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RESEARCH ARTICLE

Plant-Based Dietary Patterns and Parkinson's Disease: A Prospective Analysis of the UK Biobank

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ABSTRACT: Background: Plant-based diets have been associated with a lower risk of several chronic diseases, but the relationship with PD is unknown.
Objectives: We examined the association of three different plant-based diets with PD incidence in the UK Biobank cohort.
Methods: We conducted a prospective study among 126,283 participants from the UK Biobank cohort. Three plant-based diet indices (overall plant-based diet index, PDI; healthful plant-based diet index, hPDI; and unhealthful plant-based diet index, uPDI) were derived from 24-hour dietary recalls based on 17 food groups. Multivariable Cox regression models were used to estimate the risk of PD across quartiles of the PDIs and for each of the food groups that constituted the score. Further analyses were carried out to assess potential heterogeneity in associations between hPDI and PD across strata of some hypothesized effect modifiers.
Results: During 11.8 years of follow-up (1,490,139 person-years), 577 cases of PD incidence were reported. After multivariable adjustment, participants in the highest hPDI and overall PDI quartile had lower risk of PD (22% and 18%, respectively), whereas a higher uPDI was associated with a 38% higher PD risk. In food-based analyses, higher intakes of vegetables, nuts, and tea were associated with a lower risk of PD (28%, 31% and 25%, respectively). Stratifying by Polygenic Risk Score (PRS), results were significant only for those with a lower PRS for PD.
Conclusions: Following a healthful plant-based diet and in particular the inclusion of readily achievable intakes of vegetables, nuts and tea in the habitual diet are associated with a lower risk of PD. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: diet; epidemiology; food quality; Parkinson's disease

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Neurological disorders are the leading cause of disability, whereas Parkinson's disease (PD) is the fastest growing in prevalence, disability, and deaths, affecting around 1% of those over 60 years and 3% of those over 80 years in industrialized countries. Given the global increase in population growth and aging, this trend is expected to continue.[1-3] PD is a common neurodegenerative disorder that causes progressive motor and nonmotor disability. Parkinsonism is a group of symptoms that encompass motor impairment features such as akinesia (or bradykinesia), rigidity, tremor, and postural instability. Patients with PD also have nonmotor symptoms that include neuropsychiatric, sleep, gastrointestinal, and autonomic dysfunction.[1,4,5] To date, there is no cure for PD, so strategies for primary prevention are needed. However, the causes of the disease are widely unknown, and the main risk factors that have been identified are non-modifiable (age and genetic factors) or difficult to modify (exposure to industrial chemicals and pollutants).[2] Therefore, the identification of modifiable PD risk factors such as dietary and lifestyle factors may open new avenues for primary PD prevention.

The potential neuroprotective properties of some nutrients, foods, and dietary patterns have been investigated. For example, due to the neuroprotective activity of vitamins A, C, E, and beta-carotene, these compounds have been postulated to reduce PD risk, but long-term studies and meta-analyses of population-based studies have been inconclusive.[5] More consistent data suggest that caffeine intake (from coffee and tea) might reduce PD risk and slow its progression, whereas dairy intake might increase the risk.[5]

Recently, dietary patterns have been studied in relation to chronic disease risks to account for the totality of food intake and potential synergistic effects of different components. In the widely recognized report on "Healthy Diets from Sustainable Food Systems," the EAT-Lancet Commission has recommended a shift toward plant-based dietary patterns, not only for population health but also for planetary health.[6,7] Plant-based diets such as the traditional Mediterranean diet and vegetarian diets are characterized by higher consumption of plant foods and lower or no intake of animal foods.[8,9] Growing evidence suggests that these diets, usually rich in fiber, vitamins, and bioactive compounds, could prevent the development of chronic diseases, including cognitive impairment, by reducing oxidative stress and inflammation and exerting neuroprotective effects.[8-10] However, not all plant-based foods are necessarily healthy. For example, potatoes, refined sugars, and refined grains are plant foods that have been associated with an increased risk of several chronic diseases.[11-15]

The evidence on dietary patterns and risk of PD is scarce. Earlier studies suggest that high intakes of animal fat are associated with increased risk of PD, whereas plant-based diets might be protective, but the data are very limited.[16,17] Therefore, in the present study we explore the prospective associations between healthful and unhealthful plant-based dietary indices[18] and incidence of PD in the large-scale population-based UK Biobank cohort.

Patients and Methods

Study Population: The UK Biobank

The UK Biobank is an ongoing national health resource carried out in the United Kingdom aimed to prevent, diagnose, and treat a wide range of diseases and to promote health.[19,20] This cohort includes over 500,000 participants aged between 40 and 69 years at recruiting time (2006–2010). Details of the study have been described elsewhere.[19] Briefly, participants were recruited in 22 assessment centers in England, Scotland, and Wales. This baseline visit included a touchscreen questionnaire to provide data on sociodemographic characteristics, lifestyle, and health. Moreover, trained professionals undertook physical measurements, and participants were asked to provide biological samples.

From the initial 502,411 participants, we excluded participants who withdrew their informed consent, those with no data on diet or other key variables, and those with implausible energy intakes (>17,573KJ or < 3347KJ for men and > 14,644KJ or < 2092KJ for women).[21] To more accurately calculate habitual intake we also excluded those with fewer than two dietary recalls.[22] Participants with prevalent PD at baseline or those who were diagnosed before completing their last 24-hour dietary assessment were also excluded to reduce the risk of reverse causality. Finally, a total of 126,283 participants were available for this analysis (see eFig. 1 in Data S1).

The UK Biobank study received ethical approval from the NHS North-West Multi-Centre Research Ethics Committee (Ref. 11/NW/0382), and all participants provided written informed consent of their participation.

Dietary Assessment and Calculation of Plant-Based Diet Indices

Diet information was assessed using the Oxford WebQ dietary questionnaire.[23] Participants were asked about the frequency of consumption of approximately 200 foods items and 30 drinks over the past 24 hour using standard portions. The reliability and validity of this questionnaire have been previously described.[24]

We calculated an overall plant-based diet index (PDI), a healthful plant-based diet index (hPDI), and an unhealthful plant-based diet index (uPDI) following the method described in previous studies.[18,25-27] The three indices were calculated using 17 food groups that were created based on nutrient and culinary similarities. These food groups were further classified into three groups as follows: healthy plant foods (wholegrains, fruits, vegetables, nuts, legumes and vegetarian protein alternatives, and tea and coffee), unhealthy plant foods (fruit juices, refined grains, potatoes, sugar-sweetened beverages, sweets, and desserts), and animal foods (animal fat, dairy, eggs, fish or seafood, meat, and miscellaneous animal-derived foods). Alcoholic beverages were excluded as their association with health is unclear. Margarine was not included due to its change in fatty acid composition in recent years to avoid trans fatty acids. In this study, information about vegetable oils was not available so they were not part of the healthy plant score.

The scores were created by adding up the number of servings of each food of the corresponding food group and then calculating the average of the intakes of all available recalls (from 2 to 5) preceding the diagnosis of PD or the end of follow-up, whichever came first.

The foods that constitute each group have been detailed in eTable 1 in Data S1. The 17 food groups were ranked into quartiles excluding those with zero values (no consumption) to achieve a normal distribution across the quartiles. Those with zero values were treated as a separate category, so we had five categories for each food group. Quartiles were constructed separately by sex and combined. Then, with positive scores, a score of five was assigned to the highest quartile, whereas a score of two was assigned to the lowest quartile. A score of one was assigned to those who reported no intakes. For reverse scores, the pattern was the inverse: one was assigned to the highest intakes and 5 to those who reported zero intake. The positives and reverse scores are summarized in eTable 1 in Data S1. Finally, the scores of all groups were summed to calculate PDI, hPDI, and uPDI. The scores range between 17 and 85 (17 times 5). The scores of the three indices were normally distributed (eFig. 2 in Data S1). We additionally created a score comprising only healthy plant foods (ohPDI) that ranged between 6 and 30 (6 times 5).

To sum up, higher values of PDI reflect a diet rich in plant-based foods regardless of the type; higher scores of hPDI reflect a diet with greater amount of healthy plant-based foods, and finally, higher scores of the uPDI are associated to unhealthy plant-based diets. All of them, however, reflect lower intake of animal-based foods.

Ascertainment of the Outcome

For the present analysis we included incident PD cases defined using the Hospital Inpatient and Death Registry data. Participants diagnosed with incident PD, based on hospital admission data (September 30, 2021, from the Hospital Episode Statistics [HES] for England; July 31, 2021, for Scottish Morbidity Records [SMR]; March 31, 2016, for the Patient Episode Database for Wales [PEDW]), were considered as cases.

Assessment of Covariates

Sociodemographic, dietary, and lifestyle characteristics were assessed using a touchscreen questionnaire between 2006 and 2010. Anthropometric measurements and biological samples were collected from all study participants by trained staff, and data on self-reported medical conditions were collected at baseline via physician-led interview.[19] More information about covariates can be found in eMethods 1.

Statistical Analysis

The baseline characteristics of the participants were categorized by quartiles of plant-based diet scores to distribute men and women equally across the quartiles. Data are presented as means ± standard deviation for continuous variables, and frequencies and percentages for categorical variables. We used one-factor ANOVA or Pearson χ^2 tests to compare the quantitative or categorical variables, respectively.

We used multivariable-adjusted Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for PD risk across quartiles of the different plant-based diet indices. Follow-up began at baseline (enrollment date) and ended with a PD diagnosis, death, or the end of follow-up, whichever came first.

Cox regression model 1 was adjusted for sex and stratified by age and region. Model 2 was additionally adjusted for education level, body mass index (BMI), smoking status, alcohol intake, and quintiles of mean energy intake in kJ/day. The fully adjusted model also included self-reported diet variation at baseline, multimorbidity and polypharmacy index. Multiple morbidity index was calculated to account for 42 other pre-existing long-term medical conditions (LTCs), excluding PD.[28] The index was then categorized into four groups: none, 1, 2, and ≥ 3 LTCs. Similarly, the numbers of self-reported treatments (medications) reported at baseline were categorized as none, 1–3, 4–6, 7–9, ≥10. We also ran a sensitivity model additionally adjusting for tertiles of polygenic risk score (PRS) for PD.[29] More detailed information about the adjustment variables can be found in eMethods 2.

Ethnicity was shown in descriptive tables but was not included as a covariate in the Cox models due to the limited diversity of the study population (>90% white) and because it did not change the final result.

Tests for linear trend were carried out modeling the PDIs as continuous exposure variables. Cubic splines with three knots (percentiles at 10, 50, 90) were used to assess potential nonlinearity in associations between PDIs and endpoints.

In addition to our main model, we performed Cox regression analyses for each of the 17 food groups that constituted the plant-based diet score. All food groups were divided into quintiles except when this resulted in an uneven distribution of the scores. This was the case of sugary drinks, animal fat, and eggs that were categorized in quartiles; nuts in tertiles; and miscellaneous animal-based foods were only divided into two groups. Based on our results, we performed two additional regressions separating coffee and tea.

Further subgroup analyses were carried out to assess potential heterogeneity in associations between hPDI as a continuous score and PD across strata of the following key hypothesized effect modifiers: sex (male, female), education (low: GSEs/O-Levels/GCSEs or equivalent, NVQ/HND/HNC/A-Levels/AS-Levels or equivalent, high: other professional qualifications, college/university degree), BMI (<25 and ≥ 25 kg/m^2), smoking habit (ever, never), and tertiles of PRS (low, medium, high). The likelihood ratio test (LRT) was used to test for interactions between hPDI and the covariates listed earlier in relation to PD, comparing the fits of Cox models with and without the respective interaction terms. Additionally, sensitivity analyses were carried out, whereby participants younger than 60 years were excluded from Cox regression models, because PD is more common among older people.

All statistical analyses were undertaken using Stata/IC 16.1 (StataCorp), and *P*-values<0.05 were considered statistically significant.

Results

Participant Characteristics

The cohort included 126,283 participants (1,490,139 person-years) from the United Kingdom. Of these UK Biobank participants, 55.9% were female with a mean age of 56.1 years, predominantly white, with a mean BMI of 26.7, mainly nonsmokers, and half of them had been classified as having a high education level (college/university degree or professional education). During 11.8 years of follow-up, 577 cases of PD were diagnosed.

The distribution of baseline characteristics of the participants based on quartiles of hPDI, PDI, and uPDI scores is shown in Table 1, eTables 2 and 3 in Data S1, respectively. Individuals with higher scores of hPDI and PDI and lower scores of uPDI were more likely to be older, were more physically active, had lower BMI, were non-smokers, had a higher level of education and higher household income than participants with lower hPDI and PDI and higher uPDI scores.

Table 2 shows the mean portions of each of the 17 food groups that were used to calculate the scores based on quartiles of hPDI (additional data for quartiles of PDI and uPDI can be found in eTables 4 and 5 in Data S1, respectively). As expected, in the upper quartile, the values of healthful plant foods (wholegrains, fruit, vegetables, nuts, legumes and vegetarian protein alternatives, and tea and coffee) were higher, whereas the portions of unhealthy plant foods (fruit juices, refined grains, potatoes, sugar-sweetened beverages, sweets, and desserts) and animal-derived foods (animal fat, dairy, eggs, fish or seafood, meat, and miscellaneous animal-derived foods), as well as total energy intake, were lower compared to the first quartile.

Plant-Based Diet Quality and Risk of PD

Table 3 shows Cox Proportional HRs and 95% CI for PD risk based on quartiles of the three different plant-based diet scores. In the multivariable model, the HR for the highest versus the lowest quartile of hPDI was 0.78 (95% CI 0.61–0.99; *P*-trend = 0.02). We also observed an inverse association between PDI and PD risk (HR = 0.92, 95% CI 0.64–1.03; *P*-trend = 0.03), although only participants in the third quartile had a significantly lower risk of PD (HR = 0.76; 95% CI 0.60–0.96). Regarding uPDI, those in the highest quartile had a 38% higher risk of developing PD than those in the lowest quartile (HR = 1.38, 95% CI 1.08–1.74; *P*-trend = 0.02). eFigure 3 in Data S1 shows cubic spline graphs of the fully adjusted linear associations between hPDI, uPDI, and PDI scores and PD.

Additionally, we ran the analyses adjusting for tertiles of PRS of PD. Even though the number of participants was lower (123,528), results remain very similar. Comparing the highest versus the lower quartiles of the plant-based diet score, the risk of PD was 25% lower for hPDI (HR = 0.75, 95% CI 0.59–0.96, *P*-trend 0.007), 18% lower for PDI (HR = 0.82, 95% CI 0.64, 1.04, *P*-trend 0.035), and 41% higher for uPDI (HR = 1.41, 95% CI 1.11–1.79, *P*-trend 0.015).

Food Intake and Parkinson's

Figure 1 and eTable 6 in Data S1 show the HR and 95% CI for the associations between the food groups that compose the scores and risk of PD. Participants in the top quintile of vegetable intake had a 28% lower risk of PD compared to the lowest quintile (HR = 0.72; 95% CI, 0.55–0.94; *P*-trend = 0.008). A higher consumption of nuts was also inversely associated with PD (HR = 0.69; 95% CI, 0.54–0.87; *P*-trend = 0.002). The food group of tea and coffee combined showed similar results (HR = 0.73; 95% CI, 0.56–0.95; *P*-trend = 0.012), but when looking into the foods separately we observed that only a higher tea intake was

TABLE 1 . *Baseline characteristics of UK Biobank participants based on quartiles of hPDI score*

	Total	Q1	Q2	Q3	Q4	*P*
Number of participants	126,283	33,914	30,445	30,017	31,907	
Incident Parkinson's cases	577 (0.5)	135 (0.4)	155 (0.5)	144 (0.5)	143 (0.5)	0.19
hPDI score, mean (SD)	55.5 (6.4)	47.7 (3.3)	53.7 (1.5)	57.6 (1.5)	63.4 (3.3)	<0.001
uPDI score, mean (SD)	54.0 (6.1)	57.6 (5.7)	55.1 (5.5)	53.1 (5.2)	49.9 (5.1)	<0.001
PDI score, mean (SD)	53.5 (5.3)	51.3 (5.1)	52.8 (15.1)	53.8 (5.0)	56.0 (4.9)	<0.001
Sex—female	70,565 (55.9)	18,081 (53.3)	17,074 (56.1)	17,144 (57.1)	18,266 (57.3)	<0.001
Age—years, mean (SD)	56.1 (7.8)	54.6 (8.1)	56.2 (7.8)	56.7 (7.6)	57.2 (7.4)	<0.001
BMI—kg/m^2, mean (SD)	26.7 (4.6)	27.7 (5.0)	26.8 (4.5)	26.4 (4.3)	25.8 (4.2)	<0.001
Physical activity, tertiles						<0.001
Low	41,643 (33.6)	12,659 (38.1)	10,403 (34.8)	9603 (32.6)	8978 (28.6)	
Moderate	41,032 (33.1)	10,614 (32.0)	9943 (33.3)	9825 (33.3)	10,650 (33.9)	
High	41,311 (33.3)	9946 (29.9)	9536 (31.9)	10,044 (34.1)	11,785 (37.5)	
Ethnicity						<0.001
White	115,268 (91.3)	31,112 (91.7)	27,914 (91.7)	27,429 (91.5)	28,813 (90.3)	
Mixed other	3532 (2.8)	991 (2.9)	839 (2.8)	788 (2.6)	914 (2.9)	
Asian	5846 (4.6)	1405 (4.1)	1316 (4.3)	1424 (4.7)	1701 (5.3)	
Black	466 (0.4)	113 (0.3)	104 (0.3)	108 (0.4)	219 (0.7)	
Townsend deprivation index						<0.001
Q1—least deprived	27,618 (21.9)	7070 (20.9)	6868 (22.6)	6743 (22.5)	6937 (21.7)	
Q2	26,779 (21.2)	7056 (20.8)	6537 (21.5)	6417 (21.4)	6769 (21.2)	
Q3	25,894 (20.5)	7088 (20.9)	6266 (20.6)	6147 (20.5)	6393 (20.0)	
Q4	25,576 (20.3)	6967 (20.5)	6056 (19.9)	6057 (20.2)	6496 (20.4)	
Q5—most deprived	20,268 (16.1)	5681 (16.8)	4689 (15.4)	4614 (15.4)	5284 (16.6)	
Education						<0.001
Low	32,341 (25.6)	9327 (27.5)	7954 (26.1)	7470 (24.9)	7590 (23.8)	
Medium	20,233 (16.0)	6043 (17.8)	5035 (16.5)	4573 (15.2)	4582 (14.4)	
High	65,104 (51.6)	15,976 (47.1)	15,237 (50.1)	16,021 (53.4)	17,870 (56,0)	
Smoking status						<0.001
Never	72,098 (57.1)	19,448 (57.4)	17,311 (56.9)	17,175 (57.2)	18,164 (56.9)	
Previous	45,177 (35.8)	11,415 (33.7)	10,905 (35.8)	10,866 (36.2)	11,991 (37.6)	
Current	8735 (6.9)	2988 (8.8)	2152 (7.1)	1907 (6.4)	1688 (5.3)	
Alcohol intake						<0.001
<1 g/day	6373 (5.1)	1744 (5.1)	1475 (4.8)	1471 (4.9)	1683 (5.3)	
1–7 g/day	26,488 (21.0)	6655 (19.6)	6275 (20.6)	6386 (21.3)	7172 (22.5)	
8–15 g/day	31,681 (25.1)	7997 (23.6)	7655 (25.1)	7764 (25.9)	8265 (25.9)	
>16 g/day	40,625 (32.2)	11,591 (34.2)	10,159 (33.4)	9671 (32.2)	9204 (28.9)	

(Continues)

TABLE 1 *Continued*

	Total	Q1	Q2	Q3	Q4	*P*
Total alcohol— g/day, mean (SD)	17.0 (24.5)	17.6 (25.7)	18.0 (25.0)	17.1 (24.0)	15.3 (22.7)	<0.001
Multiple morbidity index						<0.001
0 LTCs	44,708 (35.4)	11,821 (34.9)	10,819 (35.5)	10,569 (35.2)	11,499 (36.0)	
1 LTC	41,114 (32.6)	10,993 (32.4)	9783 (32.1)	10,010 (33.4)	10,328 (32.4)	
2 LTCs	23,353 (18.5)	6240 (18.4)	5703 (18.7)	5549 (18.5)	5861 (18.4)	
≥3 LTCs	17,108 (13.6)	4860 (14.3)	4140 (13.6)	3889 (13.0)	4219 (13.2)	
Polypharmacy index						<0.001
0	39,192 (31.0)	10,287 (30.3)	9348 (30.7)	9404 (31.3)	10,153 (31.8)	
1–3	58,882 (46.6)	15,899 (46.9)	14,271 (46.9)	13,941 (46.4)	14,771 (46.3)	
4–6	20,785 (16.5)	5602 (16.5)	5027 (16.5)	4964 (16.5)	5192 (16.3)	
7–9	5452 (4.3)	1503 (4.4)	1310 (4.3)	1266 (4.2)	1373 (4.3)	
≥10	1953 (1.6)	619 (1.8)	479 (1.5)	440 (1.5)	415 (1.3)	

Note: Values are *N* (%) unless noted otherwise. Relative frequencies (%) include missing values that may ≠100%.
Abbreviations: Q, quartile; hPDI, healthful plant-based diet; SD, standard deviation; uPDI, unhealthful plant-based diet; PDI, plant-based diet; BMI, body mass index; LTC: long-term conditions.

TABLE 2 *Mean food intake based on quartiles of hPDI score*

	Total	Q1	Q2	Q3	Q4	*P*
Food intake, portions/day[1]						
Wholegrains	2.16 (1.47)	1.55 (1.27)	2.01 (1.37)	2.31 (1.42)	2.80 (1.53)	<0.001
Fruit	2.24 (1.60)	1.52 (1.25)	2.01 (1.43)	2.42 (1.56)	3.07 (1.71)	<0.001
Vegetables	2.47 (1.85)	1.78 (1.45)	2.22 (1.61)	2.58 (1.78)	3.32 (2.13)	<0.001
Nuts	0.17 (0.35)	0.07 (0.22)	0.12 (0.28)	0.17 (0.33)	0.32 (0.47)	<0.001
Legumes and vegetarian protein alternatives	0.39 (0.45)	0.26 (0.33)	0.33 (0.38)	0.40 (0.43)	0.50 (0.55)	<0.001
Tea and coffee	4.37 (1.69)	3.86 (1.64)	4.26 (1.62)	4.52 (1.63)	4.87 (1.69)	<0.001
Refined grains	1.07 (1.04)	1.68 (1.18)	1.10 (0.98)	0.86 (0.86)	0.58 (0.68)	<0.001
Potatoes	0.70 (0.53)	0.87 (0.56)	0.74 (0.52)	0.65 (0.50)	0.54 (0.46)	<0.001
Sugary drinks	0.49 (0.79)	0.85 (0.98)	0.52 (0.78)	0.36 (0.65)	0.21 (0.50)	<0.001
Fruit juices	0.46 (0.53)	0.56 (0.56)	0.49 (0.53)	0.43 (0.52)	0.34 (0.49)	<0.001
Sweets and desserts	1.41 (1.18)	1.82 (1.27)	1.50 (1.16)	1.30 (1.09)	1.00 (1.00)	<0.001
Animal fat	0.68 (0.99)	1.10 (1.15)	0.73 (1.00)	0.53 (0.88)	0.33 (0.71)	<0.001
Dairy	1.09 (0.76)	1.16 (0.77)	1.09 (0.74)	1.08 (0.75)	1.02 (0.77)	<0.001
Eggs	0.29 (0.42)	0.40 (0.46)	0.30 (0.41)	0.25 (0.39)	0.20 (0.36)	<0.001
Fish or seafood	0.33 (0.40)	0.37 (0.42)	0.34 (0.40)	0.33 (0.39)	0.30 (0.38)	<0.001
Meat	1.15 (0.84)	1.47 (0.90)	1.18 (0.82)	1.07 (0.77)	0.83 (0.72)	<0.001
Miscellaneous animal-based foods	0.09 (0.31)	0.16 (0.41)	0.09 (0.30)	0.07 (0.26)	0.04 (0.19)	<0.001
Total energy intake, KJ/day	8469 (1858)	9098 (1826)	8518 (1798)	8225 (1796)	7984 (1812)	<0.001

Note: Values are mean (SD).
Abbreviations: Q, quartile; SD, standard deviation.
[1]Portions sizes were specified as a "serving" in the Oxford WebQ; "Food portion sizes" (Ministry of Agriculture, Fisheries and Food, 1993) were predominantly used as a point of reference for portion sizes.

TABLE 3 *Hazard ratios and 95% confidence intervals (CI) for the associations between quartiles (Q) of PDI, hPDI, and uPDI and risk of Parkinson's disease*

	Q1	Q2	Q3	Q4	*P*-trend
hPDI					
Median (range)	48 (31–52)	54 (51–56)	58 (55–60)	63 (59–84)	
Cases/total (%)	135/33,914 (0.40)	155/30,445 (0.51)	144/30,017 (0.48)	143/31,907 (0.45)	
Model 1	1.00	1.07 (0.85, 1.35)	0.93 (0.73, 1.18)	0.82 (0.65, 1.04)	0.045
Model 2	1.00	1.05 (0.83, 1.33)	0.89 (0.70, 1.14)	0.78 (0.61, 0.99)	0.016
Model 3	1.00	1.06 (0.84, 1.33)	0.90 (0.71, 1.15)	0.78 (0.61, 0.99)	0.017
uPDI					
Median (range)	47 (28–51)	52 (50–55)	56 (54–59)	61 (58–82)	
Cases/total (%)	161/34,819 (0.46)	161/31,287 (0.51)	128/30,420 (0.42)	127/29,757 (0.43)	
Model 1	1.00	1.25 (1.01, 1.56)	1.13 (0.89, 1.43)	1.42 (1.12, 1.79)	0.012
Model 2	1.00	1.24 (0.99, 1.54)	1.12 (0.88, 1.41)	1.39 (1.10, 1.77)	0.020
Model 3	1.00	1.24 (0.99, 1.54)	1.11 (0.88, 1.41)	1.38 (1.08, 1.74)	0.024
PDI					
Median (range)	47 (29–50)	52 (50–53)	55 (54–57)	59 (57–79)	
Cases/total (%)	156/33,000 (0.47)	152/30,465 (0.50)	130/30,430 (0.43)	139/32,388 (0.43)	
Model 1	1.00	0.93 (0.75, 1.17)	0.78 (0.62, 0.98)	0.84 (0.67, 1.05)	0.054
Model 2	1.00	0.93 (0.74, 1.16)	0.77 (0.60, 0.97)	0.82 (0.65, 1.05)	0.045
Model 3	1.00	0.93 (0.74, 1.16)	0.76 (0.60, 0.96)	0.82 (0.64, 1.03)	0.030

Note: Model 1: Cox regression model adjusted for sex and stratified by age and region. Model 2: Model 1 + education, BMI, smoking, alcohol, and energy intake. Model 3: Model 2 + diet variation, multimorbidity and polypharmacy index.
Abbreviations: Q, quartile; hPDI, healthful plant-based diet index; uPDI, unhealthful plant-based diet index; PDI, Plant-base diet index.

inversely associated with PD risk (HR = 0.75; 95% CI, 0.57–0.99; *P*-trend = 0.08).

Sensitivity Analyses

Subgroup analyses (Fig. 2) indicated differential associations between hPDI and PD across strata of education, smoking, and PRS. Results showed that the associations were significant only for those with a higher education level (HR 0.84; 95% CI 0.70–0.99, *P*-heterogeneity 0.04), former and current smokers (HR 0.82; 95% CI 0.70–0.97, *P*-heterogeneity 0.13), and those with lower PRS for PD (HR 0.72; 95% CI 0.54–0.96, *P*-heterogeneity 0.05), suggesting that dietary approaches may benefit only those without genetic risks. No differences were found regarding BMI. Because PD is more common among older people, we carried out the analysis excluding participants younger than 60 years, which demonstrated a stronger inverse association (HR 0.84; 95% CI 0.70–0.97, *P*-trend = 0.02). We additionally ran the analysis for ohPDI (eTable 7 in Data S1), considering only healthy plant-based foods to create the score, and we found a 38% lower risk of PD (HR = 0.62, 95% CI 0.48, 0.80, *P*-trend 0.035).

Discussion

Plant-based dietary indices have been examined in relation to risk of PD. We found that, after multivariable adjustment, participants in the highest quartile of hPDI had a 22% lower risk of PD. A linear, but weaker, inverse association for overall PDI was also observed. In contrast, a higher uPDI was associated with a 38% greater risk of PD.

Plant-based diets are characterized by low consumption or complete omission of different animal products. Vegan, vegetarian, pesco-vegetarian, and semi-vegetarian diets are common examples of plant-based diets.[30,31] Usually, the focus of attention has been on the restrictions (eg, no meat, no fish, no dairy) while little consideration has been given to the quality of the plant foods consumed.

Previous studies have provided some evidence of the role of diet in the development and progression of

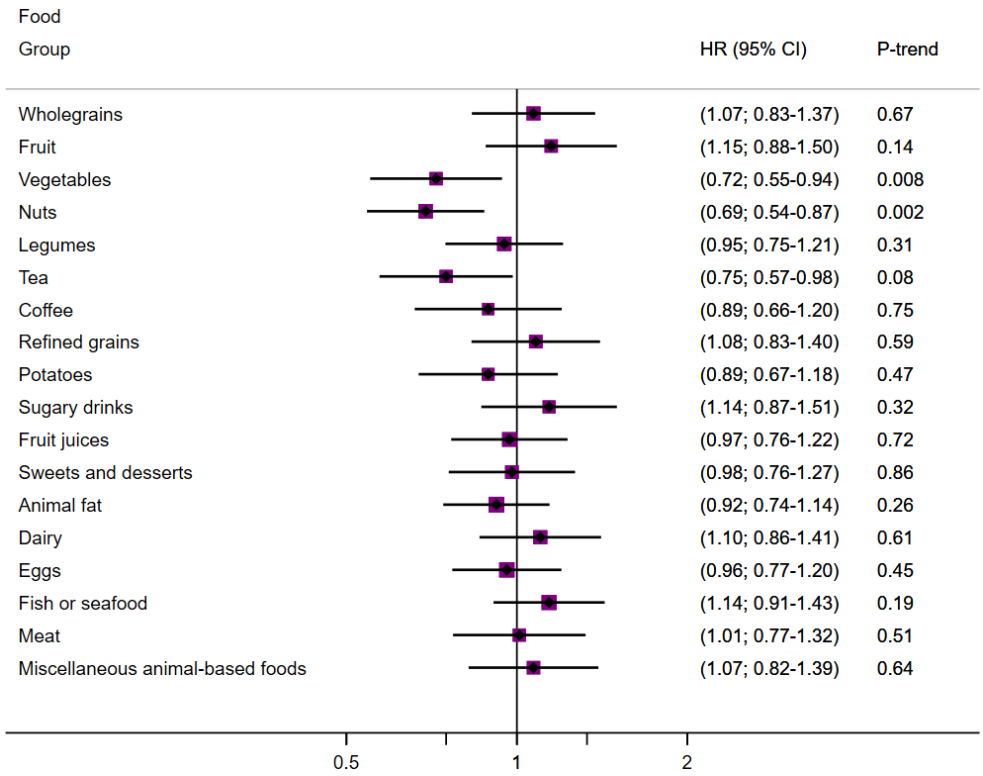

FIG. 1. Hazard ratios (HR) and 95% confidence intervals (CI) of PD. Key foods of the hPDI score modeled as continuous trend (10-point increments). Analyses were fully adjusted excluding the key food of interest. [Color figure can be viewed at wileyonlinelibrary.com]

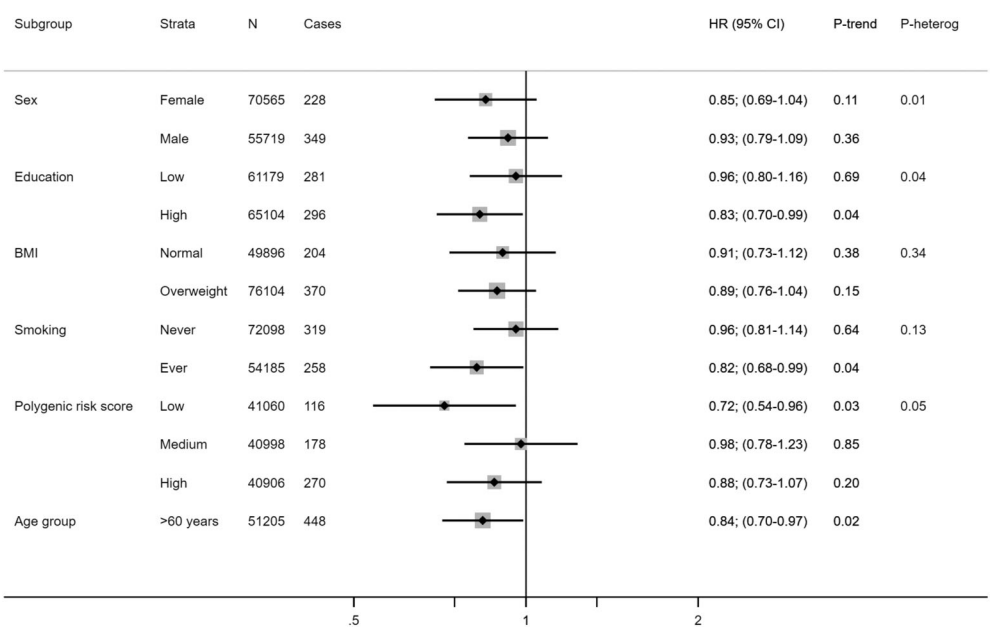

FIG. 2. Hazard ratios (HR) and 95% confidence intervals (CI) of hPDI modeled as continuous trend (10-point increments) of PD among subgroups of the UK Biobank. Analyses were fully adjusted excluding the subgroup of interest.

PD. A prospective study of the Health Professionals Follow-Up Study (1986–2002) and the Nurses' Health Study (1984–2000) showed that dietary patterns that included high consumption of fruit, vegetables, legumes, wholegrains, nuts, fish, and poultry, as well as low intakes of saturated fat and a moderate intake of alcohol protected against PD.[16] Ketogenic diets have also been considered as a possible way to reduce PD

symptoms, but the existing literature is mostly based on animal studies and pilot clinical trials, and results from larger randomized clinical trials are still lacking.[32] The traditional Mediterranean diet has been considered as a model of healthy eating and, as such, it has been associated with several health benefits; a systematic review of prospective cohort studies suggest that higher adherence was associated with a 13% decrease in incidence of PD.[33]

In recent years, there has been growing interest in the relationship between the gut microbiome and inflammatory-driven diseases, and it has been hypothesized that the initial pathophysiological changes in PD occur in the gastrointestinal tract even before the first symptoms are shown.[34] Gut dysbiosis, an alteration of the gut microbiome, has been proposed as a mechanism for neuroinflammation leading to PD, but also to other chronic diseases. Neurological function depends on neuropeptides, which are produced by the gut microbiome, while the gut itself is influenced by the central nervous system and diet.[34] Recent literature indicates that our diet can exert neuroprotective effects via its impact on the diversity and functionality of the gut microbiome rather than by diet-induced neuro-inflammation.[34,35] Diets high in polyphenols and fiber, such as the Mediterranean diet or flexitarian diets, could mitigate dysbiosis by favoring beneficial gut bacteria,[36,37] whereas ultra-processed foods have an opposite effect.[38]

Other potential mechanisms by which flavonoids, such as naringenin[39] and hesperetin,[40] can reduce PD include their impact on oxidative stress that can result in chronic inflammation,[37] interactions with neuronal signaling pathways, modulating the activity of several oxidative-related enzymes, and regulating mitochondrial function.[41-43]

In the current food-based analyses, lower PD risk was also shown for higher intakes of vegetables (especially tomatoes, salad, cruciferous, carrots), nuts, and tea (median intakes from which results were significant were 3, 0.5, and 5 portions/day, respectively). Previously, there was limited evidence in the literature on the effects of specific foods and nutrients on PD, and some findings are inconsistent. Gao et al examined different dietary patterns within the Health Professionals Follow-Up Study (1986–2002) and the Nurses' Health Study (1984–2000) and found that diets including a high intake of fruit, vegetables, legumes, wholegrains, nuts, fish, and poultry and a low intake of saturated fat and a moderate intake of alcohol could decrease the risk of PD.[16] In the same cohorts, higher habitual intakes of total flavonoid intake and, specifically anthocyanins (present in berries), were associated with a reduced PD risk of 40%, 24%, and 23% respectively.[44]

Caffeine has received more attention than any other substance in relation to PD. An umbrella review concluded that caffeine was associated with a probable decreased risk of PD after data were pooled from 20 population-based studies.[45] Similarly, results from a prospective study among almost 30,000 Finnish participants revealed that both coffee and tea intakes were inversely and linearly associated with PD.[46]

In line with our results, walnut extract improved symptoms of PD, reduced oxidative stress, and protected neurons in mice.[47] Moreover, a review of observational studies within the Nurse's Health Study stated that higher nut intake was associated with better cognitive function.[48] We did not find any association between dairy intake and PD. However, an umbrella review of systematic reviews and meta-analyses in humans concluded that milk intake may increase risk.[49]

The strengths of this study include the prospective design, large sample size, and comprehensive data on diet, risk factors, and confounders for PD risk. However, there are some limitations to consider. For instance, PD incidence was diagnosed using hospital admissions but not self-reported data (self-reported cases were recorded at baseline, so they were prevalent cases and, therefore, excluded in this analysis). Information on covariates and diet was based on self-reported questionnaires. Nonetheless, to represent habitual, long-term dietary habits, we used average scores based on repeated assessments at different time points. Moreover, we categorized food items in food groups (healthy and unhealthy) based on existing literature but, when categorizing, information on individual food items is missing, and we cannot consider the cooking method. Also, although we adjusted for a range of potential confounders, there is still the possibility of residual confounding. Finally, extrapolation of the results to other populations should be carefully considered given the characteristics of the cohort, and the analyses need replication in other cohorts.

PD is the second most common neurodegenerative disease worldwide, and we have shown that diet is an important modifiable risk factor. The study of overall dietary patterns and their role in human health are of great importance to develop easy-to-follow, food-based dietary guidelines for public health benefit. Moreover, healthful plant-based diets are beneficial for planetary health and are aligned with the dietary recommendations for the prevention of chronic diseases across the globe including those for a *Planetary Health Diet* by *EAT Lancet Commission on Food, Planet, Health*.[6]

Conclusions

Our novel study strengthens the knowledge around the health benefits of adhering to healthy plant-based dietary patterns, in this case, providing novel data that higher adherence reduces PD risk. These results are

important to help refine and inform public health messages that consider plant-based diets and provide evidence that simple dietary change has the potential to reduce PD risk.

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Data Availability Statement

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

References

1. Homayoun H. Parkinson disease. Ann Intern Med 2018;169(5):ITC33–ITC47.
2. Ray Dorsey E, Elbaz A, Nichols E, Abd-Allah F, Abdelalim A, Adsuar JC, et al. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the global burden of disease study 2016. Lancet Neurol 2018;17(11):939–953.
3. GBD 2019 Dementia Collaborators. The burden of dementia due to down syndrome, Parkinson's disease, stroke, and traumatic brain injury: a systematic analysis for the global burden of disease study 2019. Neuroepidemiology 2021;55(4):286–296.
4. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. JAMA 2020;323(6):548–560.
5. Breasail M, Smith MD, Tenison E, Henderson EJ, Lithander FE. Parkinson's disease: the nutrition perspective. Proc Nutr Soc 2021;81(1):12–26.
6. Willett W, Rockström J, Loken B, Springmann M, Lang T, Vermeulen S, et al. Food in the Anthropocene: the EAT–lancet commission on healthy diets from sustainable food systems. Lancet 2019;393(10170):447–492.
7. Tilman D, Clark M. Global diets link environmental sustainability and human health. Nature 2014;515(7528):518–522.
8. Eichelmann F, Schwingshackl L, Fedirko V, Aleksandrova K. Effect of plant-based diets on obesity-related inflammatory profiles: a systematic review and meta-analysis of intervention trials. Obes Rev 2016;17(11):1067–1079.
9. Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, vegan diets and multiple health outcomes: a systematic review with meta-analysis of observational studies. Crit Rev Food Sci Nutr 2017;57(17):3640–3649.
10. Menzel J, Jabakhanji A, Biemann R, Mai K, Abraham K, Weikert C. Systematic review and meta-analysis of the associations of vegan and vegetarian diets with inflammatory biomarkers. Sci Rep 2020;10(1):21736.
11. Muraki I, Rimm EB, Willett WC, Manson JE, Hu FB, Sun Q. Potato consumption and risk of type 2 diabetes: results from three prospective cohort studies. Diabetes Care 2016;39(3):376–384.
12. Yang Q, Zhang Z, Gregg EW, Flanders WD, Merritt R, Hu FB. Added sugar intake and cardiovascular diseases mortality among US adults. JAMA Intern Med 2014;174(4):516–524.
13. Baden MY, Shan Z, Wang F, Li Y, Manson JAE, Rimm EB, et al. Quality of plant-based diet and risk of Total, ischemic, and hemorrhagic stroke. Neurology 2021;96(15):e1940–e1953.
14. Chen Z, Drouin-Chartier JP, Li Y, Baden MY, Manson JAE, Willett WC, et al. Changes in plant-based diet indices and subsequent risk of type 2 diabetes in women and men: three U.S. prospective cohorts. Diabetes Care 2021;44(3):663–671.
15. Key TJ, Papier K, Tong TYN. Plant-based diets and long-term health: findings from the EPIC-Oxford study. Proc Nutr Soc 2022;81(2):190–198.
16. Gao X, Chen H, Fung TT, Logroscino G, Schwarzschild MA, Hu FB, et al. Prospective study of dietary pattern and risk of Parkinson disease. Am J Clin Nutr 2007;86(5):1486–1494.
17. McCarty MF. Does a vegan diet reduce risk for Parkinson's disease? Med Hypotheses 2001;57(3):318–323.
18. Satija A, Bhupathiraju SN, Rimm EB, Spiegelman D, Chiuve SE, Borgi L, et al. Plant-based dietary patterns and incidence of type 2 diabetes in US men and women: results from three prospective cohort studies. PLoS Med 2016;13(6):e1002039.
19. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12(3):e1001779.
20. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. Am J Epidemiol 2017;186(9):1026–1034.
21. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 1997;65(4 Suppl):1220S–1228S. discussion 1229S-1231S.
22. Greenwood DC, Hardie LJ, Frost GS, Alwan NA, Bradbury KE, Carter M, et al. Validation of the Oxford WebQ online 24-hour dietary questionnaire using biomarkers. Am J Epidemiol 2019;188(10):1858–1867.
23. Piernas C, Perez-Cornago A, Gao M, Young H, Pollard Z, Mulligan A, et al. Describing a new food group classification system for UK biobank: analysis of food groups and sources of macro- and micronutrients in 208,200 participants. Eur J Nutr 2021;60(5):2879–2890.
24. Liu B, Young H, Crowe FL, Benson VS, Spencer EA, Key TJ, et al. Development and evaluation of the Oxford WebQ, a low-cost, web-based method for assessment of previous 24 h dietary intakes in large-scale prospective studies. Public Health Nutr 2011;14(11):1998–2005.
25. Heianza Y, Zhou T, Sun D, Hu FB, Qi L. Healthful plant-based dietary patterns, genetic risk of obesity, and cardiovascular risk in the UK biobank study. Clin Nutr 2021;40(7):4694–4701.
26. Satija A, Bhupathiraju SN, Spiegelman D, Chiuve SE, Manson JAE, Willett W, et al. Healthful and unhealthful plant-based diets and the risk of coronary heart disease in U.S. Adults. J Am Coll Cardiol 2017;70(4):411–422.
27. Thompson AS, Tresserra-Rimbau A, Karavasiloglou N, Jennings A, Cantwell M, Hill C, et al. Association of Healthful Plant-based Diet Adherence with Risk of mortality and major chronic diseases among adults in the UK. JAMA Netw Open 2023;6(3):e234714.
28. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012;380(9836):37–43.
29. Thompson DJ, Wells D, Selzam S, Peneva I, Moore R, Sharp K, et al. UK Biobank release and systematic evaluation of optimised polygenic risk scores for 53 diseases and quantitative traits. medRxiv 2022;2022.06.16.22276246.
30. Selinger E, Neuenschwander M, Koller A, Gojda J, Kühn T, Schwingshackl L, et al. Evidence of a vegan diet for health benefits and risks–an umbrella review of meta-analyses of observational and clinical studies. Crit Rev Food Sci Nutr 2022;1–11. ahead of print. https://doi.org/10.1080/10408398.2022.2075311
31. Alcorta A, Porta A, Tárrega A, Alvarez MD, Vaquero MP. Foods for plant-based diets: challenges and innovations. Foods 2021;10(2):293.
32. Gough SM, Casella A, Ortega KJ, Hackam AS. Neuroprotection by the ketogenic diet: evidence and controversies. Front Nutr 2021 Nov;23(8):910.
33. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. BMJ 2008;337(7671):673–675.
34. Yemula N, Dietrich C, Dostal V, Hornberger M. Parkinson's disease and the gut: symptoms, nutrition, and microbiota. J Parkinsons Dis 2021;11(4):1491–1505.

35. Romano S, Savva GM, Bedarf JR, Charles IG, Hildebrand F, Narbad A. Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation. NPJ Parkinsons Dis 2021;7(1):27.

36. Solch RJ, Aigbogun JO, Voyiadjis AG, Talkington GM, Darensbourg RM, O'Connell S, et al. Mediterranean diet adherence, gut microbiota, and Alzheimer's or Parkinson's disease risk: a systematic review. J Neurol Sci 2022;434:120166.

37. Lubomski M, Tan AH, Lim SY, Holmes AJ, Davis RL, Sue CM. Parkinson's disease and the gastrointestinal microbiome. J Neurol 2020;267(9):2507–2523.

38. Martínez Leo EE, Segura Campos MR. Effect of ultra-processed diet on gut microbiota and thus its role in neurodegenerative diseases. Nutrition 2020;1:71.

39. Goyal A, Verma A, Dubey N, Raghav J, Agrawal A. Naringenin: a prospective therapeutic agent for Alzheimer's and Parkinson's disease. J Food Biochem 2022;46(12):e14415.

40. Khan A, Ikram M, Hahm JR, Kim MO. Antioxidant and anti-inflammatory effects of citrus flavonoid Hesperetin: special focus on neurological disorders. Antioxidants 2020;9(7):1–15.

41. Aryal S, Skinner T, Bridges B, Weber JT. The pathology of Parkinson's disease and potential benefit of dietary polyphenols. Molecules 2020;25(19):4382.

42. Leri M, Scuto M, Ontario ML, Calabrese V, Calabrese EJ, Bucciantini M, et al. Healthy effects of plant polyphenols: molecular mechanisms. Int J Mol Sci 2020;21(4):1250.

43. Tahir MS, Almezgagi M, Zhang Y, Bashir A, Abdullah HM, Gamah M, et al. Mechanistic new insights of flavonols on neurodegenerative diseases. Biomed Pharmacother 2021;137:111253.

44. Gao X, Cassidy A, Schwarzschild MA, Rimm EB, Ascherio A. Habitual intake of dietary flavonoids and risk of Parkinson disease. Neurology 2012;78(15):1138.

45. Grosso G, Godos J, Galvano F, Giovannucci EL. Coffee, caffeine, and health outcomes: an umbrella review. Annu Rev Nutr 2017;37:131–156.

46. Hu G, Bidel S, Jousilahti P, Antikainen R, Tuomilehto J. Coffee and tea consumption and the risk of Parkinson's disease. Mov Disord 2007;22(15):2242–2248.

47. Choi JG, Park G, Kim HG, Oh DS, Kim H, Oh MS. In vitro and in vivo neuroprotective effects of walnut (Juglandis semen) in models of Parkinson's disease. Int J Mol Sci 2016;17(1):108.

48. Hagan KA, Munger KL, Ascherio A, Grodstein F. Epidemiology of major neurodegenerative diseases in women: contribution of the nurses' health study. Am J Public Health 2016;106(9):1650–1655.

49. Zhang X, Chen X, Xu Y, Yang J, Du L, Li K, et al. Milk consumption and multiple health outcomes: umbrella review of systematic reviews and meta-analyses in humans. Nutr Metab 2021;18(1):7.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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