietary intake. Given the observational nature of the study, residual and unmeasured confounding are possible; thus, we should interpret modest effect sizes such as those we observed for PDI with caution. However, the results were largely unchanged when we adjusted for additional covariates, including markers of socioeconomic status. Additionally, randomized controlled trial evidence showing the protective effect of plant-based diets on intermediate

FIGURE 1 Pooled HR (95% CI) for CHD Comparing Extreme Deciles of the Plant-Based Diet Indices, Stratified by Selected Characteristics



The hazard ratios (HRs) and p values for men and women were obtained after combining all 3 cohorts. All other HR and p values were obtained by pooling estimates from the 3 cohorts using a fixed-effects model. Adjusted for age, smoking status, physical activity, alcohol intake, multivitamin use, aspirin use, family history of coronary heart disease (CHD), margarine intake, energy intake, baseline hypertension, hypercholesterolemia, and diabetes, and updated body mass index. Also adjusted for post-menopausal hormone use in NHS (Nurses' Health Study) and NHS2 and for oral contraceptive use in NHS2. BMI = body mass index; CI = confidence interval; hPDI = healthful plant-based diet index; MET = metabolic equivalent task; uPDI = unhealthful plant-based diet index.

outcomes, including weight change, lipid profile, glycemic control, and blood pressure lends further support to our findings (35-38).

CONCLUSIONS

We found a modest inverse association of higher adherence to PDI with CHD incidence in 3 prospective cohort studies in the United States. While this inverse association was stronger for a plant-based diet index that emphasized healthy plant foods, CHD risk was significantly elevated for a plant-based diet index that emphasized less healthy plant foods. Dietary guidelines and lifestyle interventions could recommend increasing intake of healthy plant foods, while reducing intake of less healthy plant foods and certain animal foods for improved cardiometabolic health.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Medical and health professionals should guide patients to increase intake of healthy plant foods, such as whole grains, fruits, vegetables, and nuts, and reduce intake of animal foods and less healthy plant foods such as SSB for CHD prevention.

TRANSLATIONAL OUTLOOK: Future research should replicate these findings in other racial/ethnic, occupational, and socioeconomic groups and explore biological mechanisms involved in the potentially cardioprotective effects of hPDI to identify personalized clinical interventions and therapies for CHD prevention.

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