Plant-Based Diets and Risk of Type 2 Diabetes and Coronary Heart Disease

PLANT-BASED DIETS AND RISK OF TYPE 2 DIABETES AND CORONARY HEART DISEASE

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Abstract

Plant-based diets, defined as “vegetarian” diets, are associated with reduced risk of type 2 diabetes (T2D) and coronary heart disease (CHD). To examine the health effects of gradual reductions in animal food consumption while increasing plant food intake, and to distinguish between healthy and less healthy plant foods, we created three graded plant-based diet indices using semi-quantitative food frequency questionnaires (SFFQ). In the overall plant-based diet index (PDI), all plant foods received positive scores while animal foods received reverse scores. In the healthful PDI (hPDI) healthy plant foods (e.g. whole grains, fruits) received positive scores, while less healthy plant foods (e.g. sweetened beverages, refined grains) and animal foods received reverse scores. In the unhealthful PDI (uPDI) less healthy plant foods received positive scores, while healthy plant foods and animal foods received reverse scores. This dissertation examined the reliability and validity of these diet indices, and evaluated their associations with T2D and CHD incidence.

In chapter 1, we used data from The Women’s and Men’s Lifestyle Validation Studies (n=1354) to examine the reliability and validity of SFFQ-assessed plant-based diet indices. We found reasonable one-year reliability for the SFFQ-assessed indices. The indices correlated with energy-adjusted 7-day diet record nutrients and plasma biomarkers in expected directions, with hPDI associated with high dietary quality, and uPDI associated with poor diet quality.

In chapters 2 and 3, we examined the associations of these indices with T2D and CHD. We included ~70,000 women from Nurses’ Health Study (NHS) (1984-2012), ~90,000 women from NHS2 (1991-2011), and ~40,000 men from Health Professionals Follow-up Study (1986-2010). Dietary data were collected every 2-4 years using SFFQs. We documented 16,162 incident T2D, and 7754 incident CHD cases during ~4,00,000 person-years of follow-up. In pooled multivariable-adjusted analysis, PDI was inversely associated with T2D and CHD. hPDI had a stronger inverse association with both endpoints, while uPDI was positively associated with both diseases.

In conclusion, we found reasonable reliability and validity for three graded plant-based diet indices assessed with SFFQs. Our study suggests that plant-based diets, especially when rich in high-quality plant foods, are associated with substantially lower risk of T2D and CHD.

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CHAPTER 1

RELIABILITY AND VALIDITY OF PLANT-BASED DIET INDICES ASSESSED WITH A SEMI-QUANTITATIVE FOOD FREQUENCY QUESTIONNAIRE

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Abstract

Background: Plant-based dietary patterns, largely defined as “vegetarian” diets have been associated with reduced risk of various diseases. In order to examine the health effects of gradual reductions in animal food consumption while increasing plant food intake, and also distinguish between healthy and less healthy plant foods, we have created three graded plant-based diet indices (overall, healthful, and unhealthful) using diet questionnaires. The current study examined the reliability and validity of these diet indices against more detailed diet assessment methods and biochemical markers.

Methods: The Women’s and Men’s Lifestyle Validation Studies (WLVS, n=720 and MLVS, n=634) are validation studies conducted among subsets of participants from the larger Nurses’ Health Study (NHS), NHS2, and Health Professionals’ Follow-up Study. Diet was assessed using a paper-based semi-quantitative food frequency questionnaire (SFFQ) twice, one year apart, as well as two 7-day diet records (7DDR), 6 months apart, during that one-year period. A graded overall plant-based diet index (PDI) was created using both SFFQ and 7DDR data by assigning positive scores to all plant foods and reverse scores to all animal foods. Two additional indices were created using SFFQ data. A healthful plant-based diet index (hPDI) was created by assigning positive scores to healthy plant foods (whole grains, fruits, vegetables, nuts, legumes, vegetable oils, tea/coffee), and reverse scores to less healthy plant foods (sugar-sweetened beverages, fruit juices, sweets, refined grains, potato/French fries) and also to animal foods (animal fat, dairy, eggs, fish/seafood, meat, miscellaneous animal foods). An unhealthful plant-based diet index was created by assigning positive scores to less healthy plant foods, and reverse scores to healthy plant foods and animal foods.

Results: The three SFFQ-assessed indices had reasonable one-year reproducibility, with energy-adjusted Pearson ICCs ranging from 0.65 to 0.77. Pearson correlations coefficients comparing the PDI from SFFQs and 7DDRs ranged from 0.62 (95% CI: 0.55, 0.68) to 0.67 (95% CI: 0.60, 0.72) after energy-adjustment and correction for measurement error in the diet records. All three indices correlated with energy-adjusted 7DDR nutrients in expected directions, with hPDI being associated with high dietary quality, and uPDI being correlated with poor diet quality. Associations with plasma biochemical markers were also in expected directions, albeit weaker than correlations with 7DDR nutrients. The hPDI was positively associated with plasma levels of HDL cholesterol and inversely associated with plasma triglyceride levels, while associations of these biomarkers with the uPDI were in the opposite directions.

Conclusions: This study found reasonable reliability and validity for three graded plant-based diet indices assessed with food frequency questionnaires. These SFFQ-assessed diet indices can be potentially used in epidemiologic analyses of diet-disease relations.

Introduction

Dietary pattern analysis is a relatively new approach in nutritional epidemiology of examining the effect of the overall diet on health as opposed to focusing on a single nutrient/food/food group (1). Several dietary patterns have been studied as they capture overall diet quality. One such dietary pattern is a plant-based diet, which has been associated with reduced risk of various diseases and intermediate conditions, including weight gain (2), an unhealthy lipid profile (3), high blood pressure (4), type 2 diabetes (T2D) (5-7), cardiovascular disease (CVD) (8,9), cancer (10,11), and mortality (12). Most of these studies have defined plant-based diets as "vegetarian" diets, in which one or more animal food groups are completely excluded from the diet. In order to better understand the health effects of gradually reducing animal food consumption while increasing intake of plant foods, we have created a graded plant-based diet index (PDI) using periodic dietary data from semi-quantitative food frequency questionnaires (SFFQ) in three ongoing prospective cohort studies in the US – the Nurses' Health Study (NHS), the NHS2, and the Health Professionals Follow-up Study (HPFS). To create this index, we positively scored all plant foods, and reverse scored all animal foods, getting a continuum of adherence to a diet that is high in plant and low in animal food consumption.

Not all plant foods are associated with improved health outcomes. Plant foods such as whole grains, fruits, vegetables, and nuts have been associated with reduced risk of various chronic diseases (13-17). However, other plant foods such as sugar-sweetened beverages (including fruit juices) and foods, refined grains, and potatoes have been associated with increased risk of several chronic diseases due to their high added sugar levels, low fiber content, and high glycemic load (18-24). To illustrate the differing risk profiles associated with different types of plant-based diets, we have created two additional graded diet indices using SFFQ data from the above mentioned cohorts: a healthful plant-based diet index (hPDI) which emphasizes healthy plant food consumption, and an unhealthful plant-based diet index (uPDI) which emphasizes consumption of less healthy plant foods. Given that self-report dietary data from SFFQs is subject to measurement error, it is important to quantify the reliability and validity of diet indices created using this assessment method. In the present study thus, we assessed the reliability of the three SFFQ-assessed plant-based diet indices, and validated them against data from multiple-day weighted diet records and nutrient biomarkers.

Methods

Study Population

The Women's Lifestyle Validation Study (WLVS) and the Men's Lifestyle Validation Study (MLVS) are validation studies conducted among subsamples of participants from three ongoing prospective cohorts in the US – NHS, NHS2, and HPFS. The NHS started in 1976 with 121,700 female nurses (aged 30-55 years), the NHS2 started in 1989 with 116,430 female nurses (aged 25-42 years), and the HPFS started in 1986 with 51,529 male health professionals (aged 40-75 years), in the US. Participants receive a follow-up questionnaire biennially on lifestyle, medication use, and disease history, and updated dietary data is collected every 2-4 years using a previously validated SFFQ.

The WLVS was initiated in 2010, when NHS and NHS2 participants aged 45-80 years, who had completed the 2006/2007 SFFQ cycle, had provided blood samples previously, had access to broadband internet, were not intending to make substantial lifestyle changes, and did not have a medical history of cardiovascular disease (CVD), cancer, or major neurological disease were invited to participate in the study. A total of 2,423 nurses responded, and from these, 796 (33%) consented to participate. The study was conducted from June, 2010 to March, 2012.

The MLVS was initiated in 2012, when HPFS participants aged 45-80 years, who had participated in previous diet and physical activity validation studies, had previously provided blood samples, and had completed the 2010 SFFQ cycle were invited to participate. The MLVS also invited Harvard Pilgrim Health Care enrollees who had been in the program for at least three years, for participation in the study. Having access to broadband internet was a requirement, and exclusion criteria were a medical history of CVD, cancer, or major neurological disease. A total of 908 men were recruited into the study. The study was conducted from March, 2012 to 2014.

For both studies, sample selection was stratified by age to obtain a uniform distribution, and African-Americans were oversampled. The studies were carried out for one year, over the course of which diet was assessed using a paper-based SFFQ once at the start of the study and once at study end, a web-based SFFQ at study end, 7-day diet records (7DDR) twice 6-months apart, and multiple 24-hour recalls. There were also were repeat assessments of physical activity through a questionnaire, 24-hour recalls, and accelerometers; doubly-labeled water measurements; fasting blood draws; 24-hr urine collections; and saliva collections. Information on year of birth, height, weight, and ethnicity was assessed at enrollment; weight information was also collected every three months till end of follow up. Figure 1.1 depicts an overview of the study activities and timeline. In the current analysis, we considered the SFFQ as the surrogate measure, and the 7DDRs as the reference method. We excluded participants if they had extreme SFFQ-assessed energy intakes (<600 kcal or >3500 kcal for women, and <800 kcal or >4200 kcal for men), had left more than 70 blank items on the SFFQs, or if they had not completed both SFFQs (paper-based) and 7DDRs. The final sample included 720 participants from the WLVS and 634 participants from the MLVS. The studies were approved by the Human Subjects Committees of the Harvard T.H. Chan School of Public Health and Brigham and Women’s Hospital.

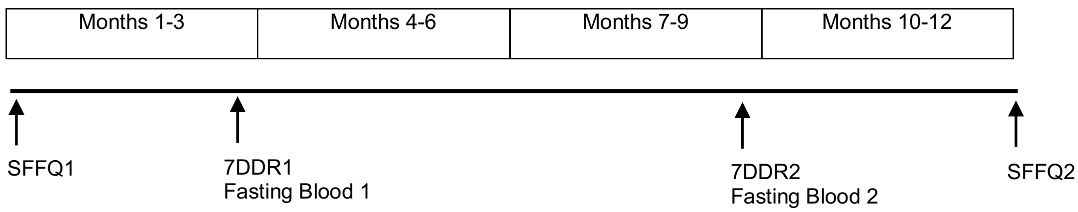

Figure 1.1: Overview of study timeline and activities

Abbreviations: SFFQ, Semi-quantitative food frequency questionnaire; 7DDR, 7-day diet record

Semi-quantitative food frequency questionnaire

The SFFQ used in these studies is a 152-item expanded version of the previously validated questionnaire that has been used over the past two decades in the NHS, NHS2, and HPFS (25-27). The questionnaire was used to ask participants how often, on average, they consumed a defined portion of each food item (e.g. one 8 oz. glass of whole milk) over the past year. Nine responses categories were available for each food item: never or less than once per month, 1-3 times per month, once per week, 2-4 times per week, 5-6 times per week, once per day, 2-3 times per day, 4-5 times per day, and 6 or more times per day. Open-ended questions collected additional information, including cold breakfast cereal brand. Information on type of fat used for cooking and baking was also collected. This questionnaire was administered in paper form at the start of the study, and again one year later. It was also administered at study-end as a web-based questionnaire. For the present study, we will only consider the two paper-based SFFQ administrations, in line with what has been consistently used in the three larger cohorts.

7-day diet records

Participants collected two 7-day diet records 6 months apart. Participants were provided with a detailed instructional DVD, a food record booklet, an Escali food scale and ruler, and instructions via telephone by trained dieticians. Reminder emails were regularly sent to participants during the 7-day period using a computerized system, which also encouraged participants to ask the study dietitians for clarifications on instructions and review the DVD if needed. Participants measured foods and recorded gram weights before and after eating to enable computation of actual intake, and provided recipes of all home prepared foods. They also collected and returned labels of store brand products. The diet records were reviewed for incomplete information, with participants contacted for clarifications if needed. The Nutrition Coordinating Center (NCC) at the University of Minnesota (28) used the Nutrition Data System for Research (NDSR2011) to analyze the 7DDRs (29,30), deriving over 150 nutrient and dietary constituents; USDA food composition sources were primarily used.

The plant-based diet indices

We created three versions of a plant-based diet index using data from the SFFQs: an overall plant-based diet index (PDI), a healthful plant-based diet index (hPDI), and an unhealthful plant-based diet index (uPDI). Frequencies of consumption of the SFFQ food items were first converted into servings consumed per day. The food items were then categorized into 18 food groups based on nutrient and culinary similarities, but within the larger categories of healthy plant foods [whole grains, fruits, vegetables, nuts, legumes, vegetable oils, and tea/coffee], less healthy plant foods [fruit juices, sugar sweetened beverages (SSB), refined grains, potatoes, and sweets & desserts], and animal foods [dairy, egg, fish/seafood, meat, animal fats, and miscellaneous animal-based foods]. The distinction between healthy and less healthy plant foods was based on existing literature on the associations of these foods with several diseases such as T2D, CVD, and certain cancers, and intermediate conditions including obesity, hypertension, lipids, and inflammation (13-24, 31-43). Alcoholic beverages were not included in the indices, as they are not associated in one direction with several disease endpoints. Margarine was also excluded from the indices, as its fatty acid composition has evolved over time from being high in trans fats, to being high in unsaturated fats. These foods can be adjusted for in etiologic analyses.

The 18 food groups were then ranked into quintiles, with each quintile-defined category receiving a score between 1 and 5. For positive scores, participants above the highest quintile of a food group received a score of 5, participants between the highest and second highest quintiles received a score of 4, and so on till participants below the lowest quintile of that food group, who received a score of 1. For reverse scores, the opposite pattern of scoring was adopted. PDI was created by assigning positive scores to all plant food groups, and reverse scores to all animal food groups. To create hPDI, we assigned positive scores to only the healthy plant food groups, and reverse scores to the less healthy plant food groups and animal food groups. To create uPDI, we assigned positive scores to the less healthy plant food groups, and reverse scores to the healthy plant food groups and the animal food groups. These food group scores were then summed up to obtain the three diet indices, which theoretically ranged from the lowest score of 18 to the highest score of 90.

We also used 7DDR data to create the overall plant-based diet index (PDI). To get comparable food data from the SFFQ and 7DDRs, the 10,145 unique foods recorded in the 7DDRs were matched to the 152 SFFQ foods. First, direct matches across the two diet assessment methods were made for single-ingredient foods, e.g. “whole milk”. Next, for composite, multiple-ingredient foods on the SFFQ, e.g. “pizza”, direct matches were again made with the comparable 7DDR foods. Multiple-ingredient foods on the 7DDR that did not have direct matches with similar foods on the SFFQ were not matched to the 7DDR, and hence were not included when creating PDI from the 7DDRs. The SFFQ-matched food items were then categorized into the 18 food groups mentioned above. If the 7DDR had single-ingredient foods without direct matches to comparable foods on the SFFQ, but that clearly belonged to a larger food group, they were also included in the food group categorization. For instance, the food item “cherries” reported on the 7DDR, but not listed in the SFFQs, was included as part of the larger food group “fruits” when creating PDI. The food groups so created were then ranked and scored in the same way discussed above to create the PDI.

Biomarker assessment

Fasting blood samples were self-collected twice, six months apart, in both studies, 2-5 months after the first SFFQ administration. At the time of sample collection, participants also filled a questionnaire about day/time of sample collection, smoking status, post-menopausal status and hormone use (women only), and other lifestyle factors. These samples were assayed for several nutrient biomarkers, including lipids and folate in both WLVS and MLVS, and fatty acids, carotenoids, tocopherols, and retinol in WLVS. Plasma fatty acids, expressed as percentages of total fatty acids, were measured by gas liquid chromatography. Plasma carotenoids and tocopherols were measured by high-performance liquid chromatography. Plasma folate was determined by chemiluminescence. Blood lipids (total cholesterol, HDL cholesterol, and triglycerides) were assayed by enzymatic methods. Mean CVs were 18.1% for fatty acids, 9.7% for carotenoids, 8.6% for retinol, 9.3% for tocopherols, 9.2% (women) and 8.4% (men) for folate, 5.6% (men) and 9.3% (women) for total cholesterol, 5.6% (men) and 8.1% (women) for HDL cholesterol, and 3.8% (men) and 9.9% (women) for triglycerides.

Statistical analysis

We calculated Pearson intraclass correlation coefficients (ICCs) between the indices computed from the two SFFQs to estimate the one-year reliability of the questionnaire-assessed indices, before and after adjustment for total energy intake (energy-adjustment done using the residual method) (26). Pearson correlation coefficients were also calculated between PDI from the SFFQ and PDI from the 7DDRs, with and without energy adjustment. We further calculated deattenuated correlation coefficients between PDI computed from the SFFQs and 7DDRs, correcting for random within-person error in the diet records to better approximate the true correlation of the SFFQ-assessed PDI with the true underlying value. We used the following formula for this (44,45):

$$\rho_c = \rho_o \sqrt{\left(1 + \frac{\gamma}{k}\right)}$$

where, ρ_c is the corrected correlation coefficient between the SFFQ and 7DDR indices, ρ_o is the observed correlation coefficient between the SFFQ and 7DDR indices, γ is the ratio of within- to between-person variation in the 7DDR-assessed PDI, and k is the number of 7DDR replicates (in this instance, k=2).

We also calculated deattenuated Pearson correlation coefficients between the three plant-based diet indices and energy-adjusted nutrients derived from the 7DDRs (excluding supplements). Rank Spearman correlation coefficients were calculated between the three indices and residuals of plasma biomarkers. Plasma levels of all biomarkers were adjusted for age, body mass index (BMI), weight, smoking status, fasting status, and postmenopausal status and hormone use (women only); plasma levels of carotenoids, tocopherols, and retinol were further adjusted for plasma total cholesterol, HDL cholesterol, and triglycerides. We used an extension (46) of the methods developed by Rosner and Glynn (47) and Perisic and Rosner (45, 48) to correct for random within-person error in plasma biomarkers, given differing numbers of repeats (k) across individuals (unbalanced data). We log transformed all variables after setting zeros to a fixed non-zero value (0.0001 unit/day), as diet index, dietary nutrient, and plasma biomarker distributions were positively skewed. We repeated the analysis in subgroups of participants who did not use supplements for the nutrient being measured by specific biomarkers.

Results

The participants had a mean age of 65 years at baseline, an average BMI of 26 kg/m^2, were fairly weight stable, and a very small proportion were current smokers (Table 1.1). Among women, 12% were premenopausal, and 24% were current users of postmenopausal hormones. Mean PDI was 54 across the SFFQ and 7DDR assessments, and mean hPDI and uPDI levels were comparable across the two SFFQ measures at 55 and 54 respectively.

Table 1.1: Descriptive characteristics of participants from WLVS (2010-2012) and MLVS (2012-2014)

	ALL (n=1354)	WOMEN (n=720)	MEN (n=634)
Age (years)	64.5 (9.0)	62 (9.6)	67 (7.4)
Height (m)	1.7 (0.1)	1.6 (0.1)	1.8 (0.1)
Weight (kg)	76 (15)	71 (15)	82 (13)
BMI (kg/m^2)	26 (4.7)	26 (5.3)	26 (3.8)
1-yr weight change (kg)	-0.1 (3.0)	-0.2 (2.9)	0.0 (3.1)
White (%)	94	91	98
Current smokers (%)	1.6	2.1	1.1
Premenopausal (%)	-	12	-
Hormone use past 6 months (%)	-	24	-
Overall Plant-based Diet Index (PDI)			
SFFQ1	54 (6.7)	54 (6.5)	55 (6.9)
SFFQ2	54 (6.8)	54 (6.5)	54 (7.1)
7DDR1	54 (6.5)	54 (6.4)	54 (6.7)
7DDR2	54 (6.7)	54 (6.3)	54 (7.1)
7DDR averaged	54 (6.8)	54 (6.6)	54 (7.1)
Healthful Plant-based Diet Index (hPDI)			
SFFQ1	55 (7.8)	55 (7.7)	55 (8.0)
SFFQ2	55 (8.1)	55 (8.0)	55 (8.2)
Unhealthful Plant-based Diet Index (uPDI)			
SFFQ1	54 (8.2)	54 (8.2)	54 (8.1)
SFFQ2	54 (8.2)	53 (8.1)	54 (8.3)

Data are means (SD) for continuous variables, and percentages for dichotomous variables

Abbreviations: SFFQ, Semi-quantitative Food Frequency Questionnaire; 7DDR, 7 Day Diet Records

The three SFFQ-assessed indices had reasonable one-year reproducibility, with ICCs ranging from 0.65 to 0.69 for PDI, 0.76 to 0.79 for hPDI, and 0.72 to 0.77 for uPDI after energy-adjustment (Table 1.2). Pearson correlation coefficients between SFFQ-assessed PDI and 7DDR-assessed PDI were moderately high, and became stronger with energy-adjustment and correction for random within-person variation in the diet records (Table 1.3). Correlation coefficients were similar for the two SFFQs ranging from 0.62 to 0.67 for SFFQ1, and 0.62 to 0.63 for SFFQ2 after energy-adjustment and deattenuation.

Table 1.2: Pearson intraclass correlation coefficients of the plant-based diet indices from two SFFQs one year apart

	Unadjusted	Energy-adjusted
WOMEN		
PDI	0.69	0.65
hPDI	0.77	0.76
uPDI	0.72	0.72
MEN		
PDI	0.72	0.69
hPDI	0.78	0.79
uPDI	0.78	0.77

All dietary variables have been log-transformed

Abbreviations: PDI, Overall plant-based diet index; hPDI, Healthful plant-based diet index; uPDI, Unhealthful plant-based diet index

Table 1.3: Pearson correlation coefficients comparing PDI from the SFFQs against 7DDRs

	Unadjusted	Energy-adjusted	Energy-adjusted and Deattenuated
WOMEN			
SFFQ1 vs. 7DDRs	0.49 (0.45, 0.53)	0.52 (0.48, 0.55)	0.62 (0.55, 0.68)
SFFQ2 vs. 7DDRs	0.49 (0.45, 0.53)	0.53 (0.49, 0.56)	0.63 (0.56, 0.69)
MEN			
SFFQ1 vs. 7DDRs	0.58 (0.55, 0.61)	0.59 (0.56, 0.62)	0.67 (0.60, 0.72)
SFFQ2 vs. 7DDRs	0.58 (0.55, 0.61)	0.55 (0.52, 0.58)	0.62 (0.56, 0.68)

All dietary variables have been log-transformed

Abbreviations: PDI, Overall plant-based diet index; hPDI, Healthful plant-based diet index; uPDI, Unhealthful plant-based diet index

After energy-adjustment and deattenuation, indices from both SFFQs were correlated in expected directions with 7DDR-assessed nutrients (Tables 1.4 and 1.5). The PDI was inversely associated with total fat, saturated fat, monounsaturated fat, dietary cholesterol, and protein, but had positive correlations with carbohydrate, total sugar, and dietary fiber. The hPDI was also inversely associated with total fat, saturated fat, and dietary cholesterol and positively associated with dietary fiber, but it was positively correlated with monounsaturated fat, polyunsaturated fat, and protein. The uPDI showed the opposite trend of associations, being inversely correlated with total fat, monounsaturated fat, polyunsaturated fat, cholesterol, protein, and dietary fiber, and positively correlated with carbohydrates and total sugar. The hPDI was positively associated with most micronutrients, while the uPDI was inversely associated with virtually all micronutrients; PDI lay somewhere in the middle, showing positive associations with some micronutrients, and no associations with others. The correlations were similar among men and women, and were comparable across the two SFFQ measurements.

Table 1.4: Pearson correlation coefficients (95% CI) comparing the plant-based diet indices from the SFFQs against nutrients from the 7DDRs, unadjusted, and energy-adjusted and deattenuated, among 720 women from WLVS

	Overall Plant-based Diet Index				Healthful Plant-based Diet Index				Unhealthful Plant-based Diet Index			
	SFFQ1		SFFQ2		SFFQ1		SFFQ2		SFFQ1		SFFQ2	
	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated
Total fat (g)	-0.06	-0.22 (-0.29, -0.14)	-0.07	-0.21 (-0.29, -0.13)	-0.14	-0.07 (-0.15, 0.01)	-0.11	-0.05 (-0.13, 0.03)	-0.13	-0.15 (-0.23, -0.07)	-0.15	-0.17 (-0.24, -0.09)
Saturated fat (g)	-0.14	-0.31 (-0.38, -0.23)	-0.16	-0.34 (-0.41, -0.26)	-0.28	-0.33 (-0.40, -0.25)	-0.27	-0.33 (-0.40, -0.25)	-0.03	0.03 (-0.05, 0.11)	-0.05	0.03 (-0.05, 0.11)
Monounsaturated fat (g)	-0.03	-0.15 (-0.23, -0.07)	-0.04	-0.13 (-0.22, -0.05)	-0.06	0.07 (-0.01, 0.16)	-0.02	0.10 (0.02, 0.18)	-0.19	-0.25 (-0.33, -0.17)	-0.19	-0.25 (-0.33, -0.17)
Polyunsaturated fat (g)	0.08	0.06 (-0.03, 0.14)	0.06	0.09 (0.00, 0.18)	0.01	0.17 (0.08, 0.25)	0.05	0.19 (0.11, 0.28)	-0.15	-0.16 (-0.25, -0.07)	-0.16	-0.20 (-0.28, -0.11)
Cholesterol (mg)	-0.26	-0.39 (-0.46, -0.32)	-0.26	-0.40 (-0.46, -0.32)	-0.21	-0.19 (-0.27, -0.11)	-0.19	-0.17 (-0.25, -0.09)	-0.22	-0.24 (-0.32, -0.16)	-0.23	-0.24 (-0.31, -0.16)
Protein (g)	-0.11	-0.31 (-0.39, -0.23)	-0.10	-0.27 (-0.35, -0.19)	-0.01	0.16 (0.07, 0.24)	0.01	0.16 (0.08, 0.24)	-0.32	-0.40 (-0.47, -0.32)	-0.33	-0.40 (-0.47, -0.32)
Carbohydrate (g)	0.31	0.41 (0.35, 0.48)	0.31	0.41 (0.35, 0.48)	-0.10	0.01 (-0.07, 0.09)	-0.09	0.01 (-0.07, 0.08)	0.09	0.29 (0.22, 0.36)	0.06	0.27 (0.19, 0.34)

Table 1.4 (Continued): Pearson correlation coefficients (95% CI) comparing the plant-based diet indices from the SFFQs against nutrients from the 7DDRs, unadjusted, and energy-adjusted and deattenuated, among 720 women from WLVS

	Overall Plant-based Diet Index				Healthful Plant-based Diet Index				Unhealthful Plant-based Diet Index			
	SFFQ1		SFFQ2		SFFQ1		SFFQ2		SFFQ1		SFFQ2	
	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated
Total sugar (g)	0.27	0.30 (0.23, 0.37)	0.28	0.31 (0.24, 0.38)	-0.15	-0.09 (-0.16, -0.01)	-0.13	-0.07 (-0.14, 0.01)	0.16	0.32 (0.25, 0.39)	0.12	0.29 (0.22, 0.36)
Fiber (g)	0.32	0.33 (0.25, 0.4)	0.34	0.38 (0.31, 0.45)	0.41	0.62 (0.56, 0.67)	0.44	0.64 (0.59, 0.69)	-0.40	-0.42 (-0.49, -0.35)	-0.39	-0.42 (-0.49, -0.36)
Retinol activity equivalents (mcg)	0.06	0.00 (-0.10, 0.09)	0.10	0.05 (-0.05, 0.15)	0.09	0.27 (0.17, 0.36)	0.11	0.28 (0.18, 0.37)	-0.24	-0.28 (-0.38, -0.19)	-0.26	-0.30 (-0.39, -0.20)
Alpha carotene (mcg)	0.25	0.27 (0.17, 0.37)	0.26	0.31 (0.20, 0.41)	0.18	0.36 (0.25, 0.46)	0.17	0.33 (0.23, 0.43)	-0.24	-0.26 (-0.36, -0.16)	-0.22	-0.25 (-0.34, -0.14)
Beta carotene (mcg)	0.19	0.18 (0.09, 0.27)	0.24	0.25 (0.16, 0.34)	0.31	0.48 (0.40, 0.56)	0.32	0.51 (0.42, 0.58)	-0.37	-0.43 (-0.51, -0.35)	-0.36	-0.41 (-0.49, -0.32)
Lutein-zeaxanthin (mcg)	0.12	0.09 (0.00, 0.18)	0.17	0.17 (0.08, 0.26)	0.31	0.46 (0.38, 0.53)	0.33	0.50 (0.42, 0.57)	-0.38	-0.46 (-0.53, -0.37)	-0.38	-0.44 (-0.52, -0.36)
Lycopene (mcg)	0.08	0.02 (-0.13, 0.17)	0.05	-0.03 (-0.18, 0.12)	0.00	0.12 (-0.03, 0.27)	-0.01	0.09 (-0.07, 0.24)	-0.18	-0.25 (-0.40, -0.08)	-0.15	-0.20 (-0.36, -0.04)

Table 1.4 (Continued): Pearson correlation coefficients (95% CI) comparing the plant-based diet indices from the SFFQs against nutrients from the 7DDRs, unadjusted, and energy-adjusted and deattenuated, among 720 women from WLVS

	Overall Plant-based Diet Index				Healthful Plant-based Diet Index				Unhealthful Plant-based Diet Index			
	SFFQ1		SFFQ2		SFFQ1		SFFQ2		SFFQ1		SFFQ2	
	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated
Beta cryptoxanthin (mcg)	0.18	0.23 (0.13, 0.34)	0.24	0.35 (0.24, 0.45)	0.14	0.28 (0.18, 0.38)	0.19	0.35 (0.24, 0.45)	-0.18	-0.22 (-0.33, -0.12)	-0.15	-0.19 (-0.29, -0.08)
Vitamin B6 (mg)	0.09	0.03 (-0.05, 0.12)	0.12	0.08 (0.00, 0.17)	0.11	0.26 (0.18, 0.34)	0.14	0.30 (0.21, 0.38)	-0.22	-0.21 (-0.29, -0.13)	-0.24	-0.23 (-0.31, -0.14)
Dietary folate equivalents (mcg)	0.13	0.13 (0.04, 0.21)	0.15	0.14 (0.06, 0.22)	0.01	0.11 (0.03, 0.19)	0.01	0.11 (0.02, 0.19)	-0.07	-0.02 (-0.10, 0.07)	-0.10	-0.04 (-0.13, 0.04)
Calcium (mg)	0.06	-0.03 (-0.11, 0.05)	0.06	-0.02 (-0.10, 0.06)	-0.02	0.10 (0.02, 0.18)	-0.02	0.10 (0.02, 0.17)	-0.14	-0.08 (-0.16, 0.00)	-0.18	-0.12 (-0.20, -0.04)
Magnesium (mg)	0.23	0.21 (0.13, 0.28)	0.24	0.25 (0.18, 0.33)	0.30	0.58 (0.53, 0.64)	0.34	0.62 (0.56, 0.67)	-0.39	-0.42 (-0.49, -0.35)	-0.39	-0.44 (-0.51, -0.38)
Potassium (mg)	0.21	0.14 (0.06, 0.22)	0.21	0.18 (0.10, 0.26)	0.21	0.48 (0.41, 0.54)	0.24	0.50 (0.44, 0.56)	-0.38	-0.39 (-0.45, -0.32)	-0.39	-0.41 (-0.48, -0.34)

All nutrients are without supplements

All dietary variables have been log-transformed

Table 1.5: Pearson correlation coefficients (95% CI) comparing the plant-based diet indices from the SFFQs against nutrients from the 7DDRs, unadjusted, and energy-adjusted and deattenuated, among 634 men from MLVS

	Overall Plant-based Diet Index				Healthful Plant-based Diet Index				Unhealthful Plant-based Diet Index			
	SFFQ1		SFFQ2		SFFQ1		SFFQ2		SFFQ1		SFFQ2	
	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated
Total fat (g)	-0.07	-0.32 (-0.39, -0.24)	-0.04	-0.30 (-0.38, -0.22)	-0.20	-0.17 (-0.25, -0.09)	-0.17	-0.14 (-0.22, -0.06)	-0.12	-0.19 (-0.27, -0.10)	-0.13	-0.20 (-0.28, -0.11)
Saturated fat (g)	-0.22	-0.45 (-0.52, -0.38)	-0.19	-0.43 (-0.49, -0.35)	-0.38	-0.42 (-0.49, -0.35)	-0.36	-0.41 (-0.47, -0.33)	-0.01	-0.01 (-0.10, 0.07)	-0.01	-0.01 (-0.10, 0.07)
Monounsaturated fat (g)	-0.03	-0.23 (-0.32, -0.15)	0.01	-0.19 (-0.28, -0.11)	-0.08	0.01 (-0.08, 0.10)	-0.05	0.04 (-0.05, 0.13)	-0.19	-0.28 (-0.36, -0.20)	-0.19	-0.27 (-0.35, -0.19)
Polyunsaturated fat (g)	0.13	0.03 (-0.06, 0.12)	0.13	-0.01 (-0.10, 0.08)	-0.04	0.06 (-0.03, 0.15)	-0.03	0.09 (0.00, 0.18)	-0.10	-0.13 (-0.22, -0.04)	-0.14	-0.18 (-0.27, -0.09)
Cholesterol (mg)	-0.36	-0.50 (-0.57 -0.42)	-0.36	-0.51 (-0.58, -0.43)	-0.27	-0.30 (-0.38, -0.21)	-0.27	-0.30 (-0.38, -0.21)	-0.17	-0.22 (-0.31, -0.13)	-0.18	-0.24 (-0.32, -0.15)
Protein (g)	-0.11	-0.32 (-0.39, -0.24)	-0.08	-0.27 (-0.35, -0.19)	0.01	0.13 (0.04, 0.21)	0.01	0.11 (0.03, 0.20)	-0.27	-0.43 (-0.50, -0.36)	-0.22	-0.36 (-0.44, -0.28)
Carbohydrate (g)	0.40	0.50 (0.43, 0.56)	0.41	0.47 (0.40, 0.53)	-0.04	0.07 (-0.01, 0.15)	-0.05	0.06 (-0.02, 0.14)	0.17	0.31 (0.23, 0.38)	0.16	0.31 (0.23, 0.38)

Table 1.5 (Continued): Pearson correlation coefficients (95% CI) comparing the plant-based diet indices from the SFFQs against nutrients from the 7DDRs, unadjusted, and energy-adjusted and deattenuated, among 634 men from MLVS

	Overall Plant-based Diet Index				Healthful Plant-based Diet Index				Unhealthful Plant-based Diet Index			
	SFFQ1		SFFQ2		SFFQ1		SFFQ2		SFFQ1		SFFQ2	
	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated
Total sugar (g)	0.37	0.40 (0.32, 0.47)	0.37	0.35 (0.28, 0.43)	-0.07	0.00 (-0.09, 0.08)	-0.10	-0.02 (-0.11, 0.06)	0.19	0.30 (0.22, 0.37)	0.18	0.31 (0.23, 0.39)
Fiber (g)	0.41	0.43 (0.35, 0.49)	0.41	0.40 (0.33, 0.47)	0.43	0.62 (0.57, 0.67)	0.44	0.64 (0.59, 0.69)	-0.29	-0.35 (-0.42, -0.27)	-0.30	-0.34 (-0.41, -0.27)
Retinol activity equivalents (mcg)	0.08	0.03 (-0.06, 0.12)	0.06	-0.03 (-0.12, 0.06)	0.13	0.23 (0.13, 0.32)	0.09	0.18 (0.08, 0.27)	-0.22	-0.29 (-0.37, -0.20)	-0.21	-0.25 (-0.34, -0.16)
Alpha carotene (mcg)	0.27	0.35 (0.24, 0.46)	0.26	0.30 (0.19, 0.41)	0.23	0.38 (0.27, 0.48)	0.19	0.33 (0.21, 0.43)	-0.18	-0.24 (-0.34, -0.13)	-0.17	-0.20 (-0.31, -0.09)
Beta carotene (mcg)	0.21	0.24 (0.15, 0.33)	0.20	0.19 (0.09, 0.27)	0.38	0.48 (0.40, 0.55)	0.32	0.43 (0.34, 0.50)	-0.30	-0.38 (-0.46, -0.29)	-0.32	-0.37 (-0.45, -0.28)
Lutein-zeaxanthin (mcg)	0.20	0.20 (0.11, 0.28)	0.16	0.12 (0.03, 0.21)	0.39	0.50 (0.42, 0.57)	0.34	0.45 (0.37, 0.52)	-0.38	-0.44 (-0.52, -0.36)	-0.37	-0.42 (-0.49, -0.34)
Lycopene (mcg)	0.08	0.12 (0.00, 0.23)	0.05	0.05 (-0.07, 0.16)	-0.04	-0.03 (-0.15, 0.08)	-0.04	-0.03 (-0.15, 0.08)	-0.06	-0.11 (-0.22, 0.01)	-0.07	-0.11 (-0.23, 0.01)

Table 1.5 (Continued): Pearson correlation coefficients (95% CI) comparing the plant-based diet indices from the SFFQs against nutrients from the 7DDRs, unadjusted, and energy-adjusted and deattenuated, among 634 men from MLVS

	Overall Plant-based Diet Index				Healthful Plant-based Diet Index				Unhealthful Plant-based Diet Index			
	SFFQ1		SFFQ2		SFFQ1		SFFQ2		SFFQ1		SFFQ2	
	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated	Unadj	Energy-adj + Deattenuated
Beta cryptoxanthin (mcg)	0.25	0.30 (0.20, 0.39)	0.24	0.24 (0.14, 0.33)	0.18	0.26 (0.17, 0.36)	0.11	0.19 (0.10, 0.29)	-0.13	-0.15 (-0.24, -0.05)	-0.12	-0.11 (-0.20, -0.01)
Vitamin B6 (mg)	0.20	0.18 (0.09, 0.26)	0.19	0.14 (0.05, 0.22)	0.16	0.27 (0.19, 0.35)	0.13	0.24 (0.16, 0.32)	-0.12	-0.14 (-0.23, -0.06)	-0.11	-0.11 (-0.20, -0.03)
Dietary folate equivalents (mcg)	0.25	0.26 (0.18, 0.34)	0.23	0.21 (0.12, 0.29)	0.02	0.09 (0.01, 0.18)	0.02	0.10 (0.01, 0.18)	0.05	0.08 (0.00, 0.17)	0.04	0.09 (0.00, 0.17)
Calcium (mg)	0.16	0.06 (-0.02, 0.15)	0.15	0.06 (-0.03, 0.14)	0.00	0.10 (0.02, 0.19)	0.00	0.10 (0.01, 0.18)	-0.08	-0.07 (-0.15, 0.02)	-0.03	-0.01 (-0.09, 0.08)
Magnesium (mg)	0.35	0.33 (0.25, 0.40)	0.38	0.35 (0.27, 0.42)	0.37	0.63 (0.57, 0.68)	0.37	0.64 (0.58, 0.69)	-0.30	-0.38 (-0.45, -0.31)	-0.29	-0.35 (-0.42, -0.27)
Potassium (mg)	0.28	0.26 (0.18, 0.33)	0.30	0.25 (0.17, 0.32)	0.30	0.54 (0.47, 0.60)	0.28	0.52 (0.45, 0.58)	-0.29	-0.38 (-0.45, -0.30)	-0.28	-0.34 (-0.41, -0.26)

All nutrients are without supplements

All dietary variables have been log-transformed

Associations with nutrient biomarkers were also in the expected directions, albeit weaker than the associations observed with nutrients computed from diet record intakes (Table 1.6). While hPDI had a weak positive association with polyunsaturated fat (as a percentage of total fat), uPDI showed a similar magnitude of association but in the opposite direction. uPDI was also weakly inversely associated with monounsaturated fat (as a percentage of total fat). Again, hPDI was positively associated with plasma concentrations of all the carotenoids, retinol, and tocopherol (with the exception of delta tocopherol), while uPDI was inversely associated with most of these, and PDI showed positive correlations with some of them. In most instances, the associations became stronger when we restricted to participants not taking supplements for the specific plasma biomarkers. Both PDI and uPDI were inversely associated, while hPDI was positively associated with HDL cholesterol. On the other hand, uPDI had a positive association with triglycerides, while hPDI was inversely associated with it. The associations of hPDI with lipid parameters were largely seen among women.

Table 1.6: Spearman correlation coefficients (95% CI) comparing plant-based diet indices from the SFFQs against biochemical markers

	Overall Plant-based Diet Index				Healthful Plant-based Diet Index				Unhealthful Plant-based Diet Index			
	SFFQ1		SFFQ2		SFFQ1		SFFQ2		SFFQ1		SFFQ2	
	Crude	Deattenuated	Crude	Deattenuated	Crude	Deattenuated	Crude	Deattenuated	Crude	Deattenuated	Crude	Deattenuated
WOMEN												
Saturated fat (% total fat)	-0.03	-0.07 (-0.20, 0.07)	-0.06	-0.12 (-0.26, 0.02)	-0.01	-0.02 (-0.15, 0.11)	-0.03	-0.05 (-0.19, 0.09)	-0.03	-0.07 (-0.21, 0.07)	0.01	0.00 (-0.13, 0.14)
Monounsaturated fat (% total fat)	-0.01	-0.02 (-0.10, 0.07)	0.00	0.00 (-0.09, 0.08)	-0.05	-0.06 (-0.13, 0.02)	-0.06	-0.07 (-0.15, 0.01)	0.10	0.11 (0.03, 0.19)	0.07	0.08 (0.00, 0.16)
Polyunsaturated fat (% total fat)	0.03	0.05 (-0.06, 0.14)	0.04	0.06 (-0.04, 0.16)	0.05	0.08 (-0.03, 0.17)	0.08	0.11 (0.01, 0.21)	-0.06	-0.08 (-0.18, 0.03)	-0.07	-0.10 (-0.20, 0.00)
Total Cholesterol (mg/dL)	0.00	-0.01 (-0.10, 0.07)	-0.03	-0.04 (-0.11, 0.04)	-0.03	-0.04 (-0.11, 0.05)	-0.05	-0.06 (-0.13, 0.02)	0.04	0.02 (-0.07, 0.10)	0.01	0.00 (-0.08, 0.09)
HDL Cholesterol (mg/dL)	-0.02	-0.02 (-0.10, 0.05)	-0.08	-0.08 (-0.15, -0.01)	0.07	0.09 (0.01, 0.16)	0.06	0.10 (0.02, 0.17)	-0.10	-0.10 (-0.18, -0.03)	-0.11	-0.12 (-0.19, -0.05)
Triglycerides (mg/dL)	-0.03	-0.04 (-0.11, 0.04)	-0.01	-0.01 (-0.09, 0.07)	-0.15	-0.16 (-0.24, -0.09)	-0.16	-0.17 (-0.24, -0.10)	0.14	0.15 (0.08, 0.23)	0.14	0.15 (0.08, 0.23)
Lutein-zeaxanthin (ug/L)	-0.01	-0.01 (-0.11, 0.10)	0.11	0.13 (0.02, 0.23)	0.24	0.27 (0.17, 0.37)	0.28	0.32 (0.22, 0.41)	-0.26	-0.29 (-0.38, -0.18)	-0.20	-0.23 (-0.33, -0.12)

Table 1.6 (Continued): Spearman correlation coefficients (95% CI) comparing plant-based diet indices from the SFFQs against biochemical markers

	Overall Plant-based Diet Index				Healthful Plant-based Diet Index				Unhealthful Plant-based Diet Index			
	SFFQ1		SFFQ2		SFFQ1		SFFQ2		SFFQ1		SFFQ2	
	Crude	Deattenuated	Crude	Deattenuated	Crude	Deattenuated	Crude	Deattenuated	Crude	Deattenuated	Crude	Deattenuated
WOMEN (*Continued*)												
Lutein-zeaxanthin (ug/L)*	-0.01	-0.01 (-0.12, 0.11)	0.12	0.13 (0.01, 0.25)	0.25	0.28 (0.16, 0.38)	0.31	0.35 (0.24, 0.45)	-0.25	-0.28 (-0.38, -0.16)	-0.21	-0.24 (-0.35, -0.11)
Beta cryptoxanthin (ug/L)	0.08	0.11 (-0.02, 0.23)	0.07	0.10 (-0.03, 0.22)	0.16	0.21 (0.09, 0.33)	0.16	0.21 (0.09, 0.33)	-0.18	-0.25 (-0.37, -0.11)	-0.17	-0.23 (-0.35, -0.10)
Lycopene (ug/L)	0.14	0.17 (0.06, 0.28)	0.15	0.18 (0.07, 0.29)	0.19	0.23 (0.11, 0.34)	0.19	0.22 (0.11, 0.33)	-0.11	-0.13 (-0.24, -0.02)	-0.10	-0.11 (-0.22, 0.00)
Lycopene (ug/L)*	0.06	0.08 (-0.07, 0.22)	0.07	0.09 (-0.06, 0.23)	0.14	0.19 (0.04, 0.33)	0.15	0.20 (0.06, 0.34)	-0.16	-0.22 (-0.36, -0.08)	-0.15	-0.20 (-0.34, -0.06)
Alpha carotene (ug/L)	0.16	0.18 (0.08, 0.29)	0.19	0.22 (0.11, 0.32)	0.37	0.42 (0.32, 0.51)	0.37	0.42 (0.32, 0.51)	-0.32	-0.36 (-0.45, -0.26)	-0.27	-0.31 (-0.41, -0.21)
Beta carotene (ug/L)	0.13	0.14 (0.04, 0.24)	0.15	0.16 (0.06, 0.26)	0.35	0.39 (0.30, 0.47)	0.34	0.38 (0.28, 0.46)	-0.31	-0.35 (-0.43, -0.25)	-0.28	-0.31 (-0.40, -0.21)
Beta carotene (ug/L)*	0.13	0.15 (0.01, 0.28)	0.16	0.18 (0.05, 0.31)	0.45	0.50 (0.38, 0.60)	0.49	0.54 (0.42, 0.64)	-0.37	-0.41 (-0.52, -0.29)	-0.36	-0.40 (-0.51, -0.28)

Table 1.6 (Continued): Spearman correlation coefficients (95% CI) comparing plant-based diet indices from the SFFQs against biochemical markers

	Overall Plant-based Diet Index				Healthful Plant-based Diet Index				Unhealthful Plant-based Diet Index			
	SFFQ1		SFFQ2		SFFQ1		SFFQ2		SFFQ1		SFFQ2	
	Crude	Deattenuated	Crude	Deattenuated	Crude	Deattenuated	Crude	Deattenuated	Crude	Deattenuated	Crude	Deattenuated
WOMEN (*Continued*)												
Retinol activity equivalents (ug/L)	-0.02	-0.02 (-0.13, 0.10)	0.00	0.00 (-0.12, 0.11)	0.13	0.16 (0.05, 0.28)	0.10	0.12 (0.00, 0.23)	-0.15	-0.19 (-0.30, -0.08)	-0.14	-0.17 (-0.29, -0.06)
Retinol activity equivalents (ug/L)*	0.04	0.05 (-0.15, 0.24)	-0.01	-0.01 (-0.20, 0.18)	0.24	0.31 (0.11, 0.49)	0.16	0.21 (0.01, 0.39)	-0.22	-0.29 (-0.46, -0.09)	-0.21	-0.27 (-0.45, -0.08)
Alpha tocopherol (ug/L)	0.05	0.07 (-0.06, 0.19)	0.13	0.18 (0.05, 0.30)	0.10	0.13 (0.00, 0.25)	0.10	0.13 (0.00, 0.25)	-0.09	-0.12 (-0.25, 0.01)	-0.05	-0.07 (-0.19, 0.06)
Alpha tocopherol (ug/L)*	0.14	0.19 (-0.01, 0.37)	0.05	0.04 (-0.16, 0.23)	0.22	0.31 (0.11, 0.48)	0.13	0.19 (-0.01, 0.37)	-0.12	-0.17 (-0.36, 0.02)	-0.06	-0.10 (-0.28, 0.10)
Gamma tocopherol (ug/L)	-0.04	-0.05 (-0.16, 0.07)	-0.10	-0.12 (-0.23, -0.01)	-0.13	-0.16 (-0.27, -0.05)	-0.12	-0.15 (-0.26, -0.04)	0.06	0.07 (-0.05, 0.18)	0.06	0.07 (-0.04, 0.19)
Delta tocopherol (ug/L)	0.14	0.26 (0.08, 0.41)	0.14	0.25 (0.07, 0.40)	0.23	0.41 (0.22, 0.57)	0.21	0.37 (0.19, 0.53)	-0.16	-0.28 (-0.43, -0.10)	-0.14	-0.25 (-0.41, -0.08)
Folate (ng/ml)	0.05	0.05 (-0.05, 0.14)	0.05	0.06 (-0.04, 0.15)	0.05	0.06 (-0.04, 0.15)	0.08	0.09 (0.00, 0.18)	-0.06	-0.06 (-0.15, 0.04)	-0.08	-0.09 (-0.18, 0.00)

Table 1.6 (Continued): Spearman correlation coefficients (95% CI) comparing plant-based diet indices from the SFFQs against biochemical markers

	Overall Plant-based Diet Index				Healthful Plant-based Diet Index				Unhealthful Plant-based Diet Index			
	SFFQ1		SFFQ2		SFFQ1		SFFQ2		SFFQ1		SFFQ2	
	Crude	Deattenuated	Crude	Deattenuated	Crude	Deattenuated	Crude	Deattenuated	Crude	Deattenuated	Crude	Deattenuated
WOMEN (*Continued*)												
Folate (ng/ml)*	0.17	0.19 (0.03, 0.35)	0.06	0.07 (-0.10, 0.23)	0.07	0.07 (-0.09, 0.23)	0.10	0.11 (-0.06, 0.26)	-0.01	-0.02 (-0.17, 0.14)	-0.12	-0.13 (-0.29, 0.03)
MEN												
Total Cholesterol (mg/dL)	-0.08	-0.10 (-0.18, -0.02)	-0.06	-0.06 (-0.14, 0.02)	0.01	0.01 (-0.07, 0.10)	0.04	0.04 (-0.05, 0.12)	-0.08	-0.10 (-0.18, -0.01)	-0.09	-0.10 (-0.18, -0.01)
HDL Cholesterol (mg/dL)	-0.09	-0.10 (-0.18, -0.02)	-0.10	-0.11 (-0.19, -0.04)	0.04	0.03 (-0.05, 0.11)	0.06	0.06 (-0.02, 0.14)	-0.11	-0.11 (-0.19, -0.04)	-0.13	-0.14 (-0.21, -0.06)
Triglycerides (mg/dL)	0.04	0.04 (-0.04, 0.12)	0.04	0.05 (-0.03, 0.13)	-0.02	-0.01 (-0.10, 0.07)	-0.02	-0.02 (-0.10, 0.07)	0.09	0.10 (0.02, 0.18)	0.10	0.10 (0.02, 0.18)
Folate (ng/ml)	0.08	0.09 (0.00, 0.16)	0.02	0.01 (-0.07, 0.10)	0.03	0.02 (-0.06, 0.11)	0.02	0.02 (-0.06, 0.11)	0.05	0.05 (-0.03, 0.13)	0.01	0.01 (-0.08, 0.09)
Folate (ng/ml)*	0.12	0.14 (0.01, 0.25)	0.07	0.07 (-0.05, 0.19)	0.07	0.08 (-0.05, 0.20)	0.09	0.10 (-0.03, 0.22)	0.03	0.03 (-0.09, 0.15)	0.01	0.01 (-0.11, 0.13)

Table 1.6 (Continued): Spearman correlation coefficients (95% CI) comparing plant-based diet indices from the SFFQs against biochemical markers

All indices and biomarkers have been log-transformed

All variables were adjusted for age and BMI at enrollment, and weight, smoking status, and energy intake at the time of measurement. Biochemical measures were further adjusted for fasting status at blood draw, and postmenopausal status and hormone use (women only). For carotenoids, retinol, and tocopherol, we further adjusted for plasma lipid levels (cholesterol, HDL, and triglycerides). For plasma lipid levels, we further adjusted for batch.

** Subgroups of women who didn't take supplements for the micronutrient (557 for lutein-zeaxanthin, 572 for lycopene, 430 for beta carotene, 275 for retinol activity equivalents, 196 for alpha tocopherol, 160 for folate among women, and 281 for folate among men)*

Discussion

We evaluated the reliability and validity of three novel diet indices – an overall plant-based diet index (PDI), a healthful plant-based diet index (hPDI), and an unhealthful plant-based diet index (uPDI) – assessed via SFFQs against 7-day diet records and biochemical markers among 45-80 year-old men and women in the US. We found reasonable one-year reproducibility for the three indices, with ICCs ranging from 0.65 to 0.79. Deattenuated and energy-adjusted correlation coefficients comparing the PDI from SFFQs and 7DDRs were moderately high, ranging from 0.62 to 0.67. The three indices were also correlated with 7DDR nutrients and plasma biomarkers in expected directions. These results were fairly consistent among men and women, and across the two SFFQ measurements.

Evaluating overall diet quality using dietary patterns can help overcome the several disadvantages inherent in the single nutrient/food approach (1). These include difficulty in accounting for interactions between nutrients, intractable confounding by other nutrients, and reduced power to detect the effect of a single food in isolation. Recommendations based on dietary patterns are also more translatable, as they pertain to the diet as a whole as opposed to a number of different foods and nutrients. There are two main approaches to dietary pattern analysis (1). In the empirical approach, such as factor analysis, statistical methods are used to derive predominant dietary patterns from existing dietary data. In the *a priori* approach, existing knowledge of a hypothesized 'healthy' (or 'unhealthy') diet is used to create a diet index, such as was done in this study. Several studies have examined the reliability and validity of *a priori* diet indices. In one of the earliest reviews of this topic in 1996, Kant found that most diet indices had been evaluated only with respect to nutrient adequacy (49).

The magnitude of validity and reliability of the plant-based indices examined here are comparable to the validity and reliability of other dietary indices (50,51). For instance, the original Healthy Eating Index (HEI) as assessed by diet records and 24-hr recalls was found to be associated with higher plasma concentrations of alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, and vitamin C in a small sample of women (52), and in the larger NHANES population (53). The original HEI was also inversely associated with serum total, LDL, and HDL cholesterol in one of these analyses (53). Other studies have evaluated variations of the Diet Quality Index (DQI) as assessed by FFQs, and found significant associations with plasma levels of nutrient biomarkers and cholesterol parameters (51,54). One of these studies (54), carried out among participants from HPFS (one of the cohorts used in this study) found the DQI-Revised as assessed by the SFFQ to be positively associated with plasma concentrations of alpha-carotene (r=0.43), beta-carotene (r=0.35), lutein (r= 0.31), and alpha-tocopherol (r=0.25), inversely correlated with plasma total cholesterol (r=0.22), and associated in expected directions with nutrients from 7DDRs.

The inverse associations of hPDI with total fat, saturated fat, and cholesterol, and the positive associations with unsaturated fatty acids, fiber, protein, and various micronutrients from the 7DDRs show that the hPDI is a good measure of overall diet quality. The uPDI on the other hand is a measure of poor diet quality, being inversely associated with all 7DDR-assessed nutrients with the exception of total carbohydrates and sugar. Thus the SFFQ is able to adequately capture diet quality through variations of a plant-based diet. These findings are corroborated by the similar associations observed with plasma biomarkers, albeit in lower magnitudes. The weaker correlations with plasma biomarkers could be due to various reasons (26). Plasma concentrations of several nutrient biomarkers are under tight homeostatic control, resulting in little correlation between the dietary intake of that nutrient and its plasma levels. Some nutrients are endogenously synthesized, further attenuating correlations with dietary intake. This, for instance, could explain the low correlations observed with plasma saturated and monounsaturated fatty acids. There are also several determinants of plasma nutrient concentrations other than just nutrient intake. While we tried to control for some of these in our analysis, there could be others which we were not able to adequately account for, making it difficult to remove extraneous variation in the biomarker, further attenuating associations with dietary intake assessed by SFFQs. Despite these limitations, documenting significant associations with nutrient biomarkers is important, as their errors are usually uncorrelated with those of self-report assessments. The healthful and unhealthful plant-based diet indices were also associated in opposing directions with plasma HDL cholesterol and triglycerides, further confirming their ability to capture diet quality, and predict intermediate risk factors.

Ours is the first study evaluating the reproducibility and validity of plant-based diet indices in a large sample of men and women in the US. We used 7DDRs as the reference method, as SFFQs have fewer correlated errors with diet records than other self-report assessment methods (26). Major sources of error in an SFFQ are the fixed list of foods, long-term recall, varying perceptions of portion sizes, and differing interpretations of questions. The diet record on the other-hand is open-ended, does not depend on memory, allows for direct assessment of portion sizes by weight or other dimensions, and the errors related to interpretation are largely from the dietician coding rather than the recording of the participant. One source of error that is likely to remain correlated when comparing SFFQs and diet records is the food composition database used to compute nutrients. However, as we examined correlations of 7DDR nutrients with food-based indices, this source of correlated error was likely minimal. We also showed independent correlations of the indices with plasma biomarkers, although a disadvantage is that no one biomarker exists that can capture the underlying construct of a plant-based diet. Another limitation of the study is that we did not compute hPDI and uPDI from the 7DDRs, and hence couldn’t examine their correlations with corresponding indices from SFFQs, limiting our ability to correct for measurement error in large-scale epidemiologic analyses with these indices. We also didn’t include composite recipes from the 7DDRs when creating the PDI as we were not able to match these directly to SFFQ food items. Nevertheless, it is reasonable to assume that participants who are higher in their consumption of a food group from matched food items are also higher in their consumption of that food group from unmatched recipes, resulting in similar food group rankings. As PDI is based on rankings of food group intakes, this would result in similar overall PDI scores with and without including the additional 7DDR foods, with minimal consequent impact on SFFQ-7DDR correlations. Lastly, given the homogeneity of the WLVS and MLVS, our results may not be generalizable to other populations. Future studies should be done to replicate these findings in more diverse populations.

Conclusions

In conclusion, we found reasonable reliability and validity of three novel plant-based diet indices assessed using SFFQs among male and female health professionals in the US. These diet indices can thus be potentially used in large-scale SFFQ-based epidemiologic studies to examine associations of overall diet quality with disease endpoints.

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CHAPTER 2

PLANT-BASED DIETARY PATTERNS AND INCIDENCE OF TYPE 2 DIABETES IN US MEN AND WOMEN

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Abstract

Background: Plant-based diets have been recommended to reduce risk of type 2 diabetes (T2D). However not all plant foods are necessarily beneficial. We examined the association of an overall plant-based diet, and hypothesized healthful and unhealthful versions of a plant-based diet, with T2D incidence in three prospective cohort studies in the US.

Methods: We included 69,949 women from Nurses' Health Study (NHS) (1984-2012), 90,239 women from NHS2 (1991-2011), and 40,539 men from Health Professionals Follow-up Study (1986-2010), free of chronic diseases at baseline. Dietary data are collected every 2-4 years using a semi-quantitative food frequency questionnaire. Using this, we created an overall plant-based diet index (PDI), where plant foods received positive scores while animal foods received reverse scores. We also created a healthful PDI (hPDI) where healthy plant foods (whole grains, fruits, vegetables, nuts, legumes, oils, tea/coffee) received positive scores, while less healthy plant foods (fruit juices, sweetened beverages, refined grains, potato/fries, sweets) and animal foods (animal fat, dairy, egg, fish/seafood, poultry/red meat, miscellaneous animal foods) received reverse scores. Lastly, we created an unhealthful PDI (uPDI) by assigning positive scores to less healthy plant foods, and reverse scores to healthy plant foods and animal foods.

Results: We documented 16,162 incident T2D cases during 4,102,369 person-years of follow-up. In pooled multivariable-adjusted analysis, both the overall and healthful plant-based diet indices were inversely associated with T2D [(PDI: HR for extreme deciles, 0.51; 95% CI, 0.47-0.55; p trend<0.001) (hPDI: HR for extreme deciles, 0.55; 95% CI, 0.51-0.59; p trend<0.001)]. The association with PDI was considerably attenuated when we additionally adjusted for body mass index (BMI) categories (HR, 0.80; 95% CI, 0.74-0.87; p trend<0.001), while that with hPDI remained largely unchanged (HR, 0.66; 95% CI, 0.61-0.72; p trend<0.001). The unhealthful plant-based diet index was positively associated with T2D even after BMI adjustment (HR for extreme deciles, 1.16; 95% CI, 1.08-1.25; p trend<0.001). Limitations of the study include self-reported diet assessment with possibility of measurement error, and potential for reverse or unmeasured confounding given the observational nature of the study design.

Conclusions: Our study suggests that plant-based diets, especially when rich in high-quality plant foods, are associated with substantially lower risk of developing T2D. This supports current recommendations to shift to diets rich in healthy plant foods, with lower intake of less healthy plant and animal foods.

Introduction

Type 2 diabetes (T2D) is associated with increased morbidity, mortality, and healthcare costs in the US (1). Several plant foods, such as whole grains, fruits, and vegetables are associated with a lower risk of T2D (2-4), while certain animal foods, such as red and processed meats, are positively associated with T2D risk (5). Additionally, the recently released 2015 Dietary Guidelines Advisory Committee report recommends shifting away from intake of certain animal foods and moving towards a plant-rich diet (6). Thus, we evaluated the hypothesis that a plant-based diet is protective against T2D.

Prior studies on plant-based diets and T2D (7-9) have defined them as 'vegetarian' diets, categorizing study populations dichotomously into participants who do or do not consume some or all animal foods. An important question from clinical and public health standpoints, however, is whether gradually moving towards a plant-rich diet by progressively decreasing animal food intake lowers T2D risk. If so, public health recommendations could suggest incremental dietary changes. Existing studies of vegetarian diets and T2D are also limited by a lack of differentiation among plant foods with divergent effects on T2D, because less nutrient-dense plant foods such as refined grains, potatoes, and sugar-sweetened beverages are associated with higher T2D risk (10-12).

We thus conceptualized a graded dietary pattern that positively weighs plant foods and negatively weighs animal foods, similar to the approach used by Martínez-González et al (13). We examined the association of this overall plant-based diet, and *a priori*, healthful and unhealthful versions of a plant-based diet, with T2D incidence in three large prospective cohort studies in the US. We hypothesized that these plant-based diets would be inversely associated with T2D risk.

Methods

Study protocols for all cohorts were approved by institutional review boards of Brigham and Women's Hospital and the Harvard Chan School; completion of the self-administered questionnaire was considered to imply informed consent.

Study population

The Nurses' Health Study (NHS) started in 1976 with 121,701 female nurses (aged 30-55 years) (14), the NHS2 started in 1989 with 116,430 female nurses (aged 25-42 years) (15), and the Health Professionals Follow-up Study (HPFS) started in 1986 with 51,529 male health professionals (aged 40-75 years) (16), from across the US. Follow-up questionnaires collect information on lifestyle and medical history biennially, with a response rate of ~90% per cycle. In the current analysis, the 1984, 1986, and 1991 cycles were the baseline for NHS, NHS2, and HPFS respectively, when data on most covariates of interest were first comprehensively measured. Participants with diabetes, cancer (except nonmelanoma skin cancer), cardiovascular disease (CVD), reported energy intake levels outside predefined limits (<600 or >3500 kcal/day for women and <800 or >4200 kcal/day for men), or incomplete dietary data at baseline were excluded. The final analysis included 69,949 women in NHS, 90,239 women in NHS2, and 40,539 men in HPFS at baseline.

Dietary assessment

Dietary data were collected every 2-4 years using a semi-quantitative food frequency questionnaire. Participants were asked how often they consumed a defined portion of ~130 food items over the previous year. Response categories ranged from "never or less than once/month" to "≥6 times/day". The reliability and validity of the questionnaires have been described previously (17-20).

Plant-based diet indices

We created an overall plant-based diet index (PDI), a healthful plant-based diet index (hPDI) an unhealthful plant-based diet index (uPDI). The procedure we used to create these indices is similar to the one used by Martínez-González et al. (13); their 'provegetarian food pattern' is similar in composition to our PDI. Frequencies of consumption of each food were converted into servings consumed per day. Then 18 food groups were created by adding up the servings of foods that belong to each food group. These food groups were created on the basis of nutrient and culinary similarities, within larger categories of healthy and less healthy plant foods, and animal foods. We distinguished between healthy and less healthy plant foods using existing knowledge of associations of the foods with T2D, other outcomes (CVD, certain cancers), and intermediate conditions (obesity, hypertension, lipids, inflammation). Plant foods not clearly associated in one direction with several health outcomes, specifically alcoholic beverages, were not included in the indices. We also excluded margarine from the indices, as its fatty acid composition has changed over time from high trans to high unsaturated fats. We controlled for alcoholic beverage and margarine consumption in the analysis.

Healthy plant food groups included whole grains, fruits, vegetables, nuts, legumes, vegetable oils, and tea/coffee, whereas less healthy plant food groups included fruit juices, sugar sweetened beverages, refined grains, potatoes, and sweets & desserts. Animal food groups included dairy, egg, fish/seafood, meat (poultry and red meat), animal fats, and miscellaneous animal-based foods.

Table S2.1 details examples of foods constituting the food groups. The 18 food groups were ranked into quintiles, and each quintile was assigned a score between 1 and 5. For PDI, participants above the highest quintile of all plant food groups received a score of 5, those above the second highest quintile but below the highest quintile received a score of 4, and so on till participants below the lowest quintile who received a score of 1 (positive scores). On the other hand, participants above the highest quintile of all animal food groups received a score of 1, those between the highest and second highest quintiles received a score of 2, and so on till participants below the lowest quintile who received a score of 5 (reverse scores). For 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 reverse scores to healthy plant food groups and animal food groups. The 18 food group scores were summed to obtain the indices, with a theoretical range of 18 (lowest possible score) to 90 (highest possible score). The observed ranges at baseline were 24-85 (PDI), 28-86 (hPDI), and 27-90 (uPDI) across the cohorts. The indices were analyzed as deciles, with energy intake adjusted at the analysis stage.

<u>Ascertainment of type 2 diabetes</u>

Participants who self-reported physician-diagnosed diabetes were sent a supplementary questionnaire with established validity to confirm diagnosis (21,22). Only confirmed cases that met ≥1 of the following criteria were included (as per the National Diabetes Data Group) (23): A] ≥1 classic symptoms plus fasting blood glucose≥140 mg/dL (≥7.8 mmol/L) or random blood glucose≥200 mg/dL (11.1 mmol/L); B] no symptoms, but raised blood glucose levels on two different occasions, i.e. fasting blood glucose≥140 mg/dL, and/or random blood glucose≥200 mg/dL, and/or 2-hr blood glucose after oral glucose tolerance testing≥200 mg/dL; C] treatment with hypoglycemic drugs. The threshold for fasting plasma glucose was changed to ≥126 mg/dL (≥7.0 mmol/L) starting 1998 (24). HbA1c≥6.5% was further added to the diagnosis criteria starting 2010 (25).

Assessment of covariates

We collected height at baseline and updated information on weight, physical activity, smoking, multivitamin use, ethnicity, family history of T2D, hypertension, and hypercholesterolemia through biennial questionnaires. In NHS and NHS2, we also assessed information on menopausal status, post-menopausal hormone use, and oral contraceptive use.

Statistical analysis

We calculated person-time for each participant from questionnaire return date until T2D diagnosis, death, censoring, or end of follow-up (30th June 2012 in NHS, 30th June 2011 in NHS2, and 1st January 2010 in HPFS). For the primary analysis, we categorized the indices into deciles, so as to not make assumptions about linearity, and limit the influence of outlying observations. We used Cox proportional-hazards regression to evaluate the associations between deciles of each index and T2D incidence. Age (years) was used as the time scale with stratification by calendar time (2-year intervals). We adjusted for smoking status, alcohol intake, physical activity, family history of diabetes, multivitamin use, margarine intake, energy intake, baseline hypertension and hypercholesterolemia, body mass index (BMI) categories, postmenopausal status & hormone use (women), and oral contraceptive use (NHS2). Continuous covariates were included in the model as categories for same the reasons cited above for categorizing the indices.

All dietary variables were cumulatively updated, i.e. were averaged over the entire follow-up duration to better capture long-term diet. Updating was stopped when major outcomes (CVD and cancer) developed, as diagnosis with these conditions could change an individual’s diet. Values of non-dietary covariates were updated every 2 years to account for changes in these variables over time. In order to examine potential nonlinear associations, we created continuous variables of the indices by assigning the median value to each decile and conducting tests for linear trend, examined associations per 10-unit increase in the indices, and used restricted cubic splines. We tested for effect modification by age, physical activity, family history of diabetes, and BMI, by including cross-product terms. The analysis was carried out separately for each cohort, and combined using a fixed-effects model; the Cochrane Q statistic (26), the I^2 statistic (27), and the between-study coefficient of variation (28,29) were used to assess heterogeneity among the cohorts. All statistical tests were 2-sided ($\alpha=0.05$). All analyses were performed using SAS version 9.4 for UNIX (SAS Institute).

Results

Baseline characteristics

The distribution of age-adjusted baseline characteristics according to the overall and healthful plant-based diet indices have been shown in Tables S2.2 and 2.1. Participants with higher scores on the PDI or hPDI were older, more active, leaner, and less likely to smoke than participants with lower scores. They also consumed a lower percentage of calories from saturated and monounsaturated fats, a higher percentage of calories from polyunsaturated fats and carbohydrates, and higher levels of fiber and folate.

Table 2.1: Age-standardized baseline characteristics by deciles of the Healthful Plant-based Diet Index (hPDI)

	NHS (1984)			NHS 2 (1991)			HPFS (1986)		
	Decile 1	Decile 5	Decile 10	Decile 1	Decile 5	Decile 10	Decile 1	Decile 5	Decile 10
Number of participants	7792	7305	6608	8540	9498	9439	3924	4207	3604
Median hPDI	43	54	67	43	54	67	42	54	67
hPDI range	30-48	53-55	63-84	29-47	53-55	62-86	28-47	53-55	63-84
Age (years)	48 (6.9)	50 (7.0)	53 (6.7)	35 (4.8)	36 (4.7)	37 (4.4)	50 (8.9)	53 (9.6)	55 (9.2)
White (%)	99	98	97	96	96	97	97	95	95
Current smoker (%)	28	25	19	14	12	10	13	9	5
Physical activity (MET-h/week)	11 (17)	14 (20)	20 (27)	16 (22)	20 (27)	30 (36)	18 (26)	20 (25)	29 (38)
Body Mass Index (kg/m^2)	25 (5.2)	25 (4.5)	24 (4.0)	25 (6.3)	25 (5.2)	24 (4.3)	26 (3.4)	26 (3.2)	25 (3.1)
Current multivitamin use (%)	32	37	44	35	39	45	35	41	49
Premenopausal (%)	61	48	32	98	97	96	-	-	-
Current postmenopausal hormone use (%)	7.7	11	16	1.9	2.7	3.3	-	-	-
Current oral contraceptive use (%)	-	-	-	13	10	9	-	-	-
Family history of diabetes (%)	28	28	28	35	34	33	21	20	21
History of hypertension (%)	7	7	7	8	6	5	17	19	19
History of hypercholesterolemia (%)	2	3	5	15	14	15	7	9	15
Total energy intake (kcal/d)	2159 (491)	1746 (491)	1407 (420)	2238 (504)	1777 (515)	1489 (439)	2444 (605)	1969 (589)	1686 (503)

Table 2.1 (Continued): Age-standardized baseline characteristics by deciles of the Healthful Plant-based Diet Index (hPDI)

	NHS (1984)			NHS 2 (1991)			HPFS (1986)		
	Decile 1	Decile 5	Decile 10	Decile 1	Decile 5	Decile 10	Decile 1	Decile 5	Decile 10
Saturated fat (% of energy)	14 (2.3)	13 (2.5)	11 (2.6)	13 (2.3)	11 (2.3)	9.4 (2.4)	13 (2.4)	11 (2.5)	8.4 (2.6)
Polyunsaturated fat (% of energy)	6.4 (1.6)	6.6 (1.7)	6.9 (2.1)	5.5 (1.3)	5.7 (1.4)	5.8 (1.6)	5.6 (1.3)	5.9 (1.5)	6.2 (2.0)
Monounsaturated fat (% of energy)	13 (2.0)	13 (2.3)	11 (2.7)	13 (2.1)	12 (2.3)	11 (2.6)	13 (2.1)	12 (2.5)	10 (3.1)
Trans fat (% of energy)	2.1 (0.6)	2.0 (0.6)	1.6 (0.6)	1.9 (0.6)	1.7 (0.6)	1.2 (0.5)	1.6 (0.5)	1.3 (0.5)	0.8 (0.4)
Cholesterol (mg/d)‡	308 (86)	289 (96)	247 (105)	262 (63)	246 (66)	204 (73)	347 (110)	310 (108)	236 (102)
Protein (% of energy)	16 (2.8)	18 (3.2)	19 (3.8)	18 (3.0)	19 (3.4)	20 (4.0)	17 (2.9)	19 (3.2)	19 (3.7)
Carbohydrates (% of energy)	46 (6.9)	46 (7.8)	49 (8.8)	49 (6.7)	49 (7.3)	53 (8.5)	45 (6.8)	46 (8.1)	52 (10.1)
Fiber (g/d)‡	13 (2.7)	16 (3.8)	22 (5.9)	14 (2.9)	18 (4.0)	25 (6.9)	15 (3.7)	20 (5.2)	30 (8.7)
Dietary Folate (mcg/d)‡	313 (174)	368 (211)	489 (290)	391 (241)	468 (289)	583 (328)	389 (202)	461 (253)	608 (354)
Glycemic Load‡	100 (17)	99 (19)	102 (23)	120 (20)	120 (21)	127 (24)	122 (22)	122 (25)	135 (32)
Glycemic Index‡	55 (2.8)	54 (3.5)	51 (4.2)	55 (2.8)	54 (3.2)	52 (3.6)	55 (3.0)	53 (3.4)	52 (4.2)
Alcohol (g/d)	7.1 (12)	7.2 (11)	6.4 (11)	2.8 (6.0)	3.0 (6.1)	3.4 (6.1)	12 (16)	12 (16)	11 (14)
Food group intake (servings/day)‡									
Whole grains	0.3 (0.7)	1.0 (1.0)	1.8 (1.3)	0.6 (0.8)	1.4 (1.0)	2.3 (1.3)	0.6 (0.9)	1.5 (1.2)	2.6 (1.7)
Fruits	0.6 (0.7)	1.2 (0.9)	2.2 (1.2)	0.5 (0.6)	1.2 (0.8)	1.9 (1.1)	0.8 (0.8)	1.5 (1.0)	2.7 (1.7)
Vegetables	1.9 (1.2)	2.9 (1.5)	4.5 (2.2)	1.8 (1.3)	3.2 (1.7)	5.0 (2.4)	1.9 (1.2)	3.0 (1.5)	4.8 (2.5)
Nuts	0.1 (0.4)	0.3 (0.4)	0.5 (0.5)	0.1 (0.3)	0.3 (0.3)	0.4 (0.4)	0.2 (0.5)	0.5 (0.6)	0.7 (0.8)

Table 2.1 (Continued): Age-standardized baseline characteristics by deciles of the Healthful Plant-based Diet Index (hPDI)

	NHS (1984)			NHS 2 (1991)			HPFS (1986)		
	Decile 1	Decile 5	Decile 10	Decile 1	Decile 5	Decile 10	Decile 1	Decile 5	Decile 10
Legumes	0.2 (0.2)	0.4 (0.2)	0.5 (0.4)	0.2 (0.2)	0.4 (0.3)	0.6 (0.4)	0.3 (0.3)	0.4 (0.3)	0.7 (0.5)
Vegetable oil	0.2 (0.5)	0.5 (0.7)	1.0 (1.0)	0.1 (0.3)	0.3 (0.4)	0.5 (0.5)	0.1 (0.2)	0.2 (0.3)	0.4 (0.5)
Tea & Coffee	2.4 (1.8)	3.0 (1.9)	3.6 (2.0)	1.5 (1.7)	2.2 (1.9)	2.8 (2.0)	1.8 (1.8)	2.4 (1.9)	2.6 (2.0)
Fruit juices	0.8 (0.8)	0.7 (0.7)	0.5 (0.6)	0.7 (0.9)	0.7 (0.8)	0.6 (0.7)	0.8 (0.9)	0.8 (0.9)	0.7 (0.8)
Refined grains	2.0 (1.5)	1.6 (1.3)	1.1 (0.9)	1.9 (1.2)	1.6 (0.9)	1.4 (0.7)	2.0 (1.3)	1.5 (1.1)	1.2 (0.8)
Potato	0.6 (0.4)	0.5 (0.3)	0.3 (0.2)	0.7 (0.4)	0.5 (0.3)	0.4 (0.2)	0.7 (0.4)	0.6 (0.4)	0.4 (0.3)
Sugar sweetened beverages	0.5 (0.8)	0.2 (0.5)	0.1 (0.3)	0.9 (1.2)	0.5 (0.8)	0.2 (0.4)	0.7 (0.8)	0.3 (0.6)	0.2 (0.3)
Sweets & desserts	1.4 (1.3)	1.1 (1.1)	0.9 (0.7)	1.5 (1.3)	1.3 (1.0)	1.0 (0.7)	1.8 (1.5)	1.5 (1.2)	1.0 (0.9)
Animal Fat	0.7 (1.1)	0.3 (0.7)	0.2 (0.4)	0.4 (0.7)	0.1 (0.4)	0.1 (0.2)	0.6 (1.0)	0.3 (0.6)	0.1 (0.3)
Dairy	1.8 (1.4)	1.8 (1.2)	1.8 (1.0)	2.3 (1.5)	2.3 (1.3)	2.2 (1.1)	2.2 (1.6)	2.0 (1.2)	1.7 (1.0)
Eggs	0.4 (0.4)	0.3 (0.3)	0.3 (0.3)	0.3 (0.2)	0.2 (0.2)	0.1 (0.1)	0.5 (0.5)	0.3 (0.4)	0.2 (0.3)
Fish & seafood	0.3 (0.2)	0.3 (0.2)	0.3 (0.3)	0.2 (0.2)	0.3 (0.2)	0.3 (0.3)	0.3 (0.3)	0.4 (0.3)	0.4 (0.4)
Poultry	0.2 (0.2)	0.3 (0.2)	0.3 (0.3)	0.3 (1.0)	0.3 (1.0)	0.4 (1.0)	0.8 (1.9)	0.9 (2.0)	1.0 (2.2)
Unprocessed red meat	0.7 (0.4)	0.6 (0.4)	0.5 (0.3)	0.4 (0.9)	0.4 (1.0)	0.3 (1.0)	0.7 (1.4)	0.6 (1.4)	0.5 (1.4)
Processed red meat	0.4 (0.4)	0.3 (0.3)	0.2 (0.2)	0.2 (0.5)	0.1 (0.6)	0.1 (0.5)	0.5 (1.3)	0.4 (1.4)	0.2 (1.1)
Misc. animal-based foods	0.5 (0.4)	0.4 (0.4)	0.3 (0.3)	0.3 (0.8)	0.2 (0.7)	0.1 (0.5)	0.5 (1.6)	0.4 (1.3)	0.2 (0.9)

Table 2.1 (Continued): Age-standardized baseline characteristics by deciles of the Healthful Plant-based Diet Index (hPDI)

Data are means (SD) for continuous variables, or percentages for dichotomous variables

‡Values are energy-adjusted

Abbreviations: MET, Metabolic Equivalent Task; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study

Plant-based diet indices and T2D incidence

During 4,102,369 person-years of follow-up, we documented 16,162 T2D cases. PDI was inversely associated with T2D incidence in all three cohorts after adjusting for potential confounders (Table 2.2). Adjustment for BMI attenuated the relationship, but associations remained significant (pooled Hazard Ratio [HR] for extreme deciles, 0.80; 95% Confidence Interval [CI], 0.74-0.87; HR per 10-unit increase, 0.88; 95% CI, 0.86-0.91; p trend<0.001).

Table 2.2: HRs (95% CI) for Type 2 Diabetes according to deciles of the Overall Plant-based Diet Index

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* Trend†
Nurses' Health Study												
Median	45.5	48.8	50.8	52.4	54.0	55.2	56.7	58.2	60.2	63.6		
Cases/ Person-years	902/ 165059	901/ 162584	839/ 168132	883/ 165825	776/ 164319	729/ 167845	750/ 169967	640/ 159687	686/ 175345	605/ 163941		
Age-adjusted	1.00	1.00 (0.91, 1.09)	0.90 (0.82, 0.99)	0.96 (0.87, 1.05)	0.86 (0.78, 0.95)	0.79 (0.71, 0.87)	0.79 (0.72, 0.87)	0.72 (0.65, 0.79)	0.71 (0.64, 0.79)	0.66 (0.59, 0.73)	0.78 (0.75, 0.81)	<0.001
Multivariable adjusted	1.00	0.96 (0.87, 1.05)	0.85 (0.77, 0.93)	0.87 (0.79, 0.95)	0.77 (0.70, 0.85)	0.69 (0.63, 0.77)	0.68 (0.61, 0.75)	0.60 (0.54, 0.67)	0.59 (0.53, 0.66)	0.51 (0.46, 0.57)	0.68 (0.65, 0.72)	<0.001
Multivariable adjusted + BMI	1.00	1.00 (0.91, 1.10)	0.93 (0.85, 1.03)	0.99 (0.90, 1.09)	0.92 (0.83, 1.02)	0.87 (0.78, 0.96)	0.88 (0.80, 0.98)	0.81 (0.73, 0.90)	0.85 (0.76, 0.94)	0.83 (0.74, 0.93)	0.88 (0.84, 0.93)	<0.001
Nurses' Health Study 2												
Median	45.3	48.8	51.0	52.5	54.0	55.3	57.0	58.7	61.0	64.3		
Cases/ Person-years	692/ 162514	640/ 168175	542/ 164772	487/ 168383	531/ 149724	503/ 171201	533/ 179002	450/ 162962	446/ 165312	376/ 164951		
Age-adjusted	1.00	0.96 (0.83, 1.10)	0.82 (0.71, 0.94)	0.81 (0.70, 0.94)	0.81 (0.70, 0.93)	0.74 (0.63, 0.85)	0.72 (0.62, 0.83)	0.67 (0.58, 0.78)	0.69 (0.60, 0.80)	0.57 (0.48, 0.66)	0.77 (0.72, 0.81)	<0.001

Table 2.2 (Continued): HRs (95% CI) for Type 2 Diabetes according to deciles of the Overall Plant-based Diet Index

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* Trend†
Nurses' Health Study 2 *(Continued)*												
Multivariable adjusted	1.00	0.94 (0.82, 1.08)	0.81 (0.70, 0.94)	0.80 (0.69, 0.93)	0.80 (0.69, 0.92)	0.72 (0.61, 0.83)	0.69 (0.60, 0.81)	0.64 (0.55, 0.75)	0.64 (0.55, 0.75)	0.53 (0.44, 0.62)	0.74 (0.69, 0.78)	<0.001
Multivariable adjusted + BMI	1.00	0.98 (0.88, 1.09)	0.88 (0.78, 0.98)	0.82 (0.73, 0.92)	0.94 (0.84, 1.06)	0.88 (0.78, 0.99)	0.97 (0.86, 1.09)	0.86 (0.75, 0.97)	0.91 (0.80, 1.03)	0.83 (0.72, 0.95)	0.93 (0.87, 0.98)	0.01
Health Professionals Follow-Up Study												
Median	45.0	48.5	50.6	52.3	54.0	55.5	57.0	58.6	61.0	64.4		
Cases/ Person-years	423/ 78216	381/ 74195	358/ 76914	368/ 81339	329/ 80419	302/ 80686	284/ 69591	279/ 80963	302/ 80753	225/ 79592		
Age-adjusted	1.00	0.92 (0.80, 1.06)	0.83 (0.72, 0.95)	0.84 (0.73, 0.96)	0.75 (0.65, 0.87)	0.69 (0.60, 0.80)	0.70 (0.60, 0.82)	0.62 (0.53, 0.72)	0.68 (0.59, 0.79)	0.51 (0.43, 0.60)	0.73 (0.69, 0.77)	<0.001
Multivariable adjusted	1.00	0.90 (0.78, 1.03)	0.82 (0.71, 0.95)	0.82 (0.71, 0.94)	0.74 (0.64, 0.86)	0.68 (0.58, 0.79)	0.68 (0.58, 0.80)	0.59 (0.51, 0.70)	0.64 (0.54, 0.74)	0.48 (0.41, 0.57)	0.70 (0.66, 0.75)	<0.001
Multivariable adjusted + BMI	1.00	0.95 (0.83, 1.09)	0.92 (0.80, 1.06)	0.92 (0.80, 1.06)	0.87 (0.75, 1.00)	0.79 (0.68, 0.92)	0.84 (0.72, 0.98)	0.74 (0.63, 0.87)	0.85 (0.72, 0.99)	0.70 (0.59, 0.83)	0.84 (0.78, 0.89)	<0.001

Table 2.2 (Continued): HRs (95% CI) for Type 2 Diabetes according to deciles of the Overall Plant-based Diet Index

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* Trend†
Pooled results (fixed-effects model)												
Age-adjusted	1.00	0.97 (0.91, 1.04)	0.86 (0.81, 0.92)	0.89 (0.84, 0.96)	0.82 (0.77, 0.88)	0.75 (0.70, 0.81)	0.75 (0.70, 0.81)	0.68 (0.63, 0.73)	0.70 (0.65, 0.75)	0.60* (0.56, 0.65)	0.76 (0.74, 0.79)	<0.001
Multivariable adjusted	1.00	0.94 (0.88, 1.01)	0.83 (0.78, 0.89)	0.84 (0.78, 0.90)	0.77 (0.72, 0.83)	0.69 (0.64, 0.75)	0.68 (0.63, 0.73)	0.61 (0.56, 0.66)	0.61 (0.57, 0.66)	0.51 (0.47, 0.55)	0.70 (0.68, 0.73)	<0.001
Multivariable adjusted + BMI	1.00	0.99 (0.93, 1.05)	0.91 (0.85, 0.97)	0.92* (0.86, 0.98)	0.92 (0.86, 0.98)	0.85 (0.80, 0.91)	0.90 (0.84, 0.97)	0.81 (0.75, 0.87)	0.87 (0.81, 0.93)	0.80 (0.74, 0.87)	0.88 (0.86, 0.91)	<0.001

Multivariable adjusted model: Adjusted for age (years), smoking status (never, past, current [1-14, 15-24, or ≥25 cigarettes/day]), physical activity (<3, 3-8.9, 9-17.9, 18-26.9, or ≥27 MET hours/week), alcohol intake (0, 0.1-4.9, 5-9.9, 10-14.9, or ≥15 g/day), multivitamin use (yes or no), family history of diabetes (yes or no), margarine intake (quintiles), energy intake (quintiles), baseline hypertension (yes or no), baseline hypercholesterolemia (yes or no). Also adjusted for postmenopausal hormone use in NHS & NHS2 (premenopausal, postmenopausal current, past or never user), and for oral contraceptive use in NHS2 (never, past, or current user)

Multivariable model + BMI: Additionally adjusted for BMI (<21, 21-22.9, 23-24.9, 25-26.9, 27-29.9, 30-32.9, 33–34.9, 35-39.9, or ≥40 kg/m^2)

† P value when each decile was assigned the median value and treated as a continuous variable

** P value for Q-statistic<0.05, indicating statistically significant heterogeneity among the three studies*

After multivariable adjustment, a strong inverse association was observed between hPDI and T2D (Table 2.3), which was only modestly attenuated after BMI adjustment (pooled HR for extreme deciles, 0.66; 95% CI, 0.61-0.72; HR per 10-unit increase, 0.83; 95% CI, 0.80-0.85; p trend<0.001). There was significant heterogeneity in the pooled estimates controlled for BMI due to greater attenuation in NHS2. In contrast, the unhealthful plant-based diet index was positively associated with T2D (pooled HR for extreme deciles, 1.16; 95% CI, 1.08-1.25; p trend<0.001) (Figure 2.1).

Table 2.3: HRs (95% CI) for Type 2 Diabetes according to deciles of the Healthful Plant-based Diet Index

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* Trend†
Nurses' Health Study												
Median	44.3	48.2	50.6	52.5	54.0	55.8	57.5	59.3	61.6	65.5		
Cases/ Person-years	1054/ 165958	993/ 168094	871/ 168590	805/ 168233	705/ 158011	783/ 170962	748/ 165507	654/ 162229	615/ 168844	483/ 166277		
Age-adjusted	1.00	0.91 (0.83, 0.99)	0.79 (0.72, 0.87)	0.73 (0.66, 0.80)	0.67 (0.61, 0.74)	0.68 (0.62, 0.75)	0.67 (0.61, 0.73)	0.59 (0.53, 0.65)	0.54 (0.49, 0.59)	0.42 (0.37, 0.47)	0.68 (0.66, 0.71)	<0.001
Multivariable adjusted	1.00	0.96 (0.88, 1.05)	0.85 (0.78, 0.93)	0.80 (0.73, 0.88)	0.75 (0.68, 0.83)	0.77 (0.70, 0.84)	0.76 (0.69, 0.84)	0.69 (0.62, 0.76)	0.65 (0.58, 0.72)	0.52 (0.46, 0.58)	0.75 (0.72, 0.78)	<0.001
Multivariable adjusted + BMI	1.00	0.98 (0.89, 1.06)	0.87 (0.79, 0.95)	0.82 (0.75, 0.90)	0.77 (0.70, 0.85)	0.79 (0.72, 0.87)	0.80 (0.72, 0.88)	0.73 (0.65, 0.80)	0.70 (0.63, 0.78)	0.60 (0.54, 0.68)	0.80 (0.76, 0.83)	<0.001
Nurses' Health Study 2												
Median	44.0	48.0	50.3	52.3	54.0	55.8	57.4	59.2	61.7	66.0		
Cases/ Person-years	725/ 167601	622/ 155811	619/ 184677	553/ 157937	547/ 174667	494/ 160349	497/ 167624	419/ 157065	416/ 167334	308/ 163931		
Age-adjusted	1.00	0.88 (0.79, 0.97)	0.77 (0.69, 0.86)	0.75 (0.67, 0.83)	0.67 (0.60, 0.75)	0.65 (0.58, 0.72)	0.61 (0.54, 0.68)	0.52 (0.46, 0.58)	0.49 (0.43, 0.55)	0.36 (0.31, 0.41)	0.64 (0.62, 0.67)	<0.001

Table 2.3 (Continued): HRs (95% CI) for Type 2 Diabetes according to deciles of the Healthful Plant-based Diet Index

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* Trend†
Nurses' Health Study 2 (*Continued*)												
Multivariable adjusted	1.00	0.99 (0.89, 1.10)	0.93 (0.84, 1.04)	0.93 (0.84, 1.04)	0.84 (0.75, 0.94)	0.85 (0.75, 0.95)	0.82 (0.73, 0.93)	0.73 (0.64, 0.83)	0.72 (0.64, 0.82)	0.58 (0.50, 0.66)	0.79 (0.75, 0.83)	<0.001
Multivariable adjusted + BMI	1.00	1.05 (0.94, 1.17)	0.99 (0.88, 1.10)	1.00 (0.89, 1.12)	0.92 (0.82, 1.03)	0.93 (0.82, 1.04)	0.93 (0.83, 1.05)	0.85 (0.75, 0.96)	0.86 (0.76, 0.98)	0.77 (0.67, 0.89)	0.89 (0.84, 0.93)	<0.001
Health Professionals Follow-Up Study												
Median	43.3	47.3	50.0	52.0	53.8	55.3	57.0	59.2	61.8	66.0		
Cases/ Person-years	397/ 78048	366/ 76324	368/ 82538	359/ 80966	346/ 77813	307/ 70470	328/ 86144	275/ 73681	268/ 79989	237/ 76697		
Age-adjusted	1.00	0.92 (0.80, 1.06)	0.88 (0.76, 1.01)	0.82 (0.71, 0.95)	0.82 (0.71, 0.95)	0.76 (0.66, 0.88)	0.71 (0.61, 0.82)	0.66 (0.56, 0.77)	0.60 (0.51, 0.70)	0.54 (0.45, 0.63)	0.76 (0.72, 0.80)	<0.001
Multivariable adjusted	1.00	0.93 (0.81, 1.07)	0.89 (0.77, 1.02)	0.83 (0.71, 0.95)	0.83 (0.72, 0.96)	0.77 (0.66, 0.90)	0.73 (0.62, 0.85)	0.67 (0.57, 0.79)	0.63 (0.53, 0.74)	0.58 (0.49, 0.68)	0.78 (0.73, 0.82)	<0.001
Multivariable adjusted + BMI	1.00	0.93 (0.81, 1.07)	0.87 (0.76, 1.01)	0.81 (0.70, 0.94)	0.82 (0.70, 0.95)	0.78 (0.67, 0.91)	0.75 (0.64, 0.87)	0.70 (0.59, 0.82)	0.66 (0.56, 0.77)	0.65 (0.55, 0.77)	0.81 (0.77, 0.86)	<0.001

Table 2.3 (Continued): HRs (95% CI) for Type 2 Diabetes according to deciles of the Healthful Plant-based Diet Index

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* Trend†
Pooled results (fixed-effects model)												
Age-adjusted	1.00	0.90 (0.85, 0.96)	0.80 (0.75, 0.85)	0.75 (0.71, 0.80)	0.70* (0.65, 0.74)	0.68 (0.64, 0.73)	0.66 (0.61, 0.70)	0.58 (0.54, 0.62)	0.53 (0.50, 0.57)	0.42* (0.39, 0.45)	0.69* (0.67, 0.70)	<0.001*
Multivariable adjusted	1.00	0.96 (0.91, 1.03)	0.88 (0.83, 0.94)	0.85 (0.79, 0.90)	0.80 (0.74, 0.85)	0.79 (0.74, 0.85)	0.77 (0.72, 0.83)	0.70 (0.65, 0.75)	0.67 (0.62, 0.72)	0.55 (0.51, 0.59)	0.77 (0.75, 0.79)	<0.001
Multivariable adjusted + BMI	1.00	0.99 (0.93, 1.05)	0.91 (0.85, 0.97)	0.87* (0.82, 0.93)	0.83 (0.77, 0.88)	0.83 (0.78, 0.89)	0.83* (0.77, 0.89)	0.76 (0.71, 0.81)	0.74* (0.69, 0.80)	0.66* (0.61, 0.72)	0.83* (0.80, 0.85)	<0.001*

Multivariable adjusted model: Adjusted for age (years), smoking status (never, past, current [1-14, 15-24, or ≥25 cigarettes/day]), physical activity (<3, 3-8.9, 9-17.9, 18-26.9, or ≥27 MET hours/week), alcohol intake (0, 0.1-4.9, 5-9.9, 10-14.9, or ≥15 g/day), multivitamin use (yes or no), family history of diabetes (yes or no), margarine intake (quintiles), energy intake (quintiles), baseline hypertension (yes or no), baseline hypercholesterolemia (yes or no). Also adjusted for postmenopausal hormone use in NHS & NHS2 (premenopausal, postmenopausal current, past or never user), and for oral contraceptive use in NHS2 (never, past, or current user)

Multivariable model + BMI: Additionally adjusted for BMI (<21, 21-22.9, 23-24.9, 25-26.9, 27-29.9, 30-32.9, 33–34.9, 35-39.9, or ≥40 kg/m^2)

† P value when each decile was assigned the median value and treated as a continuous variable

** P value for Q-statistic<0.05, indicating statistically significant heterogeneity among the three studies*

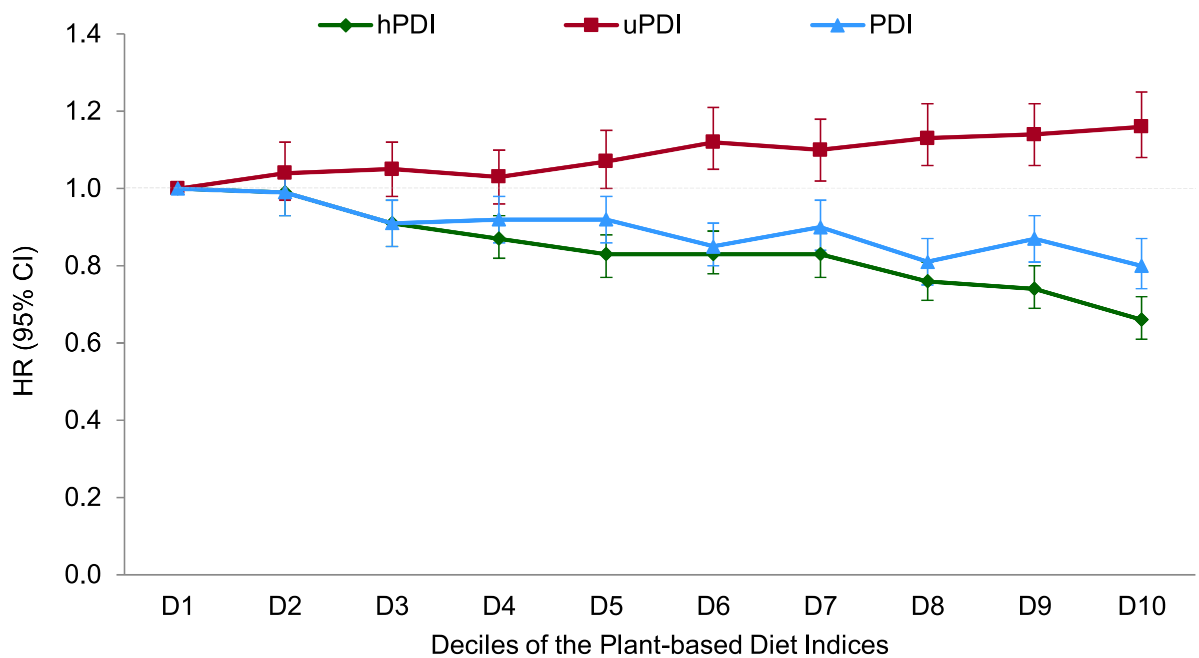

Figure 2.1: Pooled HRs (95% CIs) for T2D according to deciles of the Overall, Healthful, and Unhealthful Plant-based Diet Indices

Results were pooled across the three cohorts using a fixed-effects model

Adjusted for age (years), smoking status (never, past, current [1-14, 15-24, or ≥25 cigarettes/day]), physical activity (<3, 3-8.9, 9-17.9, 18-26.9, or ≥27 metabolic equivalent task hours/week), alcohol intake (0, 0.1-4.9, 5-9.9, 10-14.9, or ≥15 g/day), multivitamin use (yes or no), family history of diabetes (yes or no), margarine intake, (quintiles), energy intake (quintiles), baseline hypertension (yes or no), baseline hypercholesterolemia (yes or no), and body mass index (<21, 21-22.9, 23-24.9, 25-26.9, 27-29.9, 30-32.9, 33–34.9, 35-39.9, or ≥40 kg/m^2). Also adjusted for postmenopausal hormone use in NHS & NHS2 (premenopausal, postmenopausal current, past or never user), and for oral contraceptive use in NHS2 (never, past, or current user)

P-trend<0.001 for all indices. P value obtained by assigning the median value to each decile and entering this as a continuous variable in the model

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; T2D, Type 2 Diabetes; PDI, Overall Plant-based Diet Index; hPDI, Healthful Plant-based Diet Index; uPDI, Unhealthful Plant-based Diet Index

Sensitivity analyses

Our findings remained robust in several sensitivity analyses. In restricted cubic spline analysis, we did not find evidence for a non-linear association of either PDI or hPDI with T2D incidence. Thus, both indices had significant linear associations with T2D incidence, with a stronger dose-response relationship for hPDI (Figure S2.1). Similar inverse associations were observed in strata defined by physical activity and family history of diabetes (Figure 2.2). The inverse association of PDI with T2D incidence was stronger in non-obese vs obese participants (p interaction<0.001), and the inverse associations of both PDI and hPDI were stronger in older participants (p interaction=0.02) (Table S2.3). Associations of both PDI and hPDI with T2D were virtually unchanged upon further adjustment for ethnicity, marital status, recent physical exam, diet beverage intake, and indicators of socio-economic status (Table S2.4). Results were also similar when the analysis was restricted to participants with fasting plasma glucose screening in the previous 2 years [PDI (HR for extreme deciles, 0.78; 95% CI, 0.71-0.85; p trend<0.001); hPDI (HR for extreme deciles, 0.65; 95% CI, 0.59-0.71; p trend<0.001)]. Continuously updating PDI and hPDI throughout follow-up did not change results (Table S2.5). When we used baseline intakes of PDI and hPDI, associations were modestly attenuated but remained significant [PDI (HR for extreme deciles, 0.86; 95% CI, 0.80-0.93; p trend<0.001); hPDI (HR for extreme deciles, 0.70; 95% CI, 0.64-0.75; p trend<0.001)]. Associations were also modestly attenuated when we used the most recent scores prior to T2D [PDI (HR for extreme deciles, 0.84; 95% CI, 0.78-0.91; p trend<0.001) hPDI (HR for extreme deciles, 0.74; 95% CI, 0.69-0.80; p trend<0.001)]. Stratified analysis showed no significant effect modification by ethnicity for the diet indices (p for interaction was 0.92 for PDI, 0.14 for hPDI, and 0.94 for uPDI) (Figure S2.2).

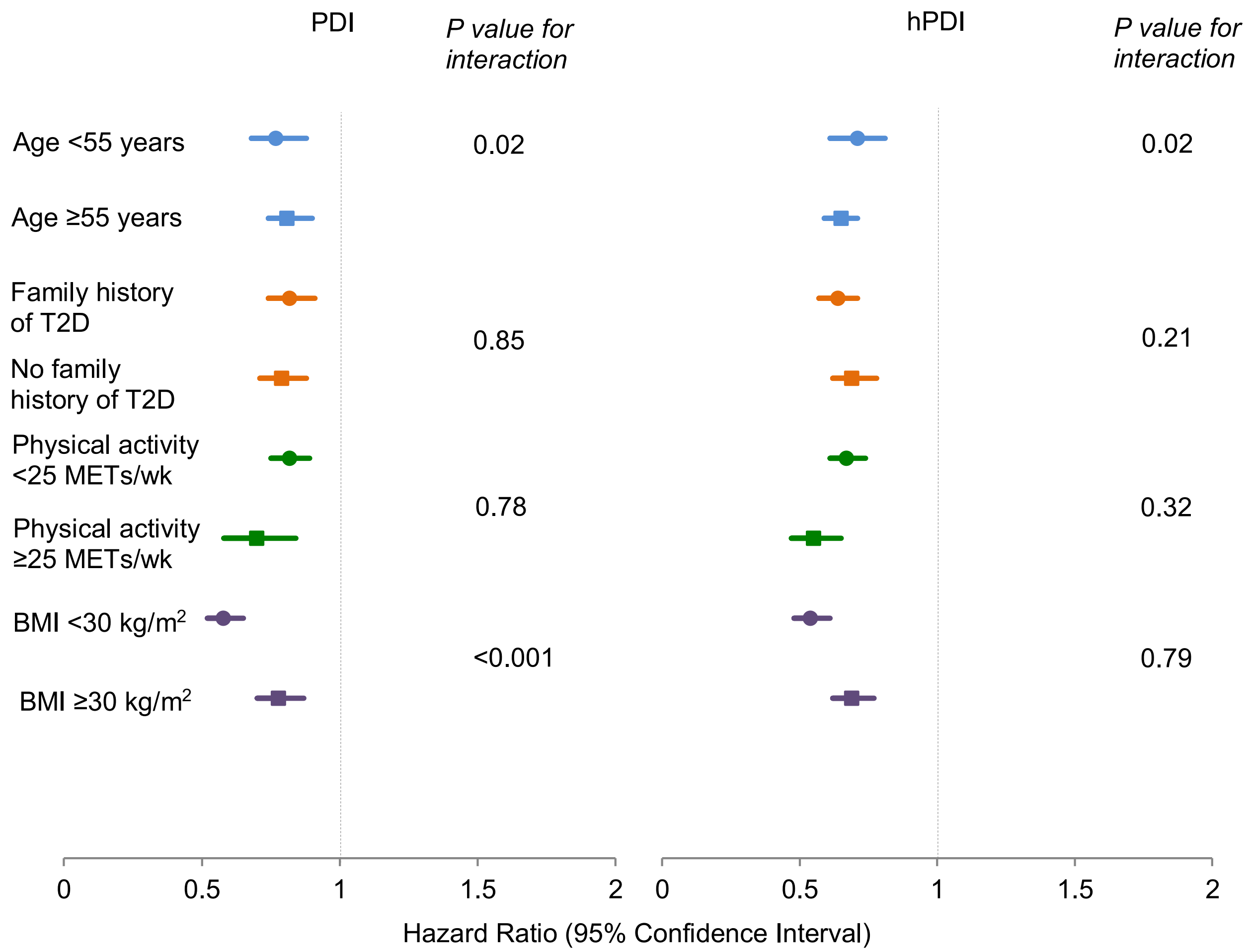

Figure 2.2: Pooled HRs (95% CI) for T2D comparing extreme deciles of the plant-based diet indices, stratified by selected characteristics

Results were pooled across the three cohorts using a fixed-effects model

Adjusted for age (years), smoking status (never, past, current [1-14, 15-24, or ≥25 cigarettes/day]), physical activity (<3, 3-8.9, 9-17.9, 18-26.9, or ≥27 metabolic equivalent task hours/week), alcohol intake (0, 0.1-4.9, 5-9.9, 10-14.9, or ≥15 g/day), multivitamin use (yes or no), family history of diabetes (yes or no), margarine intake (quintiles), energy intake (quintiles), baseline hypertension (yes or no), baseline hypercholesterolemia (yes or no), and body mass index (<21, 21-22.9, 23-24.9, 25-26.9, 27-29.9, 30-32.9, 33–34.9, 35-39.9, or ≥40 kg/m^2). Also adjusted for postmenopausal hormone use in NHS & NHS2 (premenopausal, postmenopausal current, past or never user), and for oral contraceptive use in NHS2 (never, past, or current user)

Figure 2.2 (Continued): Pooled HRs (95% CI) for T2D comparing extreme deciles of the plant-based diet indices, stratified by selected characteristics

P-trend <0.001 for both indices across all strata. P value obtained by assigning the median value to each decile and entering this as a continuous variable in the model

Abbreviations: PDI, Overall Plant-based Diet Index; hPDI, Healthful Plant-based Diet Index; MET, Metabolic Equivalent Task; BMI, Body Mass Index

To examine the individual contributions of healthy plant, less healthy plant, and animal foods to T2D risk, we included variables for all three food groups simultaneously in the fully-adjusted model; this allowed for mutual adjustment for one another, and hence an evaluation of their independent associations with T2D incidence. Healthy plant foods were inversely associated with T2D while animal foods were positively associated, and less healthy plant foods were not associated with risk (Fig S2.3).

To examine the effect of consuming a healthful plant-based diet that is also high in intake of some animal foods known to be associated with reduced risk of several health outcomes [e.g. fish and yogurt intake (30-33)], we created two variations of hPDI. When we modified hPDI to give positive scores to fish and seafood intake, the pooled HRs were slightly attenuated (HR for extreme deciles, 0.73; 95% CI, 0.68-0.79; HR per 10-unit increase, 0.87; 95% CI, 0.85-0.89; p trend<0.001). Results for a modified hPDI with positive scores to yogurt were not substantially different (HR for extreme deciles, 0.65; 95% CI, 0.60-0.71; HR per 10-unit increase, 0.83; 95% CI, 0.81-0.85; p trend<0.001).

Previous analysis in these cohorts have found other dietary patterns such as the Mediterranean diet (aMED), the alternate Healthy Eating Index (aHEI), and Dietary Approaches to Stop Hypertension (DASH), to be inversely associated with T2D (34-36). Thus, in order to examine the independent associations of the plant-based diet indices with T2D incidence, we individually controlled for these patterns (Tables S2.6 and S2.7). Pooled HRs for both PDI and hPDI remained largely unchanged when the Mediterranean diet was controlled for, and were only slightly attenuated with the alternate Healthy Eating Index or Dietary Approaches to Stop Hypertension in the same model.

Discussion

We found significant, linear, inverse associations of plant-based diets, especially a healthier version (hPDI), with T2D incidence in three prospective cohorts in the US. In contrast, a less healthy version of a plant-based diet (uPDI) was associated with increased T2D risk. These associations were independent of BMI and other diabetes risk factors.

There are several mechanisms through which a healthful plant-based diet could lower the risk of T2D (37,38). Such a diet would be rich in dietary fiber, antioxidants, unsaturated fatty acids, and micronutrients such as magnesium, and low in saturated fat. Randomized clinical trials (RCTs) have shown beneficial effects of diets high in viscous and soluble fiber on improving postprandial glucose, as well as long-term glucose metabolism (39). In addition, several prospective studies have shown dietary fiber to be associated with reduced levels of inflammatory markers (40,41). Evidence from animal studies and from epidemiologic studies among humans has shown antioxidants such as polyphenols to have beneficial effects on glucose metabolism, probably through reduced oxidative stress and improved endothelial function (42). High unsaturated fatty acid and low saturated fat contents in diets have also been shown to have anti-inflammatory properties (43), while specific micronutrients such as magnesium are known to play a key role in glucose metabolism (44). Thus, a healthful plant-based diet could enhance glycemic control, improve insulin sensitivity, and decrease chronic inflammation, thereby reducing T2D risk. In addition, the high fiber and low calorie contents of many plant foods could further reduce T2D risk by promoting weight loss/maintenance (37,38). Another less well understood mechanism could be through the gut microbiome. A healthful plant-based diet could promote a gut microbial environment that facilitates the metabolism of fiber and polyphenols, and discourages the metabolism of bile acids, choline and L-carnitine, and amino acids, further reducing T2D risk (45). An unhealthful plant-based diet, on the other hand, would have high glycemic index and load, reduced fiber, lower micronutrient, and higher calorie contents, which could adversely affect the above mentioned pathways, resulting in increased T2D risk (2,10,12). Such a diet would also have high levels of added sugar, which have been strongly shown to be associated with increased weight gain and T2D risk (12,46). Given that BMI represents a pathway through which plant-based diets may affect T2D risk, controlling for it would have resulted in an underestimation of their true effects. Results from the final model controlling for BMI characterize plant-based diet associations that are independent of their potential beneficial effects on body weight. The association of the overall plant-based diet index was also significantly stronger for the non-obese individuals, which could represent true biological interaction with BMI, for instance due to differential mediation by BMI in obese and non-obese individuals, or be a methodological artifact, for instance as a result of differential confounding or measurement error in the two strata.

Only a few prospective studies have examined the association of plant-based diets with T2D. The Adventist Health Studies found significantly higher T2D mortality (RR 3.6, 95% CI: 1.9-7.1) and incidence (RR 1.74, 95% CI: 1.36-2.22) among non-vegetarians than vegetarians (7,8). They also found consumption of vegan, lacto-ovo vegetarian, and semi-vegetarian diets to be associated with lower T2D risk relative to non-vegetarian diets (9). All of these studies were carried out among Seventh-day Adventists, a religious group which encourages a lacto-ovo vegetarian diet. Because the prevalence of vegetarianism is low in the US [~3% (47)], it is difficult to study the relationship between vegetarianism and health outcomes in the general US population. Defining a plant-based diet in terms of a continuous gradation of adherence to a diet high in plant and low in animal foods has allowed us to study its association with T2D in more than 200,000 participants, utilizing detailed dietary data collected at multiple time points over more than two decades.

Our study highlights the varying risk profiles associated with different versions of plant-based diets, emphasizing the importance of considering the quality of plant foods consumed. Participants in the highest decile of uPDI consumed half the amount of healthy plant-foods, and almost double the amount of less healthy plant-foods consumed by participants in the highest decile of hPDI. The healthier version proposed in this study may inform future public health recommendations regarding plant-based diets. We also found that even a modest lowering in animal food consumption was associated with substantially lower T2D incidence. For instance, in the highest decile of hPDI, participants consumed ~4 servings/day of animal foods, relative to 5-6 servings/day in the lowest decile. This has important public health implications, as plant-based diets need not completely exclude animal foods. Numerous studies have previously documented null or inverse associations of several animal foods (e.g. low-fat dairy, lean poultry, fish and seafood), and consistent positive association of certain animal foods (e.g. red and processed meats) with T2D and other diseases. Additionally, in our analysis the association of hPDI with T2D changed only slightly upon positively scoring fish and yogurt intake. Thus, the gradual reduction in animal food intake suggested here can be achieved largely through reducing intake of low-quality animal foods.

Our findings provide support for the 2015 Dietary Guidelines Advisory Committee recommendation that diets rich in healthy plant foods and lower in certain animal foods such as red and processed meats are beneficial for the prevention of chronic diseases (6). Another rationale for shifting towards a plant-based diet is to improve food sustainability because food systems that rely heavily on animal foods require more natural resources than those more reliant on plant foods (48). Thus, dietary guidelines that recommend a healthful plant-based diet would be compatible with the health of humans as well as our eco-system. The hPDI was only moderately correlated with other commonly used dietary patterns such as the Mediterranean diet, aHEI, and DASH, reflecting that this is a novel diet index that captures unique aspects of a healthful plant-based diet. This, coupled with the strong inverse association of the hPDI with T2D independent of these other dietary patterns highlights the importance of focusing on a healthful plant-based diet for a potentially environmentally sustainable approach to T2D prevention.

Our study has several limitations. Because diet was self-reported, measurement errors are inevitable. However, the use of cumulative measures of diet over time not only reduces these errors but also represents long-term dietary habits (18). We also made assumptions about the healthfulness of different plant foods, which although based on prior evidence, has an element of subjectivity, and hence need to be replicated in future studies. While we controlled for several potential confounders, given the observational nature of these studies, residual or unmeasured confounding cannot be ruled out. However, several randomized controlled trials have found vegetarian diets to positively impact intermediate endpoints, such as body weight, blood pressure, lipid profile, and insulin sensitivity in those who were free of T2D (49-51), and in patients with the disease (52-56). The socio-economic homogeneity of the study population also enhances internal validity due to implicit control of confounders. Given that we found similar associations between the plant-based diet indices and T2D among different ethnic groups, it is likely that these findings are generalizable to diverse racial/ethnic groups. Nevertheless, these studies were carried out among health professionals in the US, and hence it would be important to replicate these findings in other populations representing diverse countries and occupational groups.

Conclusions

We found an inverse association between an overall plant-based diet and T2D incidence in three prospective cohorts. This inverse association became substantially stronger for a healthier version of the diet, but was positive for an unhealthful version. Our study supports current recommendations to shift to diets rich in healthy plant foods, with lower intake of less healthy plant and animal foods.

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SUPPLEMENTAL MATERIAL

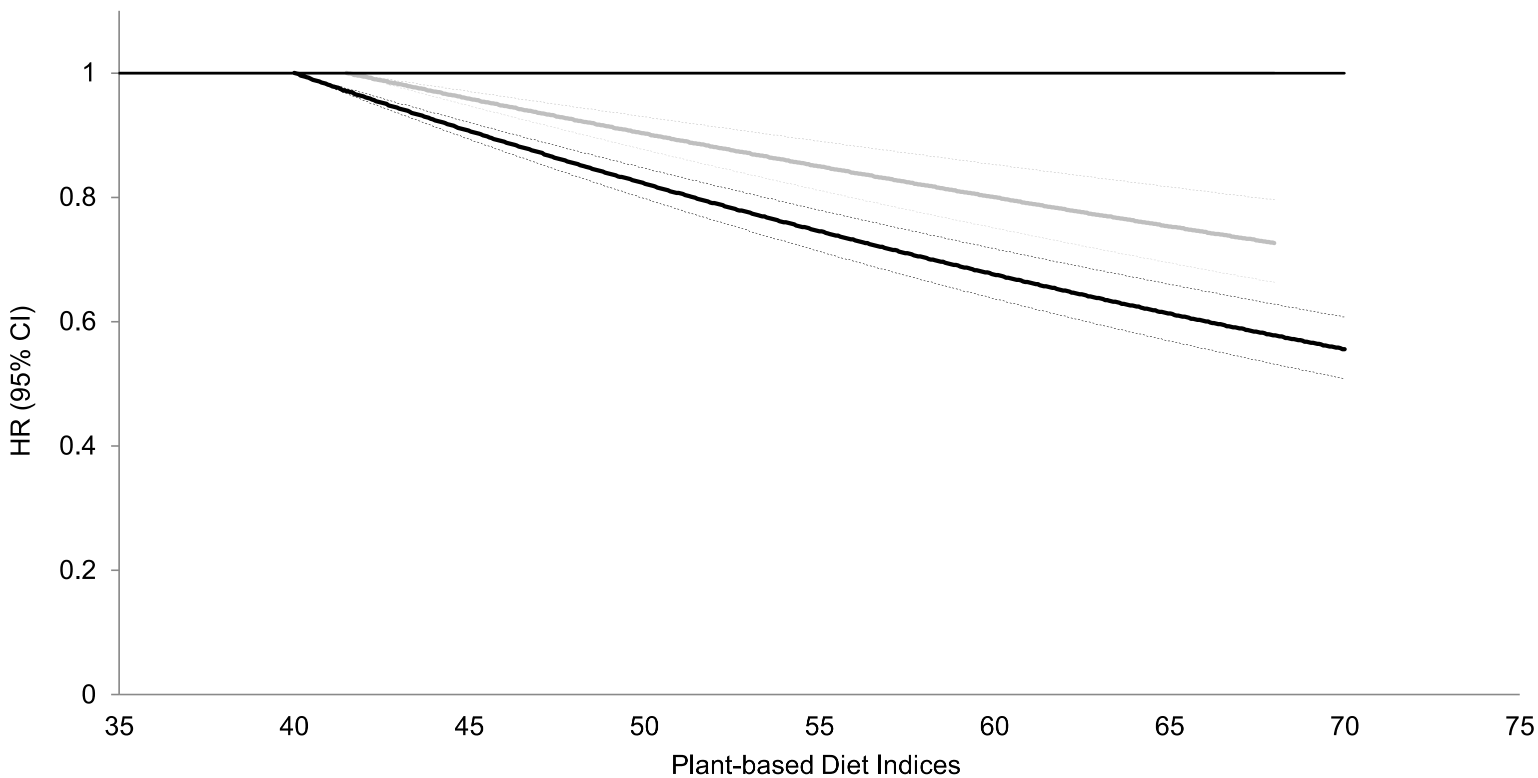

Figure S2.1: Dose-response relationship between intake of plant-based diet indices and incidence of type 2 diabetes

Adjusted for age, smoking status, physical activity, alcohol intake, multivitamin use, family history of diabetes, margarine intake, energy intake, baseline hypertension, baseline hypercholesterolemia, and body mass index. Also adjusted for postmenopausal hormone use in NHS & NHS2, and oral contraceptive use in NHS2

Analysis carried out after combining all three cohorts

Figure S2.1 (Continued): Dose-response relationship between intake of plant-based diet indices and incidence of type 2 diabetes

The graph is left-truncated i.e., the X axis begins at 35, as the minimum values of the cumulatively updated indices are 41.5 (PDI) and 40 (hPDI), and the value ‘0’ is theoretically implausible

No spline variables got selected into the model based on stepwise selection; hence the results of the model with the linear term alone have been shown for each index

P value for linear trend <0.001 for both indices

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; PDI, Overall Plant-based Diet Index; hPDI, Healthful Plant-based Diet Index

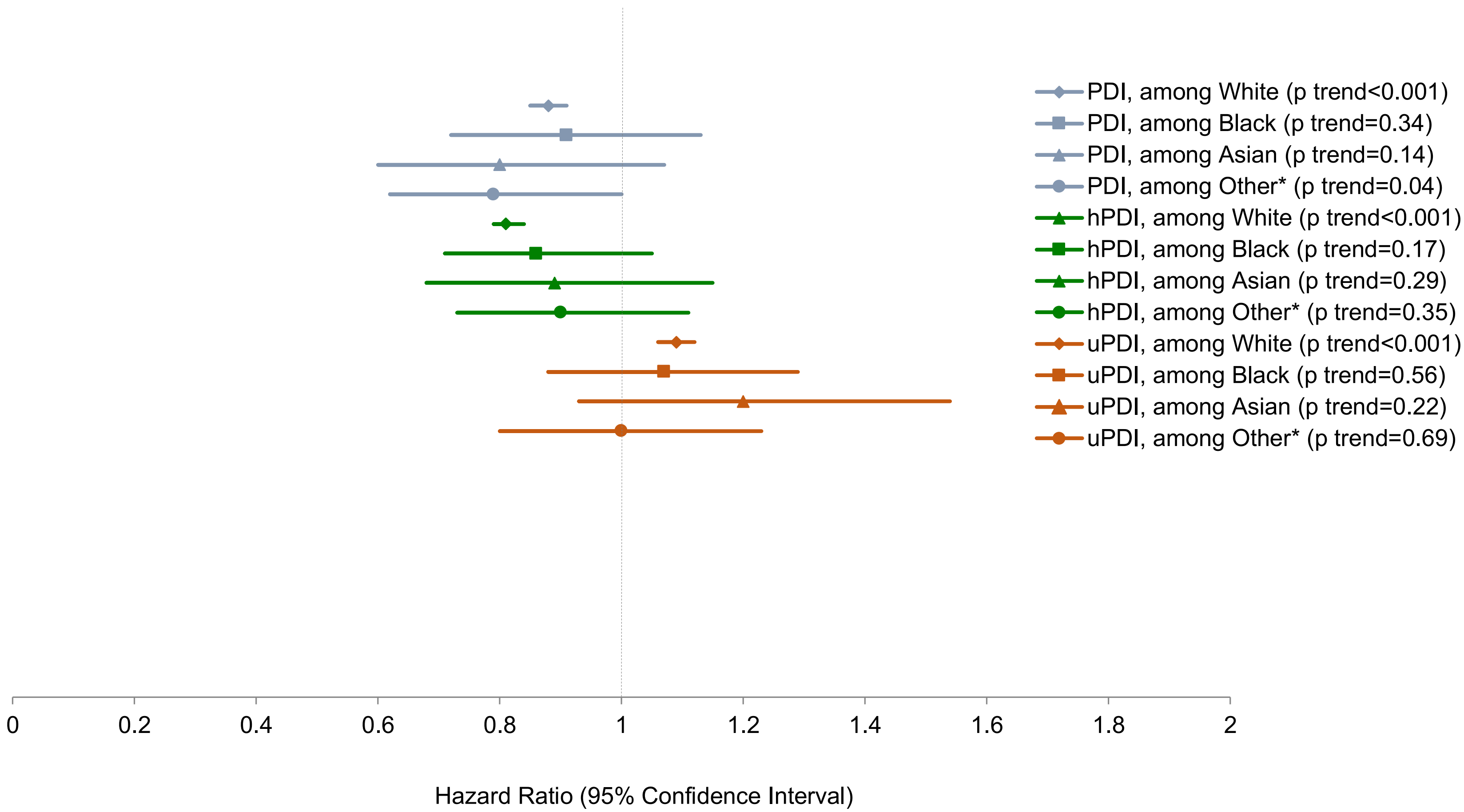

Figure S2.2: HRs (95% CI) for T2D per 10-unit increase in adherence to plant-based diet indices, stratified by ethnicity

Adjusted for age, smoking status, physical activity, alcohol intake, multivitamin use, family history of diabetes, margarine intake, energy intake, baseline hypertension, baseline hypercholesterolemia, and body mass index. Also adjusted for postmenopausal hormone use in NHS & NHS2, and oral contraceptive use in NHS2

Figure S2.2 (Continued): HRs (95% CI) for T2D per 10-unit increase in adherence to plant-based diet indices, stratified by ethnicity

Analysis carried out after combining all three cohorts

P-trend obtained by assigning the median value to each decile and entering this as a continuous variable in the model

P for interaction between ethnicity and PDI=0.92, ethnicity and hPDI=0.14, and ethnicity and uPDI=0.94

**American Indian, Hawaiian, or other ancestry*

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; T2D, Type 2 Diabetes; PDI, Overall Plant-based Diet Index; hPDI, Healthful Plant-based Diet Index; uPDI, Unhealthful Plant-based Diet Index

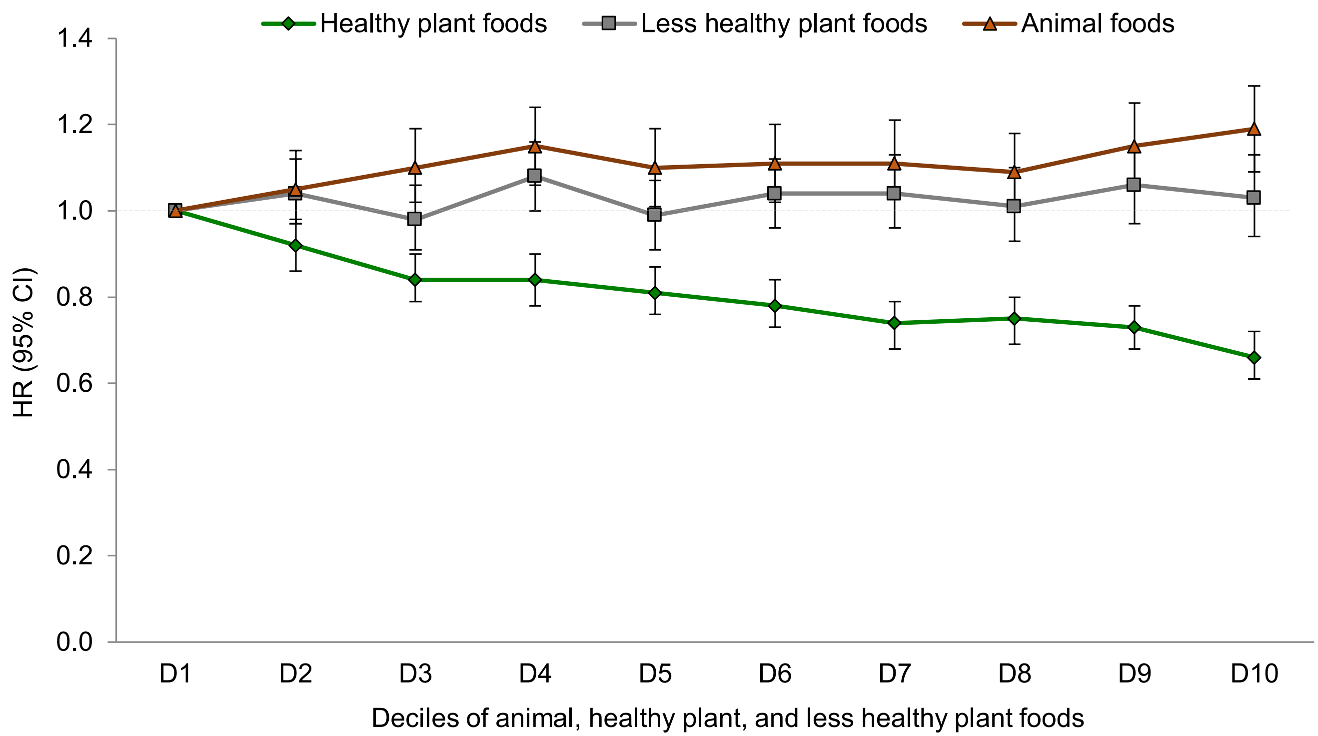

Figure S2.3: Pooled HRs (95% CIs) for T2D according to deciles of animal, healthy plant, and less healthy plant foods (servings consumed/day)

Results were pooled across the three cohorts using a fixed-effects model

Adjusted for age, smoking status, physical activity, alcohol intake, multivitamin use, family history of diabetes, margarine intake, energy intake, baseline hypertension, baseline hypercholesterolemia, and body mass index. Also adjusted for postmenopausal hormone use in NHS & NHS2, and oral contraceptive use in NHS2

Figure S2.3 (Continued): Pooled HRs (95% CIs) for T2D according to deciles of animal, healthy plant, and less healthy plant foods (servings consumed/day)

P-trend=0.49 for less healthy plant foods, and <0.001 for healthy plant foods and animal foods. P value obtained by assigning the median value to each decile and entering this as a continuous variable in the model

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; T2D, Type 2 Diabetes

Table S2.1: Examples of food items constituting the 18 food groups (from the 1984 NHS FFQ)

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
Fruits	Raisins or grapes, prunes, bananas, cantaloupe, watermelon, fresh apples or pears, oranges, grapefruit, strawberries, blueberries, peaches or apricots or plums
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
Nuts	Nuts, peanut butter
Legumes	String beans, tofu or soybeans, beans or lentils, peas or lima beans
Vegetable oils	Oil-based salad dressing, vegetable oil used for cooking
Tea & Coffee	Tea, coffee, decaffeinated coffee
Less healthy	
Fruit juices	Apple cider (non-alcoholic) or juice, orange juice, grapefruit juice, other fruit juice
Refined grains	Refined grain breakfast cereal, white bread, English muffins or bagels or rolls, muffins or biscuits, white rice, pancakes or waffles, crackers, pasta

Potatoes	French fries, baked or mashed potatoes, potato or corn chips
Sugar sweetened beverages	Colas with caffeine & sugar, colas without caffeine but with sugar, other carbonated beverages with sugar, non-carbonated fruit drinks with sugar
Sweets and Desserts	Chocolates, candy bars, candy without chocolate, cookies (home-baked & ready-made), brownies, doughnuts, cake (home-baked & ready-made), sweet roll (home-baked & ready-made), pie (home-baked & ready-made), jams or jellies or preserves or syrup or honey
Animal Food Groups	
Animal fat	Butter added to food, butter or lard used for cooking
Dairy	Skim low fat milk, whole milk, cream, sour cream, sherbet, ice cream, yogurt, cottage or ricotta cheese, cream cheese, other cheese
Egg	Eggs
Fish or Seafood	Canned tuna, dark meat fish, other fish, shrimp or lobster or scallops
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
Misc. animal-based foods	Pizza, chowder or cream soup, mayonnaise or other creamy salad dressing

Table S2.2: Age-standardized baseline characteristics by deciles of the overall plant-based diet index (PDI)

	NHS (1984)			NHS 2 (1991)			HPFS (1986)		
	Decile 1	Decile 5	Decile 10	Decile 1	Decile 5	Decile 10	Decile 1	Decile 5	Decile 10
Number of participants	7750	8381	7270	9149	5382	8681	4567	4802	4424
Median PDI	44	54	65	44	54	66	44	54	65
PDI range	28-48	53-55	61-79	28-48	53-55	62-85	24-48	53-55	62-84
Age (years)	49 (6.9)	50 (7.2)	51 (7.3)	36 (4.7)	36 (4.7)	37 (4.5)	52 (9.4)	53 (9.4)	54 (9.5)
White (%)	98	98	98	96	97	97	95	95	95
Current smoker (%)	31	24	19	17	12	9.6	14	9.5	5.3
Physical activity (MET-h/week)	13 (21)	14 (19)	16 (23)	17 (23)	20 (26)	27 (34)	18 (26)	20 (27)	28 (34)
Body Mass Index (kg/m^2)	25 (5.0)	25 (4.6)	24 (4.2)	25 (5.8)	25 (5.2)	24 (4.6)	26 (3.4)	25 (3.1)	25 (3.0)
Current multivitamin use (%)	37	37	38	35	40	44	40	42	45
Premenopausal (%)	51	49	41	97	97	96	-	-	-
Current postmenopausal hormone use (%)	11	12	13	2.5	2.5	3.3	-	-	-
Current oral contraceptive use (%)	-	-	-	13	11	8	-	-	-
Family history of diabetes (%)	29	29	28	35	34	32	20	21	20
History of hypertension (%)	9.4	8.0	6.9	6.8	6.6	5.2	20	19	19
History of hypercholesterolemia (%)	2.9	3.1	4.3	15	15	15	7.8	9.2	15
Total energy intake (kcal/d)	1422 (444)	1697 (481)	2134 (518)	1417 (447)	1747 (500)	2218 (517)	1633 (508)	1949 (580)	2416 (620)

Table S2.2 (Continued): Age-standardized baseline characteristics by deciles of the overall plant-based diet index (PDI)

	NHS (1984)			NHS 2 (1991)			HPFS (1986)		
	Decile 1	Decile 5	Decile 10	Decile 1	Decile 5	Decile 10	Decile 1	Decile 5	Decile 10
Saturated fat (% of energy)	14 (3.0)	13 (2.4)	11 (2.1)	13 (2.6)	11 (2.2)	9.5 (2.1)	13 (2.9)	11 (2.5)	9 (2.4)
Polyunsaturated fat (% of energy)	6.5 (2.0)	6.6 (1.8)	6.9 (1.6)	5.7 (1.6)	5.6 (1.3)	5.6 (1.2)	5.7 (1.6)	5.9 (1.5)	6.1 (1.5)
Monounsaturated fat (% of energy)	14 (2.7)	13 (2.3)	12 (2.2)	13 (2.6)	12 (2.4)	11 (2.3)	13.2 (2.7)	12.4 (2.6)	11.2 (2.7)
Trans fat (% of energy)	1.8 (0.6)	1.9 (0.6)	2.0 (0.6)	1.8 (0.7)	1.7 (0.6)	1.5 (0.5)	1.3 (0.5)	1.3 (0.5)	1.2 (0.5)
Cholesterol (mg/d)‡	360 (127)	285 (82)	224 (65)	300 (81)	244 (61)	189 (54)	391 (137)	310 (97)	228 (78)
Protein (% of energy)	20 (4.0)	18 (3.1)	16 (2.4)	22 (3.9)	19 (3.2)	17 (2.8)	21 (3.9)	19 (3.3)	17 (2.8)
Carbohydrates (% of energy)	39 (8.2)	46 (6.9)	52 (6.3)	43 (7.5)	50 (6.5)	56 (6.6)	39 (8.1)	47 (7.3)	54 (7.6)
Fiber (g/d)‡	13 (4.0)	16 (4.4)	20 (4.6)	14 (4.2)	18 (5.0)	22 (5.8)	16 (5.4)	20 (5.9)	26 (7.3)
Dietary Folate (mcg/d)‡	360 (262)	378 (230)	404 (193)	445 (323)	479 (294)	511 (251)	431 (299)	470 (268)	531 (252)
Glycemic Load‡	82 (20)	99 (18)	112 (16)	105 (22)	122 (20)	135 (19)	103 (25)	123 (23)	143 (24)
Glycemic Index‡	52 (4.8)	54 (3.7)	54 (2.8)	53 (4.2)	54 (3.3)	54 (2.7)	52 (4.5)	53 (3.5)	54 (3.1)
Alcohol (g/d)	9.3 (14)	6.9 (11)	5.7 (8.7)	3.5 (7.6)	2.9 (5.7)	3.3 (5.7)	14 (18)	11 (15)	9.6 (13)
Food group intake (servings/day)‡									
Whole grains	0.8 (0.9)	1.0 (1.0)	1.5 (1.2)	1.1 (0.8)	1.4 (1.1)	2.0 (1.4)	1.1 (0.9)	1.4 (1.2)	2.2 (1.7)
Fruits	0.9 (0.8)	1.3 (1.0)	1.8 (1.2)	0.9 (0.6)	1.2 (0.9)	1.7 (1.1)	1.1 (0.8)	1.5 (1.2)	2.2 (1.5)
Vegetables	2.6 (1.4)	2.9 (1.7)	3.7 (2.0)	2.6 (1.4)	3.1 (1.8)	4.2 (2.3)	2.5 (1.4)	3.0 (1.6)	4.2 (2.3)
Nuts	0.2 (0.3)	0.3 (0.4)	0.4 (0.6)	0.2 (0.2)	0.2 (0.3)	0.4 (0.5)	0.3 (0.4)	0.5 (0.6)	0.7 (0.8)

Table S2.2 (Continued): Age-standardized baseline characteristics by deciles of the overall plant-based diet index (PDI)

	NHS (1984)			NHS 2 (1991)			HPFS (1986)		
	Decile 1	Decile 5	Decile 10	Decile 1	Decile 5	Decile 10	Decile 1	Decile 5	Decile 10
Legumes	0.3 (0.2)	0.4 (0.3)	0.5 (0.3)	0.3 (0.2)	0.4 (0.3)	0.6 (0.5)	0.3 (0.2)	0.4 (0.3)	0.6 (0.5)
Vegetable oil	0.4 (0.5)	0.5 (0.7)	0.8 (0.9)	0.2 (0.3)	0.3 (0.4)	0.4 (0.5)	0.2 (0.3)	0.2 (0.4)	0.4 (0.5)
Tea & Coffee	2.6 (1.9)	3.0 (1.9)	3.5 (2.0)	1.8 (1.8)	2.2 (1.9)	2.7 (2.0)	2.1 (1.8)	2.4 (1.9)	2.6 (2.0)
Fruit juices	0.5 (0.6)	0.7 (0.7)	0.9 (0.9)	0.5 (0.5)	0.7 (0.7)	1.0 (1.0)	0.6 (0.7)	0.7 (0.8)	1.1 (1.0)
Refined grains	1.3 (1.0)	1.5 (1.2)	1.7 (1.5)	1.4 (0.8)	1.6 (0.9)	1.7 (1.1)	1.3 (0.9)	1.5 (1.1)	1.7 (1.3)
Potato	0.4 (0.3)	0.5 (0.3)	0.5 (0.4)	0.5 (0.3)	0.5 (0.3)	0.6 (0.4)	0.5 (0.3)	0.6 (0.4)	0.6 (0.5)
Sugar sweetened beverages	0.2 (0.5)	0.3 (0.6)	0.3 (0.6)	0.5 (0.8)	0.5 (0.8)	0.4 (0.8)	0.3 (0.5)	0.4 (0.6)	0.4 (0.6)
Sweets & desserts	0.9 (0.8)	1.1 (1.0)	1.3 (1.3)	1.1 (0.8)	1.2 (1.0)	1.4 (1.1)	1.2 (0.9)	1.4 (1.2)	1.6 (1.5)
Animal Fat	0.6 (0.9)	0.4 (0.8)	0.1 (0.6)	0.3 (0.5)	0.2 (0.4)	0.0 (0.3)	0.5 (0.7)	0.3 (0.6)	0.0 (0.4)
Dairy	2.3 (1.3)	1.9 (1.2)	1.3 (1.1)	2.8 (1.4)	2.4 (1.2)	1.7 (1.3)	2.5 (1.4)	2.0 (1.3)	1.4 (1.2)
Eggs	0.5 (0.4)	0.3 (0.3)	0.2 (0.2)	0.3 (0.2)	0.2 (0.2)	0.1 (0.2)	0.5 (0.5)	0.4 (0.4)	0.2 (0.3)
Fish & seafood	0.4 (0.3)	0.3 (0.3)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)	0.2 (0.3)	0.4 (0.3)	0.4 (0.4)	0.4 (0.4)
Poultry	0.3 (0.3)	0.3 (0.2)	0.3 (0.2)	0.4 (1.1)	0.3 (1.0)	0.3 (1.1)	0.9 (2.2)	0.8 (2.0)	0.9 (2.2)
Unprocessed red meat	0.7 (0.4)	0.6 (0.3)	0.5 (0.4)	0.4 (1.0)	0.4 (1.0)	0.3 (1.1)	0.7 (1.5)	0.6 (1.3)	0.5 (1.3)
Processed red meat	0.4 (0.4)	0.3 (0.3)	0.2 (0.3)	0.1 (0.6)	0.1 (0.5)	0.1 (0.6)	0.6 (1.7)	0.4 (1.4)	0.3 (1.2)
Misc. animal-based foods	0.5 (0.4)	0.4 (0.4)	0.3 (0.3)	0.4 (1.0)	0.2 (0.6)	0.1 (0.5)	0.7 (2.1)	0.3 (1.3)	0.2 (0.8)

Data are means (SD) for continuous variables, or percentages for dichotomous variables

‡*Values are energy-adjusted*

Table S2.3: HRs (95% CI) for T2D according to deciles of the overall & healthful plant-based diet indices, stratified by age

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	*P* Trend†
OVERALL PLANT-BASED DIET INDEX											
Nurses' Health Study											
<55 years	1.00	1.09 (0.87, 1.36)	0.99 (0.78, 1.24)	0.95 (0.75, 1.20)	0.93 (0.73, 1.19)	0.79 (0.61, 1.03)	0.93 (0.72, 1.20)	0.81 (0.62, 1.07)	0.92 (0.70, 1.21)	0.73 (0.53, 1.01)	0.02
≥55 years	1.00	0.99 (0.89, 1.10)	0.93 (0.84, 1.03)	1.00 (0.90, 1.11)	0.92 (0.83, 1.03)	0.88 (0.79, 0.98)	0.88 (0.78, 0.98)	0.81 (0.72, 0.91)	0.84 (0.74, 0.94)	0.84 (0.74, 0.95)	<0.001
Nurses' Health Study 2											
<55 years	1.00	1.01 (0.89, 1.13)	0.89 (0.78, 1.00)	0.82 (0.72, 0.93)	0.94 (0.83, 1.07)	0.87 (0.76, 0.99)	0.98 (0.86, 1.12)	0.82 (0.71, 0.94)	0.95 (0.83, 1.10)	0.80 (0.69, 0.93)	0.01
≥55 years	1.00	0.90 (0.70, 1.17)	0.84 (0.64, 1.09)	0.81 (0.62, 1.07)	0.95 (0.73, 1.23)	0.92 (0.71, 1.19)	0.89 (0.67, 1.17)	1.00 (0.76, 1.31)	0.76 (0.56, 1.02)	0.95 (0.71, 1.27)	0.64
Health Professionals Follow-Up Study											
<55 years	1.00	1.24 (0.90, 1.71)	0.87 (0.61, 1.24)	0.92 (0.65, 1.30)	0.88 (0.61, 1.28)	0.80 (0.54, 1.17)	0.93 (0.63, 1.39)	0.85 (0.57, 1.26)	0.77 (0.51, 1.17)	0.63 (0.39, 1.01)	0.01
≥55 years	1.00	0.91 (0.78, 1.06)	0.93 (0.79, 1.09)	0.92 (0.79, 1.08)	0.87 (0.74, 1.02)	0.80 (0.67, 0.94)	0.82 (0.69, 0.97)	0.73 (0.61, 0.86)	0.86 (0.73, 1.02)	0.71 (0.59, 0.86)	<0.001

Table S2.3 (Continued): HRs (95% CI) for T2D according to deciles of the overall & healthful plant-based diet indices, stratified by age

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	*P* Trend†
OVERALL PLANT-BASED DIET INDEX (*Continued*)											
Pooled results (fixed-effects model)											
<55 years	1.00	1.04 (0.94, 1.15)	0.90 (0.81, 1.01)	0.85 (0.77, 0.95)	0.93 (0.84, 1.04)	0.85 (0.76, 0.95)	0.97 (0.87, 1.08)	0.82 (0.73, 0.93)	0.93 (0.82, 1.05)	0.77 (0.68, 0.88)	<0.001
≥55 years	1.00	0.96 (0.88, 1.04)	0.92 (0.85, 1.00)	0.96 (0.88, 1.04)	0.91 (0.84, 0.99)	0.86 (0.79, 0.94)	0.86 (0.79, 0.94)	0.81 (0.74, 0.88)	0.84 (0.76, 0.92)	0.81 (0.74, 0.90)	<0.001
HEALTHFUL PLANT-BASED DIET INDEX											
Nurses' Health Study											
<55 years	1.00	0.86 (0.70, 1.05)	0.90 (0.73, 1.11)	0.79 (0.63, 0.98)	0.74 (0.58, 0.94)	0.72 (0.57, 0.92)	0.73 (0.56, 0.94)	0.72 (0.55, 0.94)	0.60 (0.44, 0.81)	0.54 (0.37, 0.77)	<0.001
≥55 years	1.00	1.01 (0.92, 1.11)	0.87 (0.79, 0.96)	0.83 (0.75, 0.92)	0.78 (0.70, 0.87)	0.81 (0.73, 0.90)	0.81 (0.73, 0.91)	0.73 (0.65, 0.82)	0.72 (0.65, 0.81)	0.62 (0.55, 0.70)	<0.001
Nurses' Health Study 2											
<55 years	1.00	1.04 (0.93, 1.18)	1.02 (0.91, 1.15)	1.03 (0.91, 1.17)	0.90 (0.79, 1.02)	0.93 (0.82, 1.06)	0.95 (0.83, 1.09)	0.86 (0.74, 0.99)	0.82 (0.71, 0.95)	0.76 (0.65, 0.89)	<0.001
≥55 years	1.00	1.07 (0.82, 1.38)	0.83 (0.63, 1.09)	0.86 (0.65, 1.13)	0.99 (0.76, 1.29)	0.90 (0.69, 1.18)	0.87 (0.66, 1.14)	0.81 (0.61, 1.07)	0.97 (0.74, 1.27)	0.78 (0.58, 1.06)	0.12

Table S2.3 (Continued): HRs (95% CI) for T2D according to deciles of the overall & healthful plant-based diet indices, stratified by age

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	*P* Trend†
HEALTHFUL PLANT-BASED DIET INDEX (*Continued*)											
Health Professionals Follow-Up Study											
<55 years	1.00	0.90 (0.65, 1.23)	1.01 (0.74, 1.39)	0.64 (0.45, 0.91)	0.86 (0.60, 1.22)	0.55 (0.36, 0.84)	0.60 (0.40, 0.90)	0.48 (0.30, 0.78)	0.87 (0.59, 1.29)	0.60 (0.37, 0.96)	0.002
≥55 years	1.00	0.95 (0.80, 1.11)	0.86 (0.73, 1.01)	0.85 (0.72, 1.00)	0.82 (0.70, 0.97)	0.83 (0.70, 0.98)	0.78 (0.66, 0.92)	0.74 (0.62, 0.88)	0.63 (0.53, 0.76)	0.66 (0.55, 0.80)	<0.001
Pooled results (fixed-effects model)											
<55 years	1.00	0.98 (0.89, 1.08)	0.99 (0.90, 1.09)	0.93* (0.84, 1.04)	0.86 (0.77, 0.96)	0.85* (0.76, 0.95)	0.87* (0.78, 0.97)	0.80 (0.71, 0.90)	0.78 (0.69, 0.88)	0.71 (0.61, 0.81)	<0.001
≥55 years	1.00	1.00 (0.92, 1.08)	0.86 (0.80, 0.94)	0.84 (0.77, 0.91)	0.81 (0.74, 0.88)	0.82 (0.76, 0.90)	0.81 (0.74, 0.88)	0.74 (0.68, 0.81)	0.72* (0.66, 0.79)	0.65 (0.59, 0.71)	<0.001

Adjusted for age, smoking status, physical activity, alcohol intake, multivitamin use, family history of diabetes, margarine intake, energy intake, baseline hypertension, baseline hypercholesterolemia, and body mass index. Also adjusted for postmenopausal hormone use in NHS & NHS2, and oral contraceptive use in NHS2

† *P value when we assigned the median value to each decile and entered this as a continuous variable in the model*

* *P value for Q-statistic for heterogeneity <0.05, indicating statistically significant heterogeneity in HRs among the three studies*

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; T2D, Type 2 Diabetes

Table S2.4: HRs (95% CI) for type 2 diabetes according to deciles of PDI & hPDI, controlling for additional variables

Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* Trend[†]
OVERALL PLANT-BASED DIET INDEX											
Nurses' Health Study											
1.00	1.01 (0.92, 1.10)	0.94 (0.85, 1.03)	1.00 (0.91, 1.10)	0.93 (0.84, 1.02)	0.87 (0.79, 0.97)	0.89 (0.81, 0.99)	0.82 (0.74, 0.91)	0.85 (0.77, 0.95)	0.84 (0.75, 0.94)	0.89 (0.84, 0.93)	<0.001
Nurses' Health Study 2											
1.00	0.99 (0.89, 1.10)	0.88 (0.79, 0.99)	0.83 (0.73, 0.93)	0.95 (0.85, 1.07)	0.88 (0.78, 1.00)	0.98 (0.87, 1.11)	0.87 (0.77, 0.99)	0.93 (0.82, 1.06)	0.84 (0.73, 0.97)	0.94 (0.88, 0.99)	0.04
Health Professionals Follow-Up Study											
1.00	0.95 (0.83, 1.10)	0.92 (0.80, 1.06)	0.93 (0.80, 1.07)	0.87 (0.75, 1.01)	0.80 (0.69, 0.93)	0.84 (0.72, 0.98)	0.75 (0.64, 0.87)	0.85 (0.73, 1.00)	0.70 (0.59, 0.83)	0.84 (0.78, 0.90)	<0.001
Pooled results (fixed-effects model)											
1.00	0.99 (0.93, 1.05)	0.92 (0.86, 0.98)	0.93 (0.87, 0.99)	0.92 (0.86, 0.99)	0.86 (0.80, 0.92)	0.91 (0.85, 0.98)	0.82 (0.76, 0.88)	0.88 (0.82, 0.94)	0.81 (0.75, 0.88)	0.89* (0.86, 0.92)	<0.001

Table S2.4 (Continued): HRs (95% CI) for type 2 diabetes according to deciles of PDI & hPDI, controlling for additional variables

Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* Trend†
HEALTHFUL PLANT-BASED DIET INDEX											
Nurses' Health Study											
1.00	0.98 (0.89, 1.06)	0.87 (0.79, 0.95)	0.82 (0.74, 0.90)	0.76 (0.69, 0.84)	0.79 (0.72, 0.87)	0.79 (0.72, 0.88)	0.72 (0.65, 0.80)	0.70 (0.63, 0.78)	0.60 (0.53, 0.67)	0.79 (0.76, 0.83)	<0.001
Nurses' Health Study 2											
1.00	1.04 (0.94, 1.16)	0.98 (0.88, 1.10)	1.00 (0.89, 1.12)	0.91 (0.81, 1.02)	0.92 (0.82, 1.04)	0.93 (0.82, 1.05)	0.84 (0.74, 0.96)	0.85 (0.75, 0.97)	0.76 (0.66, 0.88)	0.88 (0.84, 0.93)	<0.001
Health Professionals Follow-Up Study											
1.00	0.93 (0.80, 1.07)	0.87 (0.75, 1.00)	0.80 (0.69, 0.93)	0.80 (0.69, 0.93)	0.77 (0.66, 0.90)	0.74 (0.63, 0.86)	0.69 (0.59, 0.82)	0.65 (0.55, 0.77)	0.64 (0.54, 0.76)	0.81 (0.76, 0.86)	<0.001
Pooled results (fixed-effects model)											
1.00	0.99 (0.93, 1.05)	0.90 (0.85, 0.96)	0.87* (0.81, 0.93)	0.82 (0.77, 0.88)	0.83 (0.77, 0.88)	0.82* (0.77, 0.88)	0.75 (0.70, 0.81)	0.73* (0.68, 0.79)	0.66* (0.61, 0.71)	0.82* (0.80, 0.85)	<0.001*

† P value when we assigned the median value to each decile and entered this as a continuous variable in the model

** P value for Q-statistic for heterogeneity <0.05, indicating statistically significant heterogeneity in HRs among the three studies*

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; PDI, Overall Plant-based Diet Index; hPDI, Healthful Plant-based Diet Index

Table S2.4 (Continued): HRs (95% CI) for type 2 diabetes according to deciles of PDI & hPDI, controlling for additional variables

Adjusted for variables in the multivariable adjusted model + BMI, and ethnicity (White, Black, Other), marital status (married, widowed, divorced/separated, never married), getting a physical exam in the previous year (yes or no), and diet beverage intake (quintiles). Also adjusted for husband's education (high school or less, undergraduate, graduate school) in NHS & NHS2, family income (<29000, 30000-39000, 40000-50000, 50000-74000, 75000-99000, 100000-149000, ≥150000) in NHS2, and work status (full-time, part-time, retired), and profession (dentist, pharmacist, optometrist, osteopath, podiatrist, vet) in HPFS

Table S2.5: Pooled HRs (95% CI) for T2D according to deciles of plant-based diet indices, with different ways of modeling diet

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* Trend[†]
OVERALL PLANT-BASED DIET INDEX												
Primary analysis[§]	1.00	0.99 (0.93, 1.05)	0.91 (0.85, 0.97)	0.92* (0.86, 0.98)	0.92 (0.86, 0.98)	0.85 (0.80, 0.91)	0.90 (0.84, 0.97)	0.81 (0.75, 0.87)	0.87 (0.81, 0.93)	0.80 (0.74, 0.87)	0.88 (0.86, 0.91)	<0.001
Continuous updating	1.00	0.97 (0.91, 1.03)	0.92 (0.86, 0.98)	0.89 (0.84, 0.95)	0.93 (0.87, 0.99)	0.83 (0.78, 0.89)	0.89 (0.83, 0.96)	0.82 (0.76, 0.88)	0.88 (0.82, 0.95)	0.78 (0.72, 0.84)	0.88 (0.85, 0.91)	<0.001
Baseline intake alone	1.00	0.98 (0.92, 1.04)	0.97 (0.91, 1.04)	0.92 (0.86, 0.99)	0.97 (0.91, 1.04)	0.96 (0.90, 1.02)	0.93 (0.87, 1.00)	0.90 (0.84, 0.97)	0.92 (0.86, 0.99)	0.86 (0.80, 0.93)	0.94 (0.92, 0.97)	<0.001
Most recent intake	1.00	1.03 (0.97, 1.10)	0.99 (0.93, 1.06)	0.97 (0.91, 1.04)	0.92 (0.86, 0.99)	0.91 (0.85, 0.97)	0.90 (0.84, 0.96)	0.92 (0.85, 0.98)	0.83 (0.77, 0.89)	0.84* (0.78, 0.91)	0.91 (0.89, 0.94)	<0.001
HEALTHFUL PLANT-BASED DIET INDEX												
Primary analysis[§]	1.00	0.99 (0.93, 1.05)	0.91 (0.85, 0.97)	0.87* (0.82, 0.93)	0.83 (0.77, 0.88)	0.83 (0.78, 0.89)	0.83* (0.77, 0.89)	0.76 (0.71, 0.81)	0.74* (0.69, 0.80)	0.66* (0.61, 0.72)	0.83* (0.80, 0.85)	<0.001*
Continuous updating	1.00	0.99 (0.93, 1.05)	0.92 (0.86, 0.98)	0.88 (0.83, 0.94)	0.83 (0.78, 0.89)	0.84* (0.78, 0.90)	0.83* (0.78, 0.89)	0.77 (0.72, 0.83)	0.74 (0.69, 0.80)	0.66* (0.61, 0.72)	0.83* (0.80, 0.85)	<0.001*
Baseline intake alone	1.00	0.96 (0.90, 1.02)	0.90 (0.84, 0.96)	0.90 (0.84, 0.96)	0.87 (0.82, 0.93)	0.87 (0.81, 0.93)	0.84 (0.78, 0.90)	0.80* (0.75, 0.86)	0.76 (0.71, 0.82)	0.70* (0.64, 0.75)	0.87* (0.85, 0.89)	<0.001*

Table S2.5 (Continued): Pooled HRs (95% CI) for T2D according to deciles of plant-based diet indices, with different ways of modeling diet

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* Trend†
HEALTHFUL PLANT-BASED DIET INDEX (*Continued*)												
Most recent intake	1.00	0.95 (0.89, 1.01)	0.91 (0.86, 0.97)	0.90* (0.84, 0.95)	0.81 (0.76, 0.87)	0.81* (0.76, 0.87)	0.84 (0.79, 0.90)	0.80* (0.74, 0.86)	0.74* (0.69, 0.79)	0.74* (0.69, 0.80)	0.88* (0.86, 0.90)	<0.001*

Results were pooled across the three cohorts using a fixed-effects model

Adjusted for age, smoking status, physical activity, alcohol intake, multivitamin use, family history of diabetes, margarine intake, energy intake, baseline hypertension, baseline hypercholesterolemia, and body mass index. Also adjusted for postmenopausal hormone use in NHS & NHS2, and oral contraceptive use in NHS2

† P value when we assigned the median value to each decile and entered this as a continuous variable in the model

** P value for Q-statistic for heterogeneity <0.05, indicating statistically significant heterogeneity in HRs among the three studies*

§ Primary analysis: Stop updating when cardiovascular disease and cancer develop

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; T2D, Type 2 Diabetes

Table S2.6: Pearson correlation coefficients between various dietary indices

	PDI	hPDI	uPDI	aMED	aHEI	DASH
Nurses' Health Study						
PDI	1.00	0.21	–0.11	0.52	0.12	0.37
hPDI	0.21	1.00	–0.36	0.37	0.66	0.61
uPDI	–0.11	–0.36	1.00	–0.62	–0.54	–0.60
aMED	0.52	0.37	–0.62	1.00	0.63	0.74
aHEI	0.12	0.66	–0.54	0.63	1.00	0.70
DASH	0.37	0.61	–0.60	0.74	0.70	1.00
Nurses' Health Study 2						
PDI	1.00	0.26	–0.21	0.59	0.20	0.44
hPDI	0.26	1.00	–0.33	0.35	0.68	0.60
uPDI	–0.21	–0.33	1.00	–0.63	–0.56	–0.58
aMED	0.59	0.35	–0.63	1.00	0.61	0.73
aHEI	0.20	0.68	–0.56	0.61	1.00	0.71
DASH	0.44	0.60	–0.58	0.73	0.71	1.00
Health Professionals Follow-Up Study						
PDI	1.00	0.32	–0.10	0.58	0.26	0.47
hPDI	0.32	1.00	–0.30	0.42	0.66	0.54
uPDI	–0.10	–0.30	1.00	–0.53	–0.47	–0.52
aMED	0.58	0.42	–0.53	1.00	0.67	0.75
aHEI	0.26	0.66	–0.47	0.67	1.00	0.68
DASH	0.47	0.54	–0.52	0.75	0.68	1.00

P value <0.001 for all correlation coefficients

Abbreviations: PDI, Overall Plant-based Diet Index; hPDI, Healthful Plant-based Diet Index;

uPDI, Unhealthful Plant-based Diet Index;

aMED, Alternate Mediterranean Dietary Pattern; aHEI, Alternate Healthy Eating Index;

DASH, Dietary Approaches to Stop Hypertension

Table S2.7: Pooled HRs (95% CI) for T2D according to deciles of PDI & hPDI, adjusting for other commonly used diet indices

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* Trend†
OVERALL PLANT-BASED DIET INDEX												
Adjusting for aMED												
HRs for PDI	1.00	0.99 (0.93, 1.05)	0.92 (0.86, 0.98)	0.93* (0.87, 0.99)	0.93 (0.87, 1.00)	0.87 (0.81, 0.93)	0.92 (0.85, 0.99)	0.83 (0.77, 0.89)	0.89 (0.82, 0.96)	0.83 (0.77, 0.91)	0.90 (0.87, 0.93)	<0.001
HRs for aMED	1.00	1.02 (0.95, 1.08)	0.98 (0.91, 1.04)	0.95 (0.89, 1.02)	1.00 (0.93, 1.07)	0.96 (0.90, 1.04)	1.00 (0.93, 1.07)	0.95 (0.88, 1.03)	0.93 (0.86, 1.00)	0.92 (0.85, 1.00)	0.87 (0.77, 0.99)	0.03
Adjusting for aHEI												
HRs for PDI	1.00	0.99 (0.93, 1.06)	0.93 (0.87, 0.99)	0.94* (0.88, 1.00)	0.94 (0.88, 1.01)	0.88 (0.82, 0.94)	0.94 (0.87, 1.00)	0.85 (0.79, 0.91)	0.91 (0.85, 0.98)	0.86 (0.80, 0.93)	0.92 (0.89, 0.95)	<0.001
HRs for aHEI	1.00	0.91 (0.85, 0.96)	0.95 (0.89, 1.01)	0.89 (0.84, 0.95)	0.89 (0.83, 0.95)	0.85 (0.80, 0.91)	0.85 (0.79, 0.91)	0.74 (0.69, 0.80)	0.80 (0.74, 0.86)	0.72* (0.67, 0.78)	0.91* (0.90, 0.93)	<0.001
Adjusting for DASH												
HRs for PDI	1.00	1.01 (0.94, 1.07)	0.94 (0.88, 1.01)	0.96* (0.90, 1.03)	0.97 (0.90, 1.04)	0.91 (0.85, 0.98)	0.97 (0.90, 1.04)	0.88 (0.82, 0.95)	0.96 (0.89, 1.03)	0.91 (0.84, 0.98)	0.95 (0.91, 0.98)	0.003
HRs for DASH	1.00	0.96 (0.90, 1.02)	0.91 (0.86, 0.97)	0.93 (0.87, 0.99)	0.88 (0.82, 0.94)	0.83* (0.78, 0.89)	0.80 (0.75, 0.86)	0.82 (0.77, 0.88)	0.73 (0.67, 0.78)	0.74 (0.68, 0.80)	0.79 (0.76, 0.83)	<0.001

Table S2.7 (Continued): Pooled HRs (95% CI) for T2D according to deciles of PDI & hPDI, adjusting for other commonly used diet indices

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* Trend†
HEALTHFUL PLANT-BASED DIET INDEX												
Adjusting for aMED												
HRs for hPDI	1.00	0.98 (0.92, 1.04)	0.89 (0.84, 0.95)	0.86* (0.80, 0.92)	0.81 (0.75, 0.87)	0.81 (0.76, 0.87)	0.81 (0.75, 0.87)	0.73 (0.68, 0.79)	0.71 (0.66, 0.77)	0.63 (0.58, 0.69)	0.81* (0.78, 0.83)	<0.001*
HRs for aMED	1.00	1.04 (0.97, 1.10)	1.01 (0.95, 1.08)	1.00 (0.93, 1.07)	1.06 (0.99, 1.14)	1.04 (0.97, 1.12)	1.09 (1.02, 1.18)	1.07 (0.98, 1.15)	1.05 (0.97, 1.14)	1.08 (0.99, 1.18)	1.19 (1.04, 1.36)	0.03
Adjusting for aHEI												
HRs for hPDI	1.00	1.01 (0.94, 1.07)	0.93 (0.87, 0.99)	0.90* (0.84, 0.97)	0.86 (0.80, 0.92)	0.87 (0.81, 0.94)	0.88 (0.81, 0.94)	0.81 (0.75, 0.88)	0.80 (0.73, 0.87)	0.73 (0.66, 0.80)	0.86 (0.83, 0.89)	<0.001
HRs for aHEI	1.00	0.92 (0.86, 0.97)	0.97 (0.91, 1.04)	0.93 (0.87, 0.99)	0.94 (0.88, 1.00)	0.91 (0.85, 0.98)	0.92 (0.86, 0.99)	0.82 (0.76, 0.89)	0.90 (0.83, 0.98)	0.85 (0.77, 0.93)	0.96 (0.94, 0.98)	<0.001
Adjusting for DASH												
HRs for hPDI	1.00	1.01 (0.95, 1.08)	0.94 (0.88, 1.01)	0.92* (0.86, 0.99)	0.88 (0.82, 0.95)	0.90 (0.83, 0.96)	0.90 (0.84, 0.98)	0.84 (0.77, 0.91)	0.83 (0.76, 0.90)	0.76 (0.69, 0.83)	0.88* (0.85, 0.92)	<0.001
HRs for DASH	1.00	0.97 (0.91, 1.03)	0.93 (0.87, 0.99)	0.96 (0.90, 1.02)	0.92 (0.86, 0.99)	0.88* (0.82, 0.95)	0.86 (0.80, 0.93)	0.89 (0.83, 0.96)	0.80 (0.74, 0.87)	0.85 (0.78, 0.93)	0.87 (0.82, 0.91)	<0.001

Table S2.7 (Continued): Pooled HRs (95% CI) for T2D according to deciles of PDI & hPDI, adjusting for other commonly used diet indices

Results were pooled across the three cohorts using a fixed-effects model

Adjusted for age, smoking status, physical activity, alcohol intake, multivitamin use, family history of diabetes, margarine intake, energy intake, baseline hypertension, baseline hypercholesterolemia, and BMI. Also adjusted for postmenopausal hormone use in NHS & NHS2, and for oral contraceptive use in NHS2

† P value when we assigned the median value to each decile and entered this as a continuous variable in the model

** P value for Q-statistic for heterogeneity <0.05, indicating statistically significant heterogeneity in HRs among the three studies*

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; PDI, Overall Plant-based Diet Index; hPDI, Healthful Plant-based Diet Index; aMED, Alternate Mediterranean dietary pattern; aHEI, Alternate Healthy Eating Index; DASH, Dietary Approaches to Stop Hypertension

CHAPTER 3

PLANT-BASED DIETS AND THE RISK OF CORONARY HEART DISEASE IN US ADULTS

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Abstract

Background: Plant-based diets have been recommended for prevention of several chronic diseases, including coronary heart disease (CHD). However, all plant foods are not necessarily beneficial.

Methods: We examined the association between plant-based diets and CHD among 73,710 women in the Nurses' Health Study (NHS), 92,320 women in NHS2, and 43,247 men in the Health Professionals Follow-up Study (HPFS), free of chronic diseases at baseline (1984 for NHS, 1991 for NHS2, and 1986 for HPFS). We created an overall plant-based diet index (PDI) from dietary data collected periodically using semi-quantitative food frequency questionnaires (SFFQ), by assigning positive scores to plant foods and reverse scores to animal foods. We also created a healthful PDI (hPDI) where healthy plant foods (whole grains, fruits/vegetables, nuts/legumes, oils, tea/coffee) received positive scores, while unhealthy plant foods (juices/sweetened beverages, refined grains, potato/fries, sweets) and animal foods received reverse scores. In addition, we created an unhealthful PDI (uPDI) by assigning positive scores to unhealthy plant foods, and reverse scores to healthy plant foods and animal foods.

Results: Over 4,594,408 person-years of follow-up, we documented 7754 cases of CHD (fatal and nonfatal myocardial infarction). After pooling across the cohorts and adjusting for multiple confounders, the overall plant-based diet index was inversely associated with CHD (HR comparing extreme deciles: 0.89, 95% CI: 0.80-0.99; HR per 10-unit increase: 0.93, 95% CI: 0.89-0.97; p trend=0.002). This inverse association was stronger for the healthier version of the plant-based diet (HR comparing extreme deciles: 0.74, 95% CI: 0.66-0.82; HR per 10-unit increase: 0.87, 95% CI: 0.84-0.91; p trend<0.001). The unhealthful plant-based diet index, on

the other hand, was positively associated with CHD (HR comparing extreme deciles: 1.36, 95% CI: 1.23-1.52; HR per 10-unit increase: 1.11, 95% CI: 1.07-1.15; p trend<0.001).

Conclusions: Our study suggests that plant-based diets, especially when rich in healthier plant foods, are associated with substantially lower risk of developing CHD. These findings support current recommendations to increase intake of healthy plant-based foods, while reducing intake of less healthy plant foods and certain animal foods.

Introduction

Plant-based diets have been associated with reduced risk of various diseases (1-4), including coronary heart disease (CHD) (5-10), the leading cause of death in the world (11).[11] However, these studies suffer from some key limitations. With the exception of two more recent investigations (3,4), prior studies have defined plant-based diets as ‘vegetarian’ diets, which constitute a family of diverse dietary patterns ranging from complete exclusion of all animal foods, to the exclusion of just red meat & poultry. 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 consumption of plant foods affect cardiovascular health. Additionally, in studies of vegetarian diets all plant foods are treated equally, despite the fact that certain plant foods, such as sugar-sweetened beverages (SSB) and foods with added sugar are associated with higher cardiovascular risk (12,13). Lastly, all 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.

To overcome these limitations, we have used existing literature to hypothesize three versions of plant-based diets 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 alone (e.g. whole grains, fruits, vegetables); and an unhealthful plant-based diet index (uPDI) which emphasizes consumption of less healthy plant foods (e.g. SSB, refined grains, potato) (14). In a previous analysis (14), PDI was inversely associated with type 2 diabetes risk in three ongoing cohorts in the US, with a stronger inverse association with hPDI, and a positive association with uPDI. In the present study, we examined the associations of these plant-based diet indices with CHD incidence, utilizing periodic dietary data collected over more than 20 years in more than 200,000 male and female health professionals in the US.

Methods

Study population

The current study utilizes data from three ongoing prospective cohort studies in the US: the Nurses' Health Study (NHS), the NHS2, and the Health Professionals Follow-Up Study (HPFS). The NHS started in 1976 with a cohort of 121,701 female registered nurses, aged 30 to 55 years, from 11 states in the US. The NHS2 was initiated with the goal of evaluating lifestyle risk factors in a younger population of women. It started in 1989 with a cohort of 116,686 female registered nurses, aged 25-42 years, from 14 states. The HPFS was initiated in 1986 with a cohort of 51,529 male health professionals, aged 40-75 years, from 50 states. Participants in all three cohorts received a follow-up questionnaire every two years on lifestyle, health behaviors, and medical history, with a response rate of >90% being achieved in almost every cycle. Participants with CHD at baseline were excluded. Participants with a history of cancer (except nonmelanoma skin cancer) and stroke at baseline were also excluded, as diagnosis with these diseases can change diet. Lastly, individuals with implausible energy intake (<600 or >3500 kcal/day for NHS & NHS2 and <800 or >4200 kcal/day for HPFS) and incomplete dietary data at baseline were excluded. The final analysis included 73,710 women in NHS, 92,320 women in NHS2, and 43,247 men in HPFS at baseline (1984 for NHS, 1991 for NHS2, and 1986 for HPFS).

Dietary assessment and the plant-based diet indices

Data on diet and nutrition were collected using a semi-quantitative food frequency questionnaire (SFFQ) at baseline in all three cohorts, with periodic assessments every 2-4 years thereafter.

Participants were asked how often, on average, they consumed a defined portion of each 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". Information on brands of certain foods (e.g. breakfast cereal), and types of fats and oils was collected through open-ended questions. The reliability and validity of the questionnaires have been described previously (15-17).

Using this SFFQ data, we created three versions of a plant-based diet: an overall plant-based diet index (PDI), a healthful plant-based diet index (hPDI), and an unhealthful plant-based diet index (uPDI). A previous analysis describes in detail how these diet indices were created (14). In brief, we created 18 food groups based on nutrient and culinary similarities, within larger categories of healthy and less healthy plant foods, and animal foods. Given that alcoholic beverages are not associated in one direction with several 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. Healthy plant food groups included whole grains, fruits, vegetables, nuts, legumes, vegetable oils, and tea/coffee; less healthy plant food groups included fruit juices, SSBs, refined grains, potatoes, and sweets; and animal food groups included dairy, egg, fish/seafood, meat, animal fats, and miscellaneous animal-based foods. 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, all plant food groups were given positive scores, while all 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 the opposite pattern of scoring was adopted. The 18 food group scores were summed to obtain the indices.

Outcome ascertainment

Coronary heart disease (CHD) in this analysis was defined as fatal and non-fatal myocardial infarction. Participants self-reporting newly diagnosed CHD on the biennial questionnaires were sent a request for permission to access their medical records to confirm diagnosis, which was done through blinded review by study physicians. World Health Organization (WHO) criteria (18) were used to confirm diagnosis of nonfatal myocardial infarction (MI): the presence of typical symptoms plus either elevated enzymes or diagnostic electrocardiographic findings. Cases of CHD were defined as “probable” when confirmation was done via interview or letter and not through medical record review.

In order to identify deaths, reports from next of kin or postal authorities were used, 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. International Classification of Diseases, ninth revision (ICD-9) (19) codes 410-412 were used to classify CHD as the cause of death. CHD deaths were considered confirmed if fatal CHD was established through medical records or autopsy reports, or if CHD was listed as the cause of death on the death certificate with prior medical record evidence 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 classified as “probable”. In the present study, both confirmed and probable cases were included in the analysis.

Assessment of covariates

The biennial follow-up questionnaires assess updated information on a number of factors, including participants’ age, smoking status, multivitamin use, and family history of CHD. In the NHS and NHS2, information is also assessed on menopausal status, post-menopausal hormone use, and oral contraceptive use (NHS2 only). Self-reported data on height was collected once at baseline, with updated information on weight assessed every two years through the questionnaires; body mass index was calculated as weight (kg) divided by height-squared (meters). These questionnaires also collect updated information on self-reported diagnosis of diseases such as hypertension, hypercholesterolemia, CVD, and cancer, and on self-reported medication use. Physical activity was assessed every 2-6 years using a self-report physical activity questionnaire (PAQ), and metabolic equivalent tasks calculated to capture activity duration and intensity.

Statistical analysis

We used Cox proportional-hazards regression to estimate hazard ratios and 95% confidence intervals evaluating the association between deciles of each index and CHD. Person-time was calculated from questionnaire return date till CHD diagnosis, death, or end of follow-up, whichever came first. We used age (in years) as the time scale, with stratification by calendar time (in 2-year intervals). We adjusted for several potential confounders, including smoking status, alcohol intake, physical activity, family history of CHD, multivitamin use, aspirin use, energy intake, margarine intake, baseline hypertension, hypercholesterolemia and diabetes, BMI, postmenopausal status & hormone use (women), and oral contraceptive use (NHS2 only). The proportional hazard assumption was tested by including interaction terms between the indices and age.

A continuous variable for each index was created by assigning the median value to each decile, and conducting tests for linear trend. In addition, restricted cubic splines were fit to the fully adjusted model with each index entered as a continuous variable, in order to examine potential nonlinear associations. The indices were cumulatively averaged over the follow-up to better capture long-term diet. In the primary analysis, we stopped cumulative updating of the indices when intermediate outcomes (T2D, stroke, and cancer) develop, as diagnosis with these conditions could change an individual's diet. Values of other covariates were updated every 2 years to account for changes in these variables over time. The analysis was carried out separately for each cohort, and combined using a fixed effects model to estimate a pooled effect estimate; heterogeneity among the cohorts was examined using the Cochrane Q statistic (20) and the I^2 statistic (21).

We examined potential effect modification by age, BMI, physical activity levels, family history of CHD, and smoking status by including cross-product terms with the indices in the fully adjusted models. Additional variables that could potentially cofound the association, including ethnicity, markers of socio-economic status, marital status, and health service utilization, were further controlled for in sensitivity analysis. In primary analysis, we did not adjust for updated hypertension, hypercholesterolemia, and diabetes as these are potential intermediates in the causal pathway. However, in sensitivity analysis we repeated the analysis adjusting for these diseases. We also repeated analysis with continuous updating of the indices till the end of follow-up, using baseline indices alone, and the most recent measure of the indices, to assess the extent to which different ways of modeling diet impacts results.

Results

We have detailed the descriptive characteristics of the NHS, NHS2, and HPFS participants by deciles of the dietary indices previously (14). In brief, the cumulative average of the overall plant-based diet index (PDI) ranged from a median of 44 in the lowest decile, to 66 in the highest decile, while for the healthful plant-based diet index (hPDI), these values were 42 in the lowest decile to 67 in the highest decile. Participants with higher scores on both indices were older, more active, leaner, and less likely to smoke than participants with lower scores.

Over 4,594,408 person-years of follow-up in the three cohorts, 7754 participants developed CHD (3233 CHD cases over 1,876,942 person-years of follow-up in NHS; 541 CHD cases over 1,820,218 person-years of follow-up in NHS2; and 3980 CHD cases over 897,248 person-years of follow-up in HPFS). In age-adjusted analysis, PDI was inversely associated with CHD incidence (Table 3.1). This association was attenuated, but remained significant upon adjustment of relevant confounders (HR comparing extreme deciles: 0.89, 95% CI: 0.80-0.99; HR per 10-unit increase: 0.93, 95% CI: 0.89-0.97; p trend=0.002). A strong inverse association was observed between hPDI and CHD incidence in age-adjusted analysis, which was only slightly attenuated after multivariable adjustment (HR comparing extreme deciles: 0.74, 95% CI: 0.66-0.82; HR per 10-unit increase: 0.87, 95% CI: 0.84-0.91; p trend<0.001) (Table 3.2). On the other hand, uPDI was a strongly positively associated with CHD incidence after controlling for multiple confounders (HR comparing extreme deciles: 1.36, 95% CI: 1.23-1.52; HR per 10-unit increase: 1.11, 95% CI: 1.07-1.15; p trend<0.001) (Table 3.3).

Table 3.1: HRs (95% CI) for Coronary Heart Disease according to deciles of the Overall Plant-based Diet Index

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* trend†
Nurses' Health Study												
Median	45.3	48.7	50.7	52.2	53.7	55.0	56.5	58.0	60.0	63.5		
Cases/ PY	352/ 187744	350/ 182686	339/ 188220	295/ 176066	353/ 200375	272/ 184869	335/ 191328	299/ 185409	328/ 189536	310/ 190710		
Age-adjusted	1.00	0.98 (0.84, 1.13)	0.92 (0.79, 1.07)	0.84 (0.72, 0.98)	0.87 (0.75, 1.01)	0.71 (0.61, 0.84)	0.82 (0.71, 0.95)	0.75 (0.64, 0.87)	0.79 (0.68, 0.92)	0.70 (0.60, 0.82)	0.81 (0.76, 0.87)	<0.001
Multivariable adjusted	1.00	1.04 (0.90, 1.21)	1.04 (0.89, 1.21)	0.97 (0.83, 1.14)	1.02 (0.88, 1.19)	0.88 (0.75, 1.03)	0.97 (0.83, 1.13)	0.93 (0.79, 1.09)	0.97 (0.83, 1.14)	0.87 (0.74, 1.03)	0.92 (0.85, 0.98)	0.04
Nurses' Health Study 2												
Median	45.0	48.5	50.6	52.3	53.8	55.0	57.0	58.5	60.8	64.0		
Cases/ PY	77/ 178483	62/ 177927	58/ 187329	59/ 179158	52/ 171137	53/ 183500	45/ 197054	46/ 181810	47/ 183563	42/ 180257		
Age-adjusted	1.00	0.83 (0.59, 1.16)	0.71 (0.50, 0.99)	0.76 (0.54, 1.07)	0.65 (0.46, 0.93)	0.66 (0.46, 0.93)	0.52 (0.36, 0.75)	0.55 (0.38, 0.79)	0.55 (0.38, 0.79)	0.48 (0.33, 0.71)	0.67 (0.57, 0.77)	<0.001
Multivariable adjusted	1.00	0.91 (0.65, 1.28)	0.82 (0.58, 1.16)	0.90 (0.64, 1.28)	0.78 (0.54, 1.11)	0.83 (0.58, 1.19)	0.66 (0.45, 0.97)	0.71 (0.48, 1.03)	0.73 (0.49, 1.07)	0.68 (0.45, 1.02)	0.78 (0.66, 0.93)	0.01

Table 3.1 (Continued): HRs (95% CI) for Coronary Heart Disease according to deciles of the Overall Plant-based Diet Index

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* trend†
Health Professionals Follow-Up Study												
Median	45.0	48.3	50.5	52.2	54.0	55.3	57.0	58.3	60.5	64.0		
Cases/ PY	439/ 86565	400/ 87552	367/ 89486	443/ 96057	419/ 88338	430/ 96620	323/ 78601	397/ 89742	363/ 92395	399/ 91892		
Age-adjusted	1.00	0.91 (0.79, 1.04)	0.78 (0.68, 0.90)	0.88 (0.77, 1.01)	0.89 (0.78, 1.02)	0.83 (0.73, 0.95)	0.75 (0.65, 0.86)	0.80 (0.70, 0.91)	0.70 (0.61, 0.81)	0.79 (0.69, 0.90)	0.88 (0.83, 0.93)	<0.001
Multivariable adjusted	1.00	0.97 (0.84, 1.11)	0.86 (0.75, 0.99)	0.97 (0.85, 1.11)	1.01 (0.88, 1.15)	0.93 (0.81, 1.07)	0.86 (0.74, 1.00)	0.92 (0.80, 1.06)	0.83 (0.72, 0.96)	0.95 (0.82, 1.09)	0.96 (0.91, 1.02)	0.13
Pooled results (fixed effects model)												
Age-adjusted	1.00	0.93 (0.84, 1.02)	0.83 (0.76, 0.92)	0.85 (0.78, 0.94)	0.86 (0.78, 0.95)	0.77 (0.70, 0.85)	0.76 (0.69, 0.84)	0.76 (0.69, 0.83)	0.72 (0.66, 0.80)	0.73 (0.66, 0.80)	0.84* (0.80, 0.87)	<0.001*
Multivariable adjusted	1.00	0.99 (0.90, 1.09)	0.93 (0.84, 1.02)	0.97 (0.88, 1.07)	0.99 (0.90, 1.10)	0.90 (0.82, 1.00)	0.89 (0.80, 0.99)	0.91 (0.82, 1.01)	0.88 (0.79, 0.98)	0.89 (0.80, 0.99)	0.93 (0.89, 0.97)	0.002

Multivariable adjusted model: Adjusted for age (years), smoking status (never, past, current [1-14, 15-24, or ≥25 cigarettes/day]), physical activity (<3, 3-8.9, 9-17.9, 18-26.9, or ≥27 metabolic equivalent task hours/week), alcohol intake (0, 0.1-4.9, 5-9.9, 10-14.9, or ≥15 g/day), multivitamin use (yes or no), aspirin use (yes or no), family history of CHD (yes or no), margarine intake (quintiles), energy intake (quintiles), baseline hypertension, hypercholesterolemia, and diabetes (yes or no), and updated body mass index (<21, 21-22.9, 23-24.9, 25-26.9, 27-29.9, 30-32.9, 33–34.9, 35-39.9, or ≥40 kg/m2). Also adjusted for

Table 3.1 (Continued): HRs (95% CI) for Coronary Heart Disease according to deciles of the Overall Plant-based Diet Index

postmenopausal hormone use in NHS & NHS2 (premenopausal, postmenopausal current, past or never user), and for oral contraceptive use in NHS2 (never, past, or current user).

† *P value when we assigned the median value to each decile and entered this as a continuous variable in the model*

* *P value for Q-statistic for heterogeneity <0.05, indicating statistically significant heterogeneity in HRs among the three studies*

Table 3.2: HRs (95% CI) for Coronary Heart Disease according to deciles of the Healthful Plant-based Diet Index

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* trend†
Nurses' Health Study												
Median	44.3	48.0	50.5	52.4	54.0	55.8	57.5	59.3	61.7	65.5		
Cases/ PY	357/ 188116	325/ 186249	325/ 190481	329/ 188240	312/ 183411	323/ 192053	307/ 188053	327/ 187506	323/ 184270	305/ 188565		
Age-adjusted	1.00	0.86 (0.74, 1.00)	0.80 (0.69, 0.93)	0.79 (0.68, 0.92)	0.74 (0.64, 0.86)	0.72 (0.62, 0.83)	0.67 (0.57, 0.78)	0.70 (0.60, 0.81)	0.66 (0.57, 0.77)	0.58 (0.49, 0.67)	0.80 (0.75, 0.84)	<0.001
Multivariable adjusted	1.00	0.92 (0.79, 1.07)	0.90 (0.77, 1.05)	0.89 (0.76, 1.03)	0.87 (0.74, 1.02)	0.83 (0.71, 0.97)	0.77 (0.66, 0.90)	0.83 (0.71, 0.97)	0.79 (0.67, 0.93)	0.68 (0.58, 0.80)	0.86 (0.81, 0.91)	<0.001
Nurses' Health Study 2												
Median	44.0	48.0	50.4	52.3	54.0	55.8	57.4	59.3	61.7	65.8		
Cases/PY	67/ 184121	57/ 174123	66/ 200965	51/ 169707	62/ 190544	64/ 182868	45/ 179424	50/ 181568	45/ 175271	34/ 181626		
Age-adjusted	1.00	0.84 (0.59, 1.19)	0.85 (0.60, 1.19)	0.73 (0.51, 1.05)	0.78 (0.55, 1.10)	0.80 (0.57, 1.13)	0.57 (0.39, 0.83)	0.59 (0.41, 0.86)	0.54 (0.37, 0.79)	0.38 (0.25, 0.57)	0.68 (0.59, 0.78)	<0.001
Multivariable adjusted	1.00	0.89 (0.62, 1.27)	0.94 (0.66, 1.33)	0.82 (0.57, 1.20)	0.89 (0.62, 1.27)	0.90 (0.63, 1.28)	0.66 (0.44, 0.97)	0.69 (0.47, 1.01)	0.62 (0.42, 0.93)	0.46 (0.29, 0.71)	0.74 (0.64, 0.86)	<0.001

Table 3.2 (Continued): HRs (95% CI) for Coronary Heart Disease according to deciles of the Healthful Plant-based Diet Index

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* trend[†]
Health Professionals Follow-Up Study												
Median	43.0	47.2	50.0	52.0	53.8	55.5	57.2	59.2	62.0	66.0		
Cases/PY	369/ 88295	409/ 89314	371/ 92936	449/ 93035	391/ 88435	410/ 89572	395/ 89893	397/ 85663	384/ 91460	405/ 88645		
Age-adjusted	1.00	0.97 (0.84, 1.12)	0.86 (0.74, 0.99)	0.97 (0.85, 1.12)	0.86 (0.75, 0.99)	0.88 (0.76, 1.01)	0.81 (0.70, 0.94)	0.84 (0.73, 0.97)	0.75 (0.65, 0.86)	0.77 (0.67, 0.89)	0.88 (0.84, 0.92)	<0.001
Multivariable adjusted	1.00	1.00 (0.87, 1.16)	0.89 (0.77, 1.03)	1.01 (0.88, 1.16)	0.91 (0.79, 1.05)	0.93 (0.80, 1.07)	0.87 (0.75, 1.00)	0.91 (0.78, 1.05)	0.80 (0.69, 0.93)	0.84 (0.72, 0.97)	0.90 (0.86, 0.95)	0.001
Pooled results (fixed effects model)												
Age-adjusted	1.00	0.91 (0.82, 1.00)	0.83 (0.75, 0.92)	0.87 (0.79, 0.96)	0.80 (0.72, 0.88)	0.80 (0.72, 0.88)	0.73 (0.66, 0.80)	0.75 (0.68, 0.83)	0.69 (0.63, 0.77)	0.65* (0.59, 0.72)	0.83* (0.80, 0.86)	<0.001*
Multivariable adjusted	1.00	0.96 (0.87, 1.06)	0.90 (0.81, 0.99)	0.94 (0.85, 1.04)	0.89 (0.80, 0.99)	0.88 (0.80, 0.98)	0.81 (0.73, 0.90)	0.86 (0.77, 0.95)	0.78 (0.70, 0.87)	0.74* (0.66, 0.82)	0.87* (0.84, 0.91)	<0.001*

Multivariable adjusted model: Adjusted for age (years), smoking status (never, past, current [1-14, 15-24, or ≥25 cigarettes/day]), physical activity (<3, 3-8.9, 9-17.9, 18-26.9, or ≥27 metabolic equivalent task hours/week), alcohol intake (0, 0.1-4.9, 5-9.9, 10-14.9, or ≥15 g/day), multivitamin use (yes or no), aspirin use (yes or no), family history of CHD (yes or no), margarine intake (quintiles), energy intake (quintiles), baseline hypertension, hypercholesterolemia, and diabetes (yes or no), and updated body mass index (<21, 21-22.9, 23-24.9, 25-26.9, 27-29.9, 30-32.9, 33–34.9, 35-39.9, or ≥40 kg/m2). Also adjusted for

Table 3.2 (Continued): HRs (95% CI) for Coronary Heart Disease according to deciles of the Healthful Plant-based Diet Index

postmenopausal hormone use in NHS & NHS2 (premenopausal, postmenopausal current, past or never user), and for oral contraceptive use in NHS2 (never, past, or current user).

[†] P value when we assigned the median value to each decile and entered this as a continuous variable in the model

** P value for Q-statistic for heterogeneity <0.05, indicating statistically significant heterogeneity in HRs among the three studies*

Table 3.3: HRs (95% CI) for Coronary Heart Disease according to deciles of the Unhealthful Plant-based Diet Index

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* trend†
Nurses' Health Study												
Median	43.5	47.6	50.0	52.0	53.7	55.5	57.3	59.3	62.0	66.0		
Cases/PY	277/187390	307/195760	359/177315	267/183307	345/191152	337/192370	337/190678	320/187995	328/187329	356/183646		
Age-adjusted	1.00	1.09 (0.93, 1.28)	1.40 (1.19, 1.63)	1.02 (0.86, 1.21)	1.28 (1.09, 1.50)	1.25 (1.06, 1.46)	1.30 (1.11, 1.52)	1.24 (1.06, 1.46)	1.30 (1.11, 1.52)	1.47 (1.25, 1.72)	1.14 (1.08, 1.20)	<0.001
Multivariable adjusted	1.00	1.17 (0.99, 1.37)	1.51 (1.29, 1.76)	1.12 (0.95, 1.33)	1.40 (1.19, 1.65)	1.35 (1.15, 1.59)	1.40 (1.19, 1.65)	1.31 (1.11, 1.55)	1.33 (1.13, 1.57)	1.47 (1.24, 1.74)	1.13 (1.06, 1.19)	<0.001
Nurses' Health Study 2												
Median	43.5	47.5	50.0	52.0	54.0	56.0	58.0	60.0	62.5	66.7		
Cases/PY	38/186638	58/178794	52/180214	58/195919	51/178617	58/187860	54/173425	68/178484	49/186187	55/174080		
Age-adjusted	1.00	1.63 (1.08, 2.45)	1.47 (0.97, 2.24)	1.68 (1.12, 2.53)	1.53 (1.00, 2.32)	1.69 (1.13, 2.55)	1.73 (1.14, 2.62)	2.11 (1.42, 3.15)	1.57 (1.03, 2.40)	1.89 (1.25, 2.86)	1.22 (1.08, 1.38)	0.003
Multivariable adjusted	1.00	1.73 (1.15, 2.61)	1.57 (1.03, 2.39)	1.76 (1.16, 2.67)	1.57 (1.03, 2.41)	1.79 (1.18, 2.72)	1.79 (1.17, 2.75)	2.16 (1.43, 3.27)	1.53 (0.98, 2.38)	1.86 (1.20, 2.88)	1.19 (1.04, 1.37)	0.02

Table 3.3 (Continued): HRs (95% CI) for Coronary Heart Disease according to deciles of the Unhealthful Plant-based Diet Index

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* trend†
Health Professionals Follow-Up Study												
Median	44.0	48.0	50.2	52.0	54.0	55.6	57.3	59.0	61.5	65.0		
Cases/PY	411/ 90594	403/ 90990	396/ 86658	375/ 89329	430/ 92112	411/ 90023	408/ 94171	371/ 86722	363/ 87829	412/ 88820		
Age-adjusted	1.00	0.99 (0.86, 1.14)	1.07 (0.93, 1.23)	0.99 (0.86, 1.14)	1.15 (1.00, 1.31)	1.11 (0.96, 1.27)	1.08 (0.94, 1.24)	1.08 (0.94, 1.24)	1.09 (0.95, 1.25)	1.25 (1.09, 1.44)	1.09 (1.03, 1.14)	0.001
Multivariable adjusted	1.00	1.03 (0.89, 1.18)	1.14 (0.99, 1.31)	1.06 (0.92, 1.22)	1.23 (1.07, 1.41)	1.16 (1.00, 1.33)	1.11 (0.97, 1.28)	1.13 (0.97, 1.30)	1.11 (0.96, 1.29)	1.25 (1.08, 1.44)	1.08 (1.02, 1.14)	0.01
Pooled results (fixed effects model)												
Age-adjusted	1.00	1.06 (0.96, 1.18)	1.22* (1.10, 1.35)	1.04 (0.94, 1.15)	1.22 (1.10, 1.34)	1.19 (1.08, 1.32)	1.20* (1.08, 1.32)	1.19* (1.08, 1.32)	1.20 (1.08, 1.33)	1.37 (1.24, 1.51)	1.12 (1.08, 1.16)	<0.001
Multivariable adjusted	1.00	1.11* (1.01, 1.23)	1.30* (1.18, 1.44)	1.12 (1.01, 1.24)	1.32 (1.19, 1.46)	1.26 (1.14, 1.40)	1.26* (1.13, 1.39)	1.25* (1.12, 1.39)	1.22 (1.09, 1.36)	1.36 (1.23, 1.52)	1.11 (1.07, 1.15)	<0.001

Multivariable adjusted model: Adjusted for age (years), smoking status (never, past, current [1-14, 15-24, or ≥25 cigarettes/day]), physical activity (<3, 3-8.9, 9-17.9, 18-26.9, or ≥27 metabolic equivalent task hours/week), alcohol intake (0, 0.1-4.9, 5-9.9, 10-14.9, or ≥15 g/day), multivitamin use (yes or no), aspirin use (yes or no), family history of CHD (yes or no), margarine intake (quintiles), energy intake (quintiles), baseline hypertension, hypercholesterolemia, and diabetes (yes or no), and updated body mass index (<21, 21-22.9, 23-24.9, 25-26.9, 27-29.9, 30-32.9, 33–34.9, 35-39.9, or ≥40 kg/m2). Also adjusted for

Table 3.3 (Continued): HRs (95% CI) for Coronary Heart Disease according to deciles of the Unhealthful Plant-based Diet Index

postmenopausal hormone use in NHS & NHS2 (premenopausal, postmenopausal current, past or never user), and for oral contraceptive use in NHS2 (never, past, or current user).

[†] *P value when we assigned the median value to each decile and entered this as a continuous variable in the model*

* *P value for Q-statistic for heterogeneity <0.05, indicating statistically significant heterogeneity in HRs among the three studies*

The inverse association of hPDI and the positive association of uPDI with CHD were consistently observed across strata defined by age, BMI, family history of CHD, and smoking status (Figure 3.1); associations of both indices were significantly stronger among more physically active participants relative to those who were less active (p interaction=0.005 for hDPI and 0.004 for uPDI). In restricted cubic spline analysis, there was no evidence of significant non-linearity for the associations of any of the indices with CHD incidence (Figure 3.2A). In order to better understand the individual contributions of the three food categories of healthy plant foods, less healthy plant foods, and animal foods to CHD incidence, we entered all three simultaneously into the fully-adjusted model as linear terms, allowing for cubic splines to get selected into the model at p=0.05 (Fig 3.2B). All three food categories were significantly linearly associated with CHD incidence, with positive associations for animal (p for linearity=0.01) and less healthy plant foods (p for linearity<0.001), and inverse association for healthy plant foods (p for linearity<0.001).

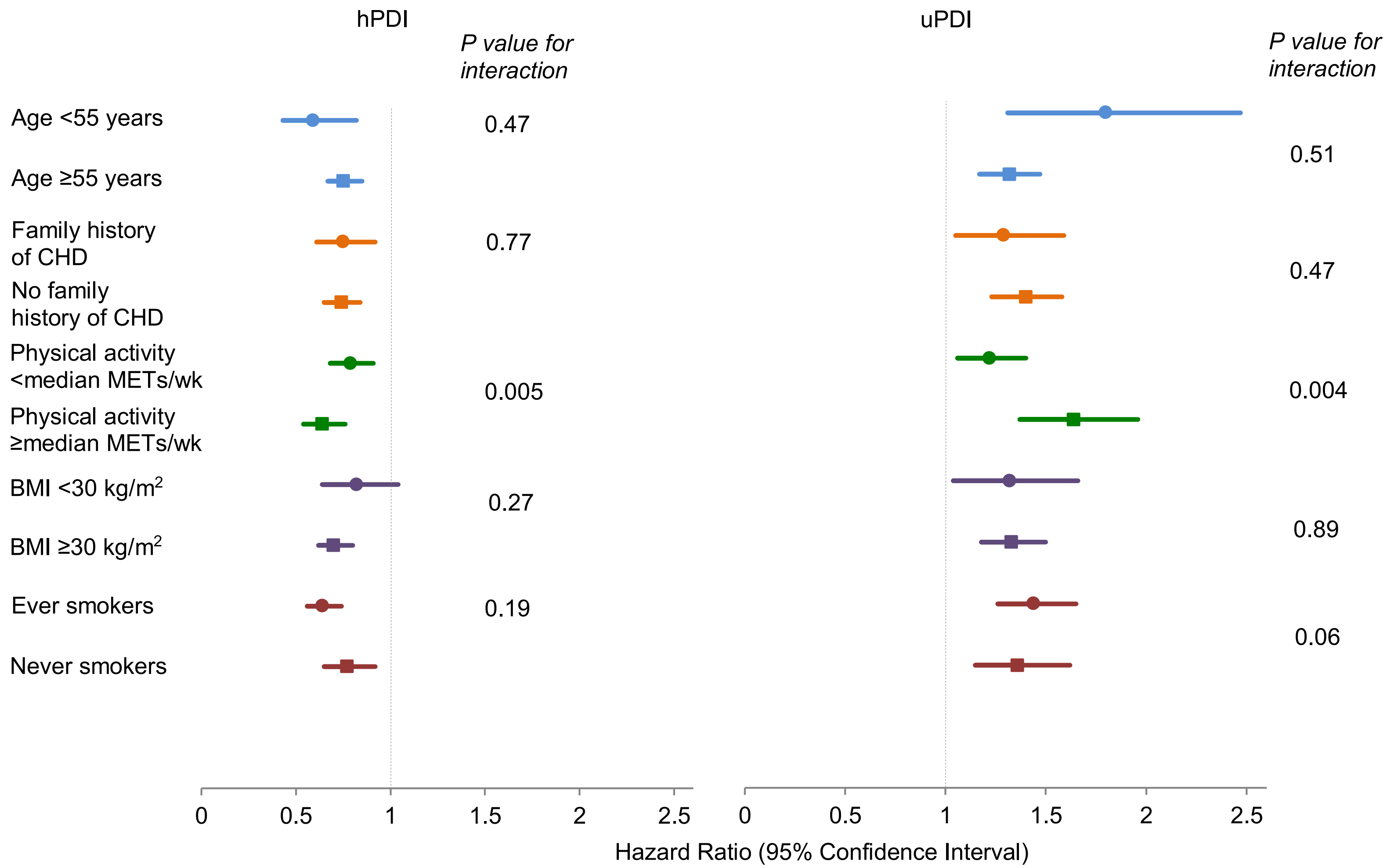

Figure 3.1: Pooled HRs (95% CI) for CHD comparing extreme deciles of the indices, stratified by selected characteristics

Adjusted for age (years), smoking status (never, past, current [1-14, 15-24, or ≥25 cigarettes/day]), physical activity (<3, 3-8.9, 9-17.9, 18-26.9, or ≥27 metabolic equivalent task hours/week), alcohol intake (0, 0.1-4.9, 5-9.9, 10-14.9, or ≥15 g/day), multivitamin use (yes or

Figure 3.1 (Continued): Pooled HRs (95% CI) for CHD comparing extreme deciles of the indices, stratified by selected characteristics

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, 21-22.9, 23-24.9, 25-26.9, 27-29.9, 30-32.9, 33–34.9, 35-39.9, or ≥40 kg/m2). Also adjusted for postmenopausal hormone use in NHS & NHS2 (premenopausal, postmenopausal current, past or never user), and for oral contraceptive use in NHS2 (never, past, or current user).

Results were pooled across the three cohorts using a fixed-effects model

Abbreviations: CHD, Coronary Heart Disease; MET, Metabolic Equivalent Task; BMI, Body Mass Index; hPDI, Healthful Plant-based Diet Index; uPDI, Unhealthful Plant-based Diet Index

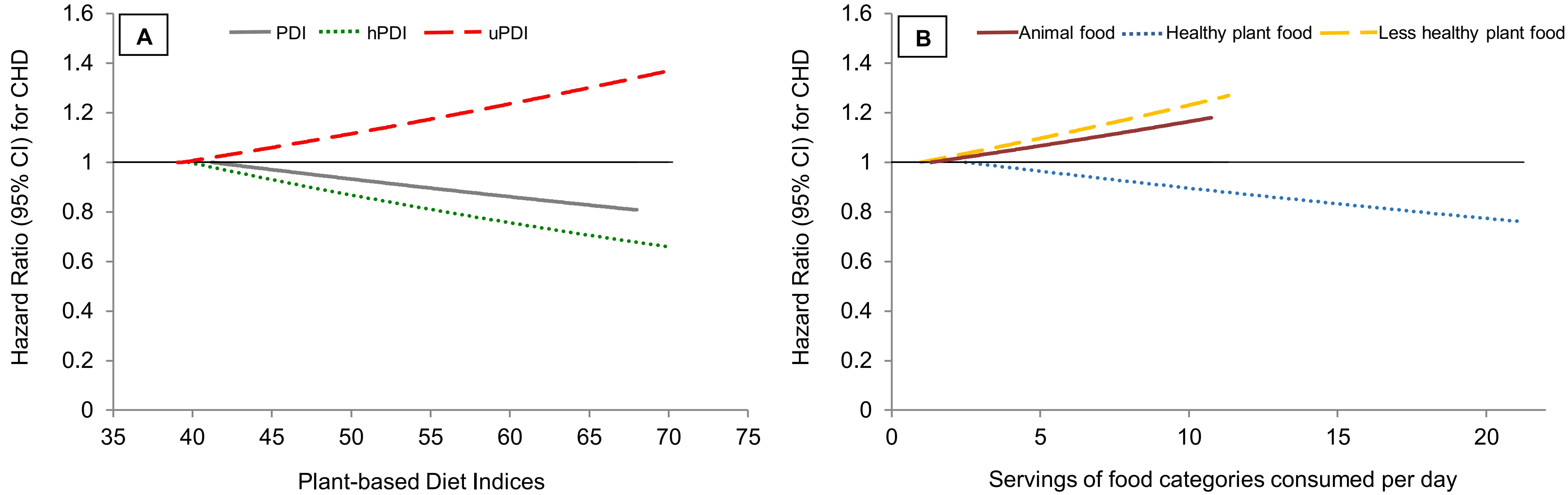

Figure 3.2: Dose-response relationship of (A) the Overall, Healthful, and Unhealthful Plant-based Diet Indices and (B) animal, healthy plant, and less healthy plant foods with CHD incidence

Analyses carried out after combining all three cohorts

Adjusted for age (years), smoking status (never, past, current [1-14, 15-24, or ≥25 cigarettes/day]), physical activity (<3, 3-8.9, 9-17.9, 18-26.9, or ≥27 metabolic equivalent task hours/week), alcohol intake (0, 0.1-4.9, 5-9.9, 10-14.9, or ≥15 g/day), multivitamin use (yes or no), aspirin use (yes/ no), family history of CHD (yes/ no), margarine intake (quintiles), baseline hypertension, hypercholesterolemia, and diabetes (yes/ no), and updated body mass index (<21, 21-22.9, 23-24.9, 25-26.9, 27-29.9, 30-32.9, 33–34.9, 35-39.9, or ≥40 kg/m2). Also adjusted for postmenopausal hormone use in NHS & NHS2 (premenopausal, postmenopausal current, past or never user), and for oral contraceptive use in NHS2 (never, past, or current user).

Figure 3.2 (Continued): Dose-response relationship of (A) the Overall, Healthful, and Unhealthful Plant-based Diet Indices and (B) animal, healthy plant, and less healthy plant foods with CHD incidence

No spline variables got selected into the model based on stepwise selection; hence the results of the model with the linear term alone have been shown for each index

P for linearity=0.001 for PDI, <0.001 for hPDI and uPDI, 0.01 for animal foods, and <0.001 for healthy and less healthy plant foods

Abbreviations: CI, Confidence Interval; CHD, Coronary Heart Disease; PDI, Overall Plant-based Diet Index; hPDI, Healthful Plant-based Diet Index; uPDI, Unhealthful Plant-based Diet Index

The results were largely unchanged 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 when we stopped updating the indices when other intermediate conditions such as hypertension and hypercholesterolemia developed (Table S3.1). Associations also remained the same when we adjusted for additional variables (ethnicity, marital status, recent physical exam, diet beverage intake, and indicators of socio-economic status) [PDI (pooled HR for extreme deciles, 0.90; 95% CI, 0.81-1.00; HR per 10-unit increase, 0.94; 95% CI, 0.89-0.98; p trend=0.005); hPDI (pooled HR for extreme deciles, 0.75; 95% CI, 0.67-0.84; HR per 10 unit increase, 0.88; 95% CI, 0.85-0.91; p trend<0.001); uPDI (pooled HR for extreme deciles, 1.34; 95% CI, 1.20-1.49; HR per 10 unit increase, 1.10; 95% CI, 1.06-1.14; p trend<0.001)]. Adjusting for potential intermediates in the causal pathway, including updated history of hypertension, hypercholesterolemia, and diabetes instead of baseline history alone slightly attenuated the associations of hPDI and uPDI with CHD incidence [hPDI (pooled HR for extreme deciles, 0.79; 95% CI, 0.71-0.88; HR per 10-unit increase, 0.90; 95% CI, 0.87-0.93; p trend<0.001); uPDI (pooled HR for extreme deciles, 1.28; 95% CI, 1.15-1.42; HR per 10-unit increase, 1.08; 95% CI, 1.04-1.12; p trend<0.001)]. However, the association of PDI with CHD remained the same (pooled HR for extreme deciles, 0.89; 95% CI, 0.80-1.00; HR per 10-unit increase, 0.93; 95% CI, 0.89-0.97; p trend=0.002). Excluding baseline diabetes instead of adjusting for it in the analysis did not change the results [hPDI (pooled HR for extreme deciles, 0.73; 95% CI, 0.65-0.82; HR per 10-unit increase, 0.87; 95% CI, 0.84-0.91; p trend<0.001].

Given the consistently inverse association observed between fish intake and CHD risk in previous studies (22), we modified hPDI to include fish intake, and the pooled HRs were largely unchanged (pooled HR for extreme deciles, 0.72; 95% CI, 0.65-0.80; HR per 10-unit increase, 0.89; 95% CI, 0.86-0.92; p trend<0.001). We also simultaneously adjusted for other commonly used dietary indices, such as the Mediterranean diet (aMED), the alternate Healthy Eating Index (aHEI), and Dietary Approaches to Stop Hypertension (DASH), given their previously observed inverse association with CHD risk in these cohorts (23-27). Pooled HRs for PDI were no longer significant when the three other dietary patterns were individually controlled for (Table S3.2). The positive association of uPDI with CHD remained significant after adjustment for aMED, but was considerably attenuated when aHEI and DASH were individually controlled for. The inverse association of hPDI with CHD was attenuated but remained significant after additionally adjusting the three other dietary patterns.

Discussion

In this analysis of three ongoing prospective cohort studies, an overall plant-based diet (PDI) was moderately associated with reduced CHD incidence. This inverse association was considerably stronger for a healthier version of a plant-based diet (hPDI), but strongly positive for a less healthy version of a plant-based diet (uPDI). 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 three indices with T2D incidence. Our current analysis extends the potentially protective effect of the healthful plant-based diet index to CHD. The mechanisms through which hPDI could reduce risk of CHD are likely to be shared with the mechanisms for T2D risk reduction (2,28,29). Specifically, greater adherence to hPDI may lead to diets high in dietary fiber, antioxidants, unsaturated fat, and micronutrients, and low in saturated fat and energy density, which could aid in weight loss/maintenance, enhance glycemic control, improve lipid profile, reduce blood pressure, improve vascular health, decrease inflammation, and improve the gut microbial environment, thereby reducing CHD risk. Greater adherence to the uPDI, on the other hand, may lead to diets with high glycemic load and index, energy density, and added sugar, and low levels of dietary fiber, unsaturated fatty acids, micronutrients, and antioxidants, resulting in increased 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 attenuated upon adjustment for some of these pathways, specifically hypercholesterolemia and hypertension.

Prospective cohort studies examining the associations of plant-based diets with CHD have focused on CHD mortality as the outcome. Most of these studies have been carried out in Europe, with three studies in the US (Adventist Health Studies), and one study in Japan. A pooled analysis of five of the above cohorts (6), two of which were Adventist Health Studies (AHS) carried out in California, USA, found a 26% reduction in CHD mortality (HR 0.76, 95% CI: 0.62-0.94) comparing vegetarians to non-vegetarians. A recent meta-analysis found similar results, with vegetarians experiencing a 29% reduction in CHD mortality (HR 0.71, 95% CI: 0.57-0.87) relative to non-vegetarians (7). Only two prospective cohort studies have examined the association of a vegetarian diet with CHD incidence in addition to mortality, one of which, carried out among Adventists in California, examined univariate associations without controlling for any confounders (10). The other study carried out in a large sample in the UK (EPIC-Oxford study), found a 32% reduction in 11-year CHD incidence (HR 0.68, 95% CI: 0.58-0.81) among vegetarians relative to non-vegetarians, after controlling for a number of potential confounders (9).

The above studies have defined plant-based diets dichotomously as being vegetarian or not. Our study adds to the above evidence base by examining the association of gradations of adherence to an overall plant-based diet with CHD incidence. This approach has the advantage of being easily translatable, as we found that even small reductions in animal food intake while increasing plant food intake can lower CHD risk. Two other studies have adopted this approach with respect to cardiovascular disease mortality, and found similar results. Over a median follow-up of 4.8 years, Martínez-González et al. (4) found a significant linear trend for an inverse association between adherence to the “pro-vegetarian” diet score and cardiovascular mortality in the PREDEMIED study (HR highest vs. lowest category 0.47, 95% CI: 0.21, 1.04, p for trend=0.039). Similarly, Lassale et al. (3) found a 20% (95% CI: 7%, 30%) reduction in CVD mortality comparing extreme categories of adherence to a pro-vegetarian food pattern in the large EPIC cohort.

We also found that a healthier version of a plant-based diet, which emphasizes plant foods known to be associated with improved health outcomes, is associated with substantially stronger reductions in CHD risk. Contrarily, when intake of less healthy plant foods is emphasized, the opposite association is observed. This emphasizes the importance of considering the quality of plant foods consumed in a predominantly plant-based diet. The results of this study are in line with the recently released 2015 Dietary Guidelines for Americans (30), 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 (31).

This is one of the largest prospective investigations of plant-based dietary patterns and incident coronary heart disease in the US, with periodic data on diet, lifestyle, and medical history collected over more than two decades. Measurement error in diet assessment is likely, although evaluating cumulatively averaged intake reduces these errors (17) while allowing for the examination of long-term dietary intake as it affects CHD risk. Residual and unmeasured confounding are possible, given these are observational studies. However, the results were largely the same when we adjusted for additional covariates, including markers of socio-economic status. Additionally, randomized controlled trial evidence showing the protective effect of plant-based diets on intermediate outcomes, including weight gain, lipid profile, and blood pressure lends further support to our findings (32-34).

Conclusions

We found a modest inverse association of an overall plant-based diet with CHD incidence in three prospective cohort studies among male and female health professionals in the US. While this inverse association was stronger for a healthier version of the diet, it was significantly positive for a less healthy version. These finding supports current recommendations to increase intake of healthy plant-based foods, while reducing intake of less healthy plant foods and certain animal foods.

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SUPPLEMENTAL MATERIAL

Table S3.1: Pooled HRs (95% CI) for CHD according to deciles of the plant-based diet indices, with different ways of modeling diet

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* trend†
OVERALL PLANT-BASED DIET INDEX												
Primary analysis§	1.00	0.99 (0.90, 1.09)	0.93 (0.84, 1.02)	0.97 (0.88, 1.07)	0.99 (0.90, 1.10)	0.90 (0.82, 1.00)	0.89 (0.80, 0.99)	0.91 (0.82, 1.01)	0.88 (0.79, 0.98)	0.89 (0.80, 0.99)	0.93 (0.89, 0.97)	0.002
Continuous updating	1.00	0.96 (0.87, 1.06)	0.92 (0.83, 1.01)	0.96 (0.87, 1.06)	0.98 (0.89, 1.08)	0.92 (0.83, 1.02)	0.87 (0.79, 0.97)	0.91 (0.82, 1.01)	0.83 (0.74, 0.92)	0.89 (0.80, 0.99)	0.92* (0.88, 0.96)	0.001
Baseline intake alone	1.00	0.93 (0.83, 1.03)	0.98 (0.89, 1.08)	0.95 (0.86, 1.04)	0.89 (0.81, 0.98)	0.92 (0.84, 1.01)	0.94 (0.83, 1.05)	0.91 (0.83, 1.01)	0.87 (0.79, 0.96)	0.87 (0.78, 0.96)	0.94 (0.91, 0.98)	0.002
Most recent intake	1.00	1.00 (0.91, 1.10)	1.01 (0.92, 1.11)	0.92 (0.84, 1.02)	0.95* (0.86, 1.06)	0.94 (0.85, 1.04)	0.96 (0.86, 1.06)	0.92 (0.83, 1.03)	0.91 (0.82, 1.01)	0.88 (0.79, 0.99)	0.95 (0.91, 0.98)	0.01
Stop updating if HT/HC develop	1.00	0.96 (0.87, 1.05)	0.90 (0.82, 1.00)	0.90 (0.81, 0.99)	0.92 (0.83, 1.01)	0.87 (0.79, 0.96)	0.92 (0.83, 1.02)	0.86 (0.77, 0.95)	0.86 (0.78, 0.96)	0.85 (0.77, 0.94)	0.93 (0.89, 0.97)	0.001
HEALTHFUL PLANT-BASED DIET INDEX												
Primary analysis§	1.00	0.96 (0.87, 1.06)	0.90 (0.81, 0.99)	0.94 (0.85, 1.04)	0.89 (0.80, 0.99)	0.88 (0.80, 0.98)	0.81 (0.73, 0.90)	0.86 (0.77, 0.95)	0.78 (0.70, 0.87)	0.74* (0.66, 0.82)	0.87* (0.84, 0.91)	<0.001*
Continuous updating	1.00	0.94 (0.85, 1.04)	0.90 (0.81, 0.99)	0.96 (0.86, 1.06)	0.91 (0.82, 1.01)	0.90 (0.81, 1.00)	0.84 (0.75, 0.93)	0.87 (0.79, 0.97)	0.80 (0.71, 0.89)	0.74* (0.66, 0.82)	0.88* (0.84, 0.91)	<0.001*

Table S3.1 (Continued): Pooled HRs (95% CI) for CHD according to deciles of the plant-based diet indices, with different ways of modeling diet

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* trend[†]
HEALTHFUL PLANT-BASED DIET INDEX (*Continued*)												
Baseline intake alone	1.00	0.98 (0.88, 1.08)	0.95 (0.86, 1.05)	0.95 (0.86, 1.06)	0.94 (0.85, 1.04)	0.91 (0.82, 1.00)	0.84 (0.76, 0.94)	0.88 (0.79, 0.97)	0.83 (0.74, 0.92)	0.73 (0.65, 0.82)	0.89 (0.86, 0.92)	<0.001
Most recent intake	1.00	0.95 (0.86, 1.04)	0.94 (0.85, 1.03)	0.91 (0.83, 1.01)	0.86 (0.78, 0.95)	0.88 (0.80, 0.97)	0.85 (0.77, 0.94)	0.91 (0.82, 1.01)	0.82 (0.74, 0.91)	0.76 (0.68, 0.84)	0.91 (0.88, 0.94)	<0.001
Stop updating if HT/HC develop	1.00	0.91 (0.82, 1.00)	0.94 (0.86, 1.04)	0.88 (0.80, 0.97)	0.91 (0.82, 1.01)	0.87 (0.79, 0.96)	0.81 (0.73, 0.90)	0.83 (0.75, 0.92)	0.78 (0.70, 0.86)	0.72 (0.65, 0.80)	0.88 (0.85, 0.91)	<0.001
UNHEALTHFUL PLANT-BASED DIET INDEX												
Primary analysis[§]	1.00	1.11* (1.01, 1.23)	1.30* (1.18, 1.44)	1.12 (1.01, 1.24)	1.32 (1.19, 1.46)	1.26 (1.14, 1.40)	1.26* (1.13, 1.39)	1.25* (1.12, 1.39)	1.22 (1.09, 1.36)	1.36 (1.23, 1.52)	1.11 (1.07, 1.15)	<0.001
Continuous updating	1.00	1.21* (1.09, 1.34)	1.27* (1.15, 1.42)	1.30* (1.17, 1.44)	1.35 (1.21, 1.49)	1.33 (1.19, 1.48)	1.31* (1.18, 1.46)	1.30 (1.17, 1.45)	1.34* (1.20, 1.50)	1.36 (1.22, 1.52)	1.11 (1.07, 1.15)	<0.001
Baseline intake alone	1.00	1.17 (1.06, 1.30)	1.30* (1.17, 1.44)	1.22* (1.10, 1.35)	1.18 (1.06, 1.31)	1.29 (1.16, 1.43)	1.26 (1.14, 1.40)	1.28 (1.15, 1.42)	1.35 (1.22, 1.50)	1.34 (1.20, 1.49)	1.10 (1.06, 1.14)	<0.001
Most recent intake	1.00	1.09 (0.98, 1.21)	1.16 (1.04, 1.29)	1.13 (1.01, 1.25)	1.18 (1.06, 1.31)	1.20 (1.08, 1.33)	1.24 (1.12, 1.37)	1.21 (1.09, 1.35)	1.17 (1.05, 1.30)	1.20 (1.07, 1.34)	1.06 (1.03, 1.10)	<0.001

Table S3.1 (Continued): Pooled HRs (95% CI) for CHD according to deciles of the plant-based diet indices, with different ways of modeling diet

	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10	HR (95% CI) per 10 units	*P* trend†
UNHEALTHFUL PLANT-BASED DIET INDEX (*Continued*)												
Stop updating if HT/HC develop	1.00	1.16 (1.05, 1.28)	1.25* (1.13, 1.38)	1.18 (1.06, 1.31)	1.22 (1.10, 1.35)	1.34 (1.21, 1.48)	1.26 (1.14, 1.40)	1.25* (1.12, 1.39)	1.32 (1.19, 1.46)	1.36 (1.23, 1.52)	1.11 (1.07, 1.15)	<0.001

Results were pooled across the three cohorts using a fixed-effects model

Adjusted for age, smoking status, physical activity, alcohol intake, multivitamin use, aspirin use, family history of CHD, margarine intake, energy intake, baseline hypertension, hypercholesterolemia, and diabetes, and updated body mass index. Also adjusted for postmenopausal hormone use in NHS & NHS2, and for oral contraceptive use in NHS2

†P value when we assigned the median value to each decile and entered this as a continuous variable in the model

** P value for Q-statistic for heterogeneity <0.05, indicating statistically significant heterogeneity in HRs among the three studies*

§ Primary analysis: Stop updating when diabetes, stroke, and cancer develop

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; CHD, Coronary Heart Disease; HT, Hypertension; HC, Hypercholesterolemia

Table S3.2: Pooled HRs (95% CI) for CHD according to deciles of PDI & hPDI, adjusting for other commonly used diet indices

	Decile 1	Decile 5	Decile 10	HR (95% CI) per 10 units	*P* Trend†
OVERALL PLANT-BASED DIET INDEX					
Adjusting for aMED					
HRs for PDI	1.00	1.05 (0.95, 1.16)	1.01 (0.90, 1.13)	0.99 (0.94, 1.04)	0.70
HRs for aMED	1.00	0.88 (0.80, 0.97)	0.76 (0.68, 0.85)	0.64 (0.54, 0.77)	<0.001
Adjusting for aHEI					
HRs for PDI	1.00	1.03 (0.93, 1.13)	0.98 (0.88, 1.09)	0.98 (0.93, 1.02)	0.28
HRs for aHEI	1.00	0.92 (0.83, 1.01)	0.70* (0.62, 0.78)	0.90* (0.87, 0.92)	<0.001*
Adjusting for DASH					
HRs for PDI	1.00	1.04 (0.94, 1.15)	1.00 (0.89, 1.11)	0.99 (0.94, 1.04)	0.61
HRs for DASH	1.00	0.85 (0.77, 0.94)	0.70 (0.62, 0.78)	0.82 (0.77, 0.86)	<0.001
HEALTHFUL PLANT-BASED DIET INDEX					
Adjusting for aMED					
HRs for hPDI	1.00	0.93 (0.84, 1.03)	0.80 (0.71, 0.91)	0.90 (0.86, 0.94)	<0.001
HRs for aMED	1.00	0.91 (0.83, 1.01)	0.84 (0.75, 0.95)	0.80 (0.66, 0.95)	0.003

Table S3.2 (Continued): Pooled HRs (95% CI) for CHD according to deciles of PDI & hPDI, adjusting for other commonly used diet indices

	Decile 1	Decile 5	Decile 10	HR (95% CI) per 10 units	*P* Trend†
HEALTHFUL PLANT-BASED DIET INDEX (*Continued*)					
Adjusting for aHEI					
HRs for hPDI	1.00	0.96 (0.87, 1.07)	0.91 (0.80, 1.04)	0.96 (0.92, 1.01)	0.13
HRs for aHEI	1.00	0.93 (0.84, 1.03)	0.73 (0.64, 0.83)	0.91* (0.88, 0.94)	<0.001
Adjusting for DASH					
HRs for hPDI	1.00	0.96 (0.86, 1.07)	0.87 (0.77, 0.99)	0.94 (0.89, 0.99)	0.02
HRs for DASH	1.00	0.87 (0.78, 0.97)	0.75 (0.66, 0.85)	0.86 (0.80, 0.92)	<0.001
UNHEALTHFUL PLANT-BASED DIET INDEX					
Adjusting for aMED					
HRs for uPDI	1.00	1.26 (1.14, 1.40)	1.23 (1.10, 1.38)	1.06 (1.01, 1.11)	0.02
HRs for aMED	1.00	0.88 (0.80, 0.97)	0.81 (0.72, 0.91)	0.72 (0.60, 0.86)	<0.001
Adjusting for aHEI					
HRs for uPDI	1.00	1.19 (1.07, 1.32)	1.10 (0.98, 1.25)	0.99 (0.95, 1.04)	0.93
HRs for aHEI	1.00	0.91 (0.82, 1.01)	0.70* (0.62, 0.79)	0.89* (0.87, 0.92)	<0.001*

Table S3.2 (Continued): Pooled HRs (95% CI) for CHD according to deciles of PDI & hPDI, adjusting for other commonly used diet indices

	Decile 1	Decile 5	Decile 10	HR (95% CI) per 10 units	*P* Trend†
UNHEALTHFUL PLANT-BASED DIET INDEX (*Continued*)					
Adjusting for DASH					
HRs for uPDI	1.00	1.22 (1.10, 1.36)	1.17 (1.04, 1.31)	1.03 (0.98, 1.07)	0.21
HRs for DASH	1.00	0.85 (0.76, 0.94)	0.72 (0.64, 0.81)	0.83 (0.78, 0.89)	<0.001

Results were pooled across the three cohorts using a fixed-effects model

Adjusted for age, smoking status, physical activity, alcohol intake, multivitamin use, aspirin use, family history of CHD, margarine intake, energy intake, baseline hypertension, hypercholesterolemia, and diabetes, and updated body mass index. Also adjusted for postmenopausal hormone use in NHS & NHS2, and for oral contraceptive use in NHS2

†P value when we assigned the median value to each decile and entered this as a continuous variable in the model

** P value for Q-statistic for heterogeneity <0.05, indicating statistically significant heterogeneity in HRs among the three studies*

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; CHD, Coronary Heart Disease; PDI, Overall Plant-based Diet Index; hPDI, Healthful Plant-based Diet Index; uPDI, Unhealthful Plant-based Diet Index; aMED, Alternate Mediterranean dietary pattern; aHEI, Alternate Healthy Eating Index; DASH, Dietary Approaches to Stop Hypertension