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# Dietary Patterns and Nonmotor Symptoms in Parkinson's Disease: A Cross-Sectional Analysis

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**ABSTRACT**

**Objective:** Evidence-based treatment for nonmotor symptoms in Parkinson's disease (PD) is limited. Lifestyle-based improvements including dietary changes may be a potential management strategy. The intent of this research was to investigate the extent to which 3 dietary indices (Mediterranean-DASH Diet Intervention for Neurodegenerative Delay [MIND], Dietary Inflammation Index [DII], and Healthy Diet Indicator [HDI-2020]) are associated with overall and individual nonmotor symptom severity among individuals with PD.

**Method:** An exploratory cross-sectional analysis of dietary (food frequency questionnaire) and clinical data was undertaken, including measures of overall nonmotor symptom severity, such as fatigue, depression, anxiety, apathy, sleep problems, daytime sleepiness, and cognitive impairment. The relationship between each dietary score and symptom outcome was assessed by linear regression for continuous variables and through general linear model analysis for tertiles of dietary adherence.

**Results:** None of the dietary indices significantly predicted the total nonmotor symptom severity score. The HDI predicted a significant decrease in fatigue scores as measured by the NeuroQoL fatigue item (standardized $\beta = -.19$, $p = 0.022$), after adjusting for age, sex, energy intake, years since diagnosis, physical activity level, education, and smoking. Self-reported depression symptoms reduced by .17 (standardized β) for each unit increase in HDI score ($p = 0.035$), after controlling for age, gender, energy intake, and years since diagnosis. No other significant associations were evident between dietary scores and any other nonmotor symptoms.

**Conclusions:** Our results indicate that fatigue and depression in PD may be modified by diet; however, more research is needed using a larger sample to replicate these findings.

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**KEYWORDS**
Nutrition; neurologic; psychiatric; lifestyle; inflammation; Mediterranean; mental health

## Introduction

Parkinson's disease (PD)–related nonmotor symptoms can occur decades before motor symptoms and are reported to have a greater impact than motor symptoms on both the individual's and caregiver's quality of life and psychological well-being (1, 2). Common nonmotor symptoms include neuropsychiatric symptoms (anxiety, depression, apathy), sleep disorders, and fatigue (3–5). Current PD treatment with dopaminergic medication does not effectively treat many nonmotor symptoms (6, 7), can lead to side effects (8), and does not reduce progression of the disease (7). Consequently, the development and testing of new treatments remain a priority (9). It is of interest to investigate the potential of health-related lifestyle change, including diet, to better manage associated symptoms of PD (10–13).

The current study focuses on 3 dietary patterns of interest, the Mediterranean-DASH Diet Intervention for Neurodegenerative Delay (MIND) (14), designed to assess consumption of foods potentially associated with brain health; the Dietary Inflammation Index (DII) (15), designed to assess the inflammatory potential of an individual's diet; and the World Health Organization (WHO) Healthy Diet Indicator (HDI-2020), which assesses adherence to the WHO healthy diet guidelines (16). The rationale for using the previous dietary indices is as follows: (1) Adherence to the MIND dietary pattern has been associated with an older age at onset of PD motor symptoms (17) and lower rates of PD and slower progression of parkinsonian motor symptoms in older adults (18). (2) Inflammatory biomarkers have been shown to predict fatigue, depression, and anxiety in PD (19–23). Higher scores on the DII are reflective of a more pro-inflammatory diet and have been associated with a higher risk of experiencing various nonmotor symptoms among the general population, including memory and cognitive decline (24), sleep disturbances (25, 26) and impaired mental health (27). (3) The HDI was chosen to assess the association between overall

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diet quality and nonmotor symptom burden, as it provides a simple score that reflects globally accepted recommendations of what constitutes a healthy diet.

The aim of this cross-sectional study was to investigate the extent to which the MIND, DII, and HDI dietary indices are associated with total nonmotor symptom severity and individual nonmotor symptoms including fatigue, depression, anxiety, apathy, insomnia, daytime sleepiness, and cognitive impairment among a sample of individuals with PD. To our knowledge, this is the first study to investigate the association between dietary patterns, rather than individual nutrient intake, and nonmotor symptom severity in PD. This study is also the first to investigate the association between the inflammatory potential of an individual's diet and PD symptoms.

## Methods

### Study design

This study is a cross-sectional analysis from a subsample of people diagnosed with PD recruited from the Oxford Parkinson's Disease Discovery Cohort (OPDC). Opportunity sampling was used to collect additional data from patients with PD including self-report questionnaires assessing dietary intake, fatigue, and physical activity. Online or paper-based questionnaires were sent to the patient to complete at home prior to attending their routine OPDC clinic appointment. If paper questionnaires were completed, patients were asked to bring them to their appointment. Ethical approval for the study protocol was granted from the South Central-Oxford A Research Ethics Committee (16/SC/0108). Data are reported according to the STROBE guidelines for cross-sectional studies (28).

### Participants and setting

Inclusion criteria was diagnosis of idiopathic PD. Patients recruited to the OPDC at >3.5 years since diagnosis were excluded. A detailed description of the method of recruitment, including inclusion/exclusion criteria for the cohort, has been published elsewhere (29). Data were collected at OPDC research clinics across the Thames Valley, England, UK, between 1 April 2017 and 28 February 2020.

### Outcome variables

Total nonmotor symptom severity was measured using the total summed score of the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale Part I (with equal weighting of items) (30). Fatigue was measured using the NeuroQoL Item Bank v.1.0-Fatigue Short Form (31). Depression, anxiety, daytime sleepiness, and cognitive impairment were assessed using the Beck Depression Inventory (32), Hospital Anxiety and Depression Scale (33, 34), Epworth Sleepiness Scale (35), and Montreal Cognitive Assessment (MoCA) adjusted for education (36), respectively. Apathy and sleep problems were assessed over the past week using the Unified Parkinson's Disease Rating Scale (UPDRS) Likert scale items 1.5 and 1.7.

### Predictor variables

Dietary intake during the previous year was assessed using the European Prospective Investigation into Cancer Food Frequency Questionnaire (EPIC FFQ). Raw food frequency scores were analyzed using the FFQ EPIC Tool for Analysis (FETA) (37).

### MIND index

The background and composition of the MIND diet index has been detailed previously (14). Reported intakes of each relevant food item were converted to daily/weekly frequencies. The frequency of consumption of each related food item was summed for each component and then assigned a score of 0, 0.5, or 1. All 15 component scores were then summed to compute the total MIND index score. A higher MIND index score relates to greater adherence to the diet (consumption of foods thought to promote brain health). The food items used to compute the MIND score in the current study are shown in Supplementary Table 1.

### Dietary Inflammation Index (DII)

The DII is a widely used literature-derived, population-based index designed to compare diverse populations on the inflammatory potential of their diets (15). As the computation of the energy-adjusted DII requires the energy-adjusted data set (which is not open access) (38), the DII was computed (15) and adjusted for energy intake in the analyses as conducted by prior research (39). Possible scores of the DII range from −8.87 (strongly anti-inflammatory) to 7.98 (strongly pro-inflammatory).

### Healthy Diet Indicator (HDI-2020) score

The WHO Healthy Diet Indicator has been used in multiple research studies, with the index components adapted to match the up-to-date WHO guidelines at the time of publication, since its original publication in 1997 (40–43). The current study adopts the HDI based on the most recent (2018) WHO and global dietary guidelines (44) referred to as HDI-2020 (16). Specific items included in the HDI score can be seen in Supplementary Table 2. The score ranges from 0 to 11, with a higher score indicating greater adherence to the WHO dietary guidelines.

### Lifestyle variables and other potential confounders

Levels of physical activity (low, moderate, or vigorous) were assessed using the International Physical Activity Questionnaire Short Form (IPAQ-SF) (45) as per the IPAQ scoring protocol (46). Self-reported smoking habits at the time of assessment were categorized as current, previous, or passive smoker or never smoked. Energy intake (kcal) was calculated using the FETA software (47). Level of education was categorized dichotomously as ≥12 years or <12 years of education.

**Table 1.** Demographics of the Subsample of Patients Within the Oxford Parkinson's Discovery Cohort

| | | MIND (0–15) | | | DII (between −8.87 and 7.98)* | | | Healthy Diet Indicator 2020 (0–11) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Total sample | T1 | T2 | T3 | T1 | T2 | T3 | T1 | T2 | T3 |
| N | 162 | 35 | 95 | 32 | 55 | 74 | 33 | 56 | 83 | 23 |
| Median diet score (IQR) | | 6.5 (1) | 8.5 (1) | 10.5 (1) | −1.8 (0.9) | 0.3 (0.8) | 2 (0.8) | 4 (1) | 5 (1) | 7 (1) |
| % male | 65 | 71 | 68 | 50 | 60 | 74 | 54 | 73 | 61 | 60 |
| Age | 67 (9) | 68 (9) | 67 (9) | 69 (7) | 67 (9) | 69 (8) | 65 (9) | 68 (9) | 68 (9) | 65 (7) |
| Years since diagnosis | 6 (2) | 6 (1) | 6 (2) | 5 (1) | 6 (2) | 6 (2) | 5 (1) | 6 (2) | 6 (1) | 5 (1) |
| Hoehn and Yahr stage^ | 2 (1–4) | 2 (0–4) | 2 (1–4) | 2 (1–4) | 2 (1–4) | 2 (0–4) | 2 (1–3) | 2 (0–4) | 2 (1–4) | 2 (1–3) |
| LEDD, mg | 635 (334) | 681 (420) | 619 (307) | 632 (316) | 586 (300) | 668 (327) | 645 (404) | 669 (395) | 627 (293) | 581 (317) |
| UPDRS part II | 12 (7) | 13 (6) | 12 (7) | 12 (7) | 14 (7) | 12 (7) | 11 (5) | 13 (6) | 13 (7) | 9 (6) |
| UPDRS part III | 32 (15) | 35 (15) | 33 (16) | 28 (13) | 35 (18) | 31 (15) | 31 (12) | 34 (14) | 33 (17) | 25 (12) |
| UPDRS part IV | 2 (3) | 2 (3) | 2 (3) | 2 (3) | 2 (3) | 2 (2) | 2 (3) | 2 (3) | 3 (3) | 1 (2) |
| Energy intake (kcal) | 1982 (555) | 1915 (461) | 2009 (633) | 1977 (377) | 2397 (545) | 1830 (430) | 1634 (390) | 2001 (498) | 1989 (602) | 1913 (526) |
| BMI | 26 (5) | 25 (3) | 26 (6) | 26 (4) | 27 (6) | 25 (4) | 26 (6) | 27 (5) | 26 (5) | 27 (5) |
| % >12 years in education | 69 | 57 | 69 | 81 | 76 | 63 | 69 | 66 | 71 | 69 |
| % never smoked | 28 | 14 | 32 | 31 | 35 | 26 | 21 | 23 | 28 | 39 |
| Physical activity level, n (%) | | | | | | | | | | |
| Low | 36 (22) | 9 (25) | 19 (20) | 8 (25) | 12 (21) | 12 (16) | 12 (36) | 10 (17) | 21 (25) | 5 (21) |
| Moderate | 40 (24) | 6 (17) | 27 (28) | 7 (21) | 12 (21) | 23 (31) | 5 (15) | 10 (17) | 26 (31) | 4 (17) |
| Vigorous | 66 (40) | 13 (37) | 41 (43) | 12 (37) | 24 (43) | 29 (29) | 13 (39) | 26 (46) | 27 (32) | 13 (56) |

Values represent mean (standard deviation) unless otherwise stated.
BMI, body mass index; DII, Dietary Inflammatory Index; IQR, interquartile range; LEDD, levodopa equivalent daily dose; MIND, Mediterranean-DASH Diet Intervention for Neurodegenerative Delay; UPDRS, Unified Parkinson's Disease Rating Scale.
*A higher score on the DII equates to a higher pro-inflammatory potential of diet.
^Mode and range.

### Bias

Following recommended guidance, FFQs that had more than 10 missing responses to a food item were excluded from the analysis to reduce underestimation of nutrient intake (47,48). To reduce the number of extreme values and to account for inaccurate dietary recall, cutoffs based on the top and bottom 0.5% of the distribution of energy intake in kcals (EI) to basal metabolic rate (BMR) was calculated following published guidance (37, 49). BMR was estimated using the Mifflin St Jeor (50) method, as it has been shown to be the most accurate when compared to other common methods of estimation in patients with PD (51). Missing value analysis on SPSS confirmed that missing data were randomly distributed and were excluded for the comparisons. Outcome variables had missing data of less than 6% (range 0%–5.6%). Missing data were excluded within regression analyses using complete-case analysis.

### Study size

No prior sample size calculation was conducted.

### Quantitative variables

Quantitative scores of nonmotor symptoms were treated as continuous or ordinal as appropriate. Energy intake was treated as a continuous scale variable. Dietary scores were included in the analysis as both continuous scale variables and as categorical ordinal variables with categorizations based on the individuals' dietary score, from low (tertile 1) to moderate (tertile 2) to high (tertile 3). Variables were assessed for normal distribution using Shapiro-Wilk test and transformed via square root or log transformation as appropriate. The UPDRS part I, BDI, and ESS scores were all significantly skewed (skew/standard error = >1.95; Shapiro-Wilk $p < 0.001$), and therefore the square root was used in analyses to enable normally distributed residuals. Hospital Anxiety and Depression Scale (HADS) Anxiety scores were significantly skewed even after square root or log transformations, and therefore the nonparametric Kruskal–Wallis test was performed. Due to the lack of variance across scores of the UPDRS Apathy item ($n = 117$, no symptoms; $n = 34$, slight symptoms; $n = 10$, mild symptoms; $n = 1$, moderate symptoms of apathy) participants were grouped into a dichotomous variable representing the presence of apathy symptoms (individuals with scores between 1 and 3) or absence of apathy symptoms (individuals with a score of 0). Total MoCA score, adjusted for education, was represented as a binary variable (mild cognitive impairment [<26] or no mild cognitive impairment [>26]) in accordance with the MoCA scoring guidance.

### Statistical analysis

Analyses were conducted using IBM SPSS Statistics 26. The relationship between each continuous dietary index score and symptom outcome was assessed using linear, logistic, or ordinal regression as appropriate. Two regression models were analyzed: (1) a basic model including confounders of age, gender, energy intake, and years since diagnosis with PD and (2) a lifestyle model that also included physical activity level, education, and smoking history. Collinearity statistics were assessed to evaluate potential of multicollinearity between variables in either model (Variance Inflation Factor (VIF) < 10 and tolerance > 0.1). Equal variance of error across groups was assessed by Levene's test. Differences between dietary scores of nonparametric

**Table 2.** Nonmotor Symptoms of the Sample According to Dietary Pattern

| | | | MIND (0–15) | | | DII (between −8.87 and 7.98)* | | | Healthy Diet Indicator 2020 (0–11) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total sample | Missing (n) | T1 | T2 | T3 | T1 | T2 | T3 | T1 | T2 | T3 |
| N | 162 | | 35 | 95 | 32 | 55 | 74 | 33 | 56 | 83 | 23 |
| Median diet score (IQR) | | 0 | 6.5 (1) | 8.5 (1) | 10.5 (1) | −1.8 (0.9) | 0.3 (0.8) | 2 (0.8) | 4 (1) | 5 (1) | 7 (1) |
| UPDRS part I | 10 (5) | 7 | 10 (3) | 11 (5) | 10 (5) | 11 (5) | 10 (5) | 10 (5) | 11 (5) | 10 (5) | 9 (6) |
| NeuroQoL Fatigue *t* score+ | 46 (29–61) | 8 | 44 (35–60) | 47 (29–61) | 46 (34–60) | 46 (29–60) | 46 (34–61) | 48 (35–58) | 48 (35–60) | 46 (29–61) | 45 (34–60) |
| BDI-II | 10 (6) | 9 | 11 (8) | 10 (6) | 8 (4) | 10 (6) | 10 (6) | 9 (6) | 10 (6) | 10 (7) | 7 (5) |
| HADS Anxiety | 4 (3) | 6 | 4 (3) | 4 (3) | 4 (2) | 4 (3) | 4 (3) | 4 (3) | 5 (4) | 4 (3) | 3 (3) |
| UPDRS-1 Apathy item^ | 0 (0–3) | 0 | 0 (0–2) | 0 (0–3) | 0 (0–1) | 0 (0–2) | 0 (0–3) | 0 (0–2) | 0 (0–2) | 0 (0–3) | 0 (0–1) |
| No apathy, n (%) | 117 | | 28 (80) | 63 (66) | 26 (81) | 39 (71) | 51 (69) | 27 (82) | 39 (70) | 58 (70) | 20 (87) |
| Apathy, n (%) | 45 | | 7 (20) | 32 (34) | 6 (19) | 16 (29) | 23 (31) | 6 (18) | 17 (30) | 25 (30) | 3 (13) |
| UPDRS 1 Sleep item^ | 2 (0–4) | 6 | 3 (0–4) | 2 (0–4) | 2 (0–4) | 2 (0–4) | 2 (0–4) | 3 (0–3) | 3 (0–4) | 2 (0–4) | 0, 2 (0–4) |
| ESS | 7 (4) | 6 | 7 (3) | 7 (4) | 6 (4) | 7 (4) | 7 (3) | 7 (5) | 7 (5) | 7 (3) | 6 (5) |
| MoCA | 26 (3) | 3 | 25 (3) | 26 (3) | 26 (2) | 26 (3) | 25 (3) | 26 (3) | 25 (3) | 26 (3) | 26 (2) |
| Score ≥26, n (%) | | | 21 (60) | 65 (68) | 23 (72) | 36 (66) | 49 (66) | 24 (73) | 35 (63) | 58 (70) | 16 (70) |
| Score <26, n (%) | | | 14 (40) | 28 (30) | 8 (25) | 17 (31) | 24 (32) | 9 (27) | 20 (36) | 23 (28) | 7 (30) |

Values represent mean (standard deviation) unless otherwise stated.
^Value represents mode and range.
+Values represent median and range
*A higher score on the DII equates to a higher pro-inflammatory potential of diet. Missing data relate to the number of individual patients with missing data from the whole sample ($n = 162$). Percentages reported exclude missing data.
BDI, Beck Depression Inventory; ESS, Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; MIND, Mediterranean-DASH Diet Intervention for Neurodegenerative Delay; MoCA, Montreal cognitive assessment; UPDRS, Unified Parkinson's Disease Rating Scale.
Apathy represents the percentage of patients who reported symptoms of apathy (1–4 on the UPDRS apathy item); no apathy equates to the percentage of patients with scores of 0 on the item values represent median and range. MoCA refers to total score adjusted for education.

outcomes were analyzed using the Kruskal–Wallis test. Differences between the mean score of each nonmotor symptom between tertiles of dietary index scores were compared using general linear model (GLM) analysis and adjusted using Bonferroni post hoc correction. Tertiles of scores for each dietary index were created using K-cluster membership classification based on mean values of *Z* scores. A significant difference in mean scores among tertile groups was confirmed by one-way analysis of variance.

## Results

### Study sample

Figure 1 shows the flow of participants into the study ($n = 162$). Demographics and symptoms, as categorized by scores of dietary indices, are shown in Tables 1 and 2, respectively. Most of the sample participants were male, with an average age of approximately 67 years, 6 years since diagnosis, and more than 12 years of education and were physically active. One person reported being a current smoker at the time of assessment; the rest of the participant sample had never smoked ($n = 45$, 27%), had previously smoked ($n = 60$, 37%), or were passive smokers ($n = 55$, 34%). The median (minimum–maximum) of the MIND, DII, and HDI scores across the whole sample were 8.5 (4.50–12.50), 0.149 (−3.73 to 4.32), and 5 (2–9), respectively. A detailed description of adherence to the HDI, split by gender, is shown in Supplementary Tables 3 and 4. One hundred twelve participants had a fatigue score of <50, representing a slightly lower-than-average fatigue level for a neurologic population. A substantial percentage of the sample reported minimal symptoms of depression (69%), daytime sleepiness (76%), anxiety (81%), and apathy (72%). A third of the sample ($n = 50$, 31%) had a score of <26 on the MoCA assessment, indicative of mild cognitive impairment.

An independent *t* test confirmed a significant mean difference ($t$ (153) = −2.04, $p = 0.043$) in MIND index score between individuals with ≤12 years or >12 years of education. Individuals with >12 years of education had a higher mean MIND score (M = 8.56, SD = 1.54) compared to those with ≤12 years education (M = 8.03, SD = 1.40). No other significant associations or differences in total dietary scores between demographic factors were reported at a $p < 0.05$ level.

### Association between dietary patterns and nonmotor symptoms

Results from unadjusted and adjusted regression analyses are summarized in Tables 3 and 4. No significant associations between dietary adherence (tertiles) on mean scores of nonmotor symptom severity or individual nonmotor symptoms were reported. Results from GLM analyses are reported in Supplementary Tables 5 and 6. Results of nonparametric differences in symptom scores between dietary tertiles are reported in Supplementary Table 7.

### Total nonmotor symptom severity

None of the 3 diet indices were significant predictors of nonmotor severity before or after adjusting for confounders. No significant nonparametric differences in UPDRS I score were also present among tertiles of dietary adherence.

### Fatigue

Prior to adjusting for confounders, fatigue was not significantly predicted by scores of the MIND index, DII, or HDI index (see Table 3). However, when split by gender, HDI

score was a significant independent predictor of fatigue levels among males ($R^2$ = .049), but not females. After adjusting for age, gender, energy intake, and years since diagnosis (basic model), HDI score was reported as a significant predictor of fatigue across the whole sample (β = −.16, $p = 0.047$). However, the basic model equation including HDI score did not significantly predict the variance in fatigue overall ($F$ (5, 148) = 1.22, $p = 0.304$) with an $R^2$ of .039. After adjusting further for physical activity level, education, and smoking (lifestyle model), the degree of change in fatigue score for 1 unit change in HDI score rose to −.194 (β), with a significance level of $p = 0.022$. However, as with the previous model, the lifestyle model overall did not significantly explain the variance of fatigue across the whole sample ($F$ (11, 135) = 1.38, $p = 0.192$, $R^2$ = .101).

In the lifestyle model, HDI score was found to be a significant predictor of NeuroQoL Fatigue $t$ score among males (β = −.22, $p = 0.036$) but not females (β = −.90, $p = 0.534$). The lifestyle model ($F$ (9, 84) = 2.07, $p = 0.042$, $R^2$ =.101) significantly explained 18% of the variance in fatigue levels among males ($R^2$ = .18). However, no significant gender differences in scores of fatigue (independent $t$ test, $p > 0.05$) were found.

### Depression

HDI score significantly predicted BDI scores ($F$ (1, 151) = 5.24, $p$ = 0.023); however, they only explained 3.4% of the variance ($R^2$ = −.034). Participants' depression score were reduced by .18 (β) for each unit increase in HDI score. The basic model did not significantly predict depression scores ($F$ (1, 151) = 1.92, $p$ = 0.095, $R^2$ = .061); however, HDI score remained a significant individual predictor of BDI score (β = −.17, $p$ = 0.035). After the inclusion of physical activity, education, and smoking history (lifestyle model), the HDI score was no longer a significant predictor of depression. A significant difference in the distribution of depression scores across tertiles of HDI score was also evident ($H$ (2) = 7.38, $p = 0.025$). Pairwise comparisons adjusted by Bonferroni correction reported significant differences between the distribution of mean ranks of depression scores between HDI tertiles 3 and 1 (highest vs lowest adherence to HDI, $p = 0.035$) and tertiles 3 and 2 (highest vs moderate adherence, $p = 0.031$).

### Anxiety, sleep problems, daytime sleepiness, cognitive impairment, and apathy

No significant linear or nonlinear associations were found among any of the 3 dietary indices.

## Discussion

### Key results

This exploratory cross-sectional study found that adherence to the WHO global dietary recommendations, as an indicator of healthy diet, was a significant predictor of fatigue and depression. HDI score was a significant negative predictor of fatigue even after controlling for age, sex, energy intake, disease duration, physical activity level, education, and smoking history. When split by sex, it became apparent that HDI was a significant negative predictor of fatigue among males but not females. In contrast, HDI was not a significant predictor of depression after controlling for additional lifestyle exposures of physical activity, education level, and smoking. However, when exploring tertiles of adherence to each diet (highest to lowest), we observed that depression was lower in individuals with the highest adherence to the HDI dietary pattern. No other significant associations were evident among the MIND, DII, or HDI scores or nonmotor symptom severity, daytime sleepiness, anxiety, apathy, or cognition. Average scores of total or individual nonmotor symptom severity did not differ among individuals with a low, moderate, or high adherence to any of the 3 investigated dietary patterns. Together, our findings indicate that fatigue and depression are associated with dietary intake among individuals with PD. More research is required to establish the direction and strength of this association. Interventions to improve diet, particularly in males, are worthy of investigation to determine their potential to manage symptoms of fatigue and depression in people with PD.

### Limitations

There are several limitations that should be considered when interpreting our findings. Data were collected via opportunity sampling and therefore no prior sample size calculation was conducted. The variance across nonmotor symptom outcomes was small across the patient sample. Most patients reported absent or minimal problems with depression, anxiety, apathy, or daytime sleepiness. Measuring fatigue is inherently difficult with a lack of correlation between physical and mental fatigue observed in people with PD (52), many of whom describe fatigue as multidimensional and variable throughout the day (47). The NeuroQoL assessment has shown good internal consistency and test-retest reliability to assess fatigue in PD (53). However, a more widely used, PD-specific assessment, rather than one validated for use across neurologic populations, may have been a more generalizable, precise measurement to assess fatigue in the present study. Future research may benefit from a multidimensional fatigue scale that better reflects the lived experiences of fatigue for patients with PD. An additional limitation was the use of the MDS-UPDRS Apathy item, rather than a more valid measure that can distinguish between apathy and related symptoms of depression, such as the Lile Apathy Rating Scale (54). It is also important to note that income of patients was not considered within the analysis. Affordability and therefore accessibility of ingredients within each diet may have limited adherence among patients with a lower income. The previously mentioned assessments were not performed routinely within the cohort and thus were not available for this analysis. Finally, there is the potential for recall error in relevant items, particularly as one-third of individuals manifested mild cognitive impairment.

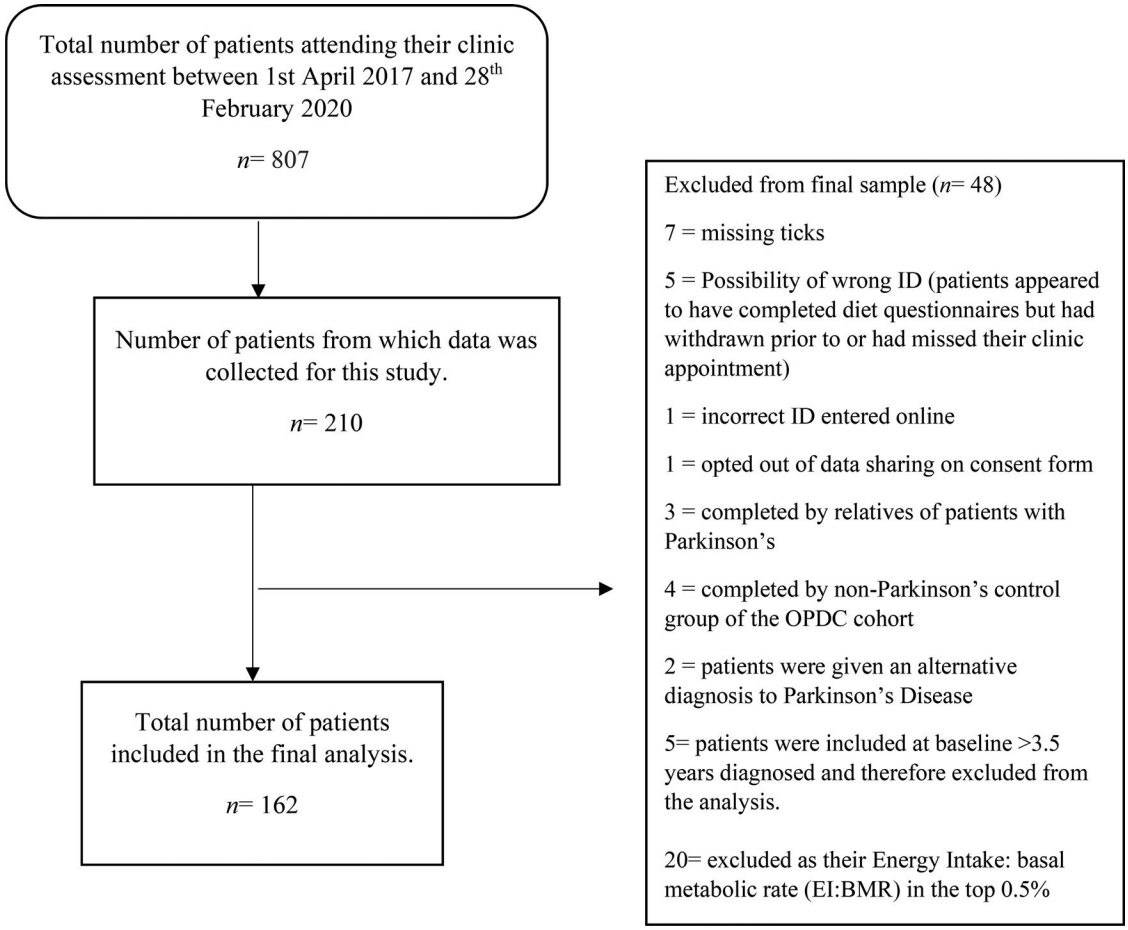


**Figure 1.** Participant flow diagram.

**Table 3.** Univariate Regression Models and the Strength of Effect of Dietary Score on Individual Nonmotor Symptom Outcomes

| | | Total sample | | | Female | | | Male | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Outcome | Diet | *n* | *p* | Estimate (β) | *n* | *p* | Estimate (β) | *n* | *p* | Estimate (β) |
| UPDRS I* | MIND | | 0.757 | −.03 | 54 | 0.734 | −.05 | 101 | 0.982 | −.00 |
| | DII | 155 | 0.350 | −.08 | | 0.652 | −.06 | | 0.372 | −.09 |
| | HDI-2020 | | 0.094 | −.14 | | 0.408 | −.12 | | 0.164 | −.14 |
| NeuroQoL Fatigue T | MIND | | 0.898 | .01 | 54 | 0.565 | −.08 | 101 | 0.538 | .06 |
| Score | DII | 154 | 0.501 | .06 | | 0.603 | .07 | | 0.649 | .05 |
| | **HDI-2020** | | 0.056 | −.16 | | 0.659 | −.06 | | **0.027** | **−.22** |
| BDI-II* | MIND | | 0.573 | −.05 | 54 | 0.550 | −.08 | 99 | 0.960 | −.00 |
| | DII | 153 | 0.862 | −.01 | | 0.678 | .06 | | 0.468 | −.07 |
| | **HDI-2020** | | **0.023** | **−.18** | | 0.092 | −.23 | | 0.145 | −.15 |
| ESS* | MIND | | 0.430 | −.06 | 55 | 0.729 | -.05 | 101 | 0.892 | −.01 |
| | DII | 156 | 0.892 | .01 | | 0.670 | −.06 | | 0.728 | .04 |
| | HDI-2020 | | 0.210 | −.10 | | 0.540 | .08 | | 0.069 | −.18 |
| MoCA^ | MIND | | 0.104 | −.19 | | 0.218 | −.23 | | 0.265 | −.16 |
| | DII | 159 | 0.866 | −.02 | 54 | 0.762 | −.05 | 105 | 0.961 | .01 |
| | HDI-2020 | | 0.378 | −.11 | | 0.496 | −.14 | | 0.545 | −.09 |
| UPDRS Apathy item ^ | MIND | | 0.739 | −.04 | | 0.258 | −.23 | | 0.561 | .09 |
| | DII | 162 | 0.436 | −.09 | 56 | 0.971 | .01 | 106 | 0.262 | −.17 |
| | HDI-2020 | | 0.283 | −.14 | | 0.624 | −.11 | | 0.374 | −.14 |

Bold values are statistically significant at the p & .05 level.

Estimate (β) = standardized beta coefficient (rounded to 2 decimal places).

*The square root of the raw score was used to ensure the assumption of normally distributed residuals. Estimate represents the change in symptom score outcome with each diet point (standardized beta coefficient, rounded to 2 decimal places). Dietary variables (MIND, DII, and HDI were entered as continuous scores). *n* refers to the number of patient data entered in each model. All outcomes were input as continuous variables apart from the MoCA and UPDRS Apathy.

^MoCA and UPDRS Apathy scores were analyzed as a dichotomous variable (with mild cognitive impairment or no mild cognitive impairment, apathy or no apathy) using logistic regression.

BDI, Beck Depression Inventory; DII, Dietary Inflammatory Index; ESS, Epworth Sleepiness Scale; HDI-2020, Healthy Dietary Indicator 2020; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; MoCA, Montreal cognitive assessment; UPDRS I, Unified Parkinson Disease Rating Scale Part I.

**Table 4.** A Summary of Multivariate Regression Models and the Strength of Effect of Dietary Score on Individual Nonmotor Symptom Outcomes

| | | | Total sample | | | Female | | | Male | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Outcome | Model | Diet | *n* | *p* | Estimate (β) | *n* | *p* | Estimate (β) | *n* | *p* | Estimate (β) |
| UPDRS I* | Basic | MIND | 155 | 0.869 | −.01 | 54 | 0.519 | −.09 | 101 | 0.831 | .02 |
| | Basic | DII | | 0.732 | −.03 | | 0.671 | .08 | | 0.443 | −.09 |
| | Basic | HDI-2020 | | 0.149 | −.12 | | 0.318 | −.14 | | 0.317 | −.10 |
| | Lifestyle | MIND | 148 | 0.748 | .03 | 53 | 0.796 | −.26 | 95 | 0.513 | .66 |
| | Lifestyle | DII | | 0.499 | −.07 | | 0.999 | .00 | | 0.321 | −.12 |
| | Lifestyle | HDI-2020 | | 0.204 | −.11 | | 0.397 | −.12 | | 0.415 | −.08 |
| NeuroQoL Fatigue *t* score | Basic | MIND | 154 | 0.935 | .01 | 54 | 0.394 | −.12 | 100 | 0.433 | .079 |
| | Basic | DII | | 0.268 | .11 | | 0.675 | .08 | | 0.315 | .11 |
| | Basic | **HDI-2020** | | **0.047** | **−.16** | | 0.591 | −.07 | | 0.069 | −.18 |
| | Lifestyle | MIND | 147 | 0.745 | −.03 | 53 | 0.602 | −.08 | 94 | 0.679 | .04 |
| | Lifestyle | DII | | 0.237 | .12 | | 0.744 | .07 | | 0.383 | .10 |
| | Lifestyle | **HDI-2020** | | **0.022** | **−.19** | | 0.534 | −.09 | | **0.036** | **−.22** |
| BDI-II* | Basic | MIND | 153 | 0.630 | −.04 | 54 | 0.381 | −.12 | 99 | 0.963 | .01 |
| | Basic | DII | | 0.489 | .07 | | 0.317 | .19 | | 0.837 | −.02 |
| | Basic | **HDI-2020** | | **0.035** | **−.17** | | 0.078 | −.24 | | 0.277 | −.11 |
| | Lifestyle | MIND | 146 | 0.843 | −.02 | 53 | 0.396 | −.14 | 93 | 0.550 | .06 |
| | Lifestyle | DII | | 0.855 | .018 | | 0.550 | .13 | | 0.508 | −.07 |
| | Lifestyle | HDI-2020 | | 0.069 | −.15 | | 0.145 | −.22 | | 0.488 | −.07 |
| ESS* | Basic | MIND | 156 | 0.706 | −.03 | 55 | 0.529 | −.09 | 101 | 0.986 | −.00 |
| | Basic | DII | | 0.488 | .07 | | 0.661 | .08 | | 0.466 | .08 |
| | Basic | HDI-2020 | | 0.410 | −.07 | | 0.658 | .06 | | 0.134 | −.15 |
| | Lifestyle | MIND | 149 | 0.935 | −.01 | 54 | 0.709 | −.06 | 95 | 0.925 | .01 |
| | Lifestyle | DII | | 0.739 | .03 | | 0.949 | .01 | | 0.671 | .05 |
| | Lifestyle | HDI-2020 | | 0.590 | −.05 | | 0.569 | .09 | | 0.225 | −.13 |
| MoCA^ | Basic | MIND | 131 | 0.054 | −.24 | 44 | 0.151 | −.30 | 84 | 0.121 | −.26 |
| | Basic | DII | 133 | 0.922 | −.01 | 45 | 0.887 | .03 | 82 | 0.901 | .02 |
| | Basic | HDI-2020 | 130 | 0.536 | −.08 | 45 | 0.487 | −.16 | 85 | 0.566 | −.101 |
| | Lifestyle | MIND | 131 | 0.070 | −.23 | 42 | 0.292 | −.30 | 79 | 0.116 | −.28 |
| | Lifestyle | DII | 132 | 0.858 | −.03 | 41 | 0.875 | .04 | 83 | 0.946 | .01 |
| | Lifestyle | HDI-2020 | 129 | 0.571 | −.08 | 42 | 0.446 | −.18 | 83 | 0.590 | −.10 |
| UPDRS Apathy^ | Basic | MIND | 162 | 0.808 | −.03 | 52 | 0.316 | −.22 | 94 | 0.408 | .14 |
| | Basic | DII | 162 | 0.780 | −.04 | 55 | 0.952 | −.02 | 93 | 0.240 | −.21 |
| | Basic | HDI-2020 | 162 | 0.350 | −.12 | 52 | 0.811 | −.06 | 94 | 0.887 | −.02 |
| | Lifestyle | MIND | 123 | 0.612 | −.07 | 48 | 0.360 | −.23 | 88 | 0.733 | .060 |
| | Lifestyle | DII | 121 | 0.687 | −.06 | 50 | 0.869 | −.05 | 88 | 0.293 | −.19 |
| | Lifestyle | HDI-2020 | 122 | 0.369 | −.138 | 49 | 0.572 | −2.01 | 88 | 0.733 | −.06 |

Bold values are statistically significant at the p & .05 level.

Basic models included age, sex, kcal, and disease duration. Lifestyle model includes age, sex, kcal, disease duration, physical activity level (PAL), education, and smoking history. Dummy PAL included moderate and vigorous, so low PA was the reference category. Dummy smoking variables entered were as follows: previous, passive, and current, so that "never smoked" was the reference category.

*The square root of the raw score was used to ensure the assumption of normally distributed residuals. Estimate represents the change in symptom score outcome with each diet point (standardized beta coefficient, rounded to 2 decimal places). Dietary variables (MIND, DII, and HDI) were entered as continuous scores. *n* refers to the number of patient data entered in each model. All outcomes were inputted as continuous variables apart from the MoCA and UPDRS Apathy.

^MoCA and UPDRS Apathy scores were analyzed as a dichotomous variable (with mild cognitive impairment or no mild cognitive impairment, apathy or no apathy) using logistic regression.

BDI, Beck Depression Inventory; DII, Dietary Inflammatory Index; ESS, Epworth Sleepiness Scale; HDI-2020, Healthy Dietary Indicator 2020; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; MoCA, Montreal cognitive assessment; UPDRS, Unified Parkinson Disease Rating Scale.

### *Interpretation*

Findings from this study suggest that fatigue and depression may be modifiable by diet among individuals with PD showing the greatest adherence to the HDI, who also have significantly lower self-reported depressive symptoms. It may be that high, rather than small or moderate, adherence to the WHO dietary guidelines is needed to exert benefits on depressive symptoms. However, in line with all cross-sectional analyses, we cannot assume a causal effect of adherence to the WHO dietary guidelines on either fatigue or depression symptoms, despite the significant association reported. The direction of association is unknown, and it may be simply that depression and fatigue influence the likelihood that an individual engages in healthy eating habits. A notable finding was that the HDI score was a significant predictor of fatigue among males but not females. We found no gender differences in the distribution of both HDI and fatigue scores, suggesting that the findings may have been driven by an interaction rather than an artifact of the data. This finding should be interpreted with caution due to the sample size of males being almost double that of females. A larger sample is required to clarify the extent of the relationship among the HDI and fatigue and depression, and future randomized controlled trials will be required to provide causal evidence of the impact of dietary manipulation on nonmotor symptoms of PD.

It is interesting that the HDI score, but not MIND or DII scores, were associated with fatigue and depression. The HDI differs from the other dietary indices in that it includes specific criteria in relation to salt consumption and the source of an individual's total energy intake, especially the percentage of calories that are derived from total fat, saturated fat, and free sugars. The Western dietary pattern, characterized by high consumption of processed foods and added

sugars, has been repeatedly associated with increased risk of depression (55, 56). The HDI may provide a more sensitive measure of the components that are commonly associated with depression. In comparison to depression, the literature describing the association between fatigue and dietary intake is less clear among both general and neurologic populations. A systematic review investigating whole diets and fatigue in multiple sclerosis reported limited published studies but indicated a potential for low-fat diets high in vegetable intake to improve subjective fatigue (57). Existing literature suggests that a balanced diet including vegetables high in polyphenols, omega-3 fatty acids, and high-fiber whole grains shows potential in improving fatigue symptoms of chronic disease. Evidence from interventional human trials is required before any definitive conclusions can be made (58).

Our results indicate that the MIND diet, although associated with a delay in onset of motor symptoms (17), is not associated with the severity of nonmotor symptoms in PD as measured here. It is important to note that the analysis by Metcalfe-Roach et al. (2021) had a nearly identical sample size ($n = 167$), controlled for similar confounders, and used the same dietary measurement. It is interesting that adherence to the MIND diet appears to be associated with motor but not nonmotor symptom outcomes as measured here. It would be of interest to assess associations between the MIND diet and peripheral, physical fatigability, which can be measured by objective motor tasks, such as finger-tapping, or force generation tests (59) rather than a self-reported assessment of subjective fatigue as used in the current study. It is also important to note that on average individuals with >12 years of education reported a higher MIND dietary score compared to those with ≤12 years of education, suggesting that an individual's education level may influence the likelihood to consume foods specific to the MIND dietary pattern. Such findings highlight the importance of controlling for education in future research investigating associations between diet and PD symptoms.

This study also adds to current understanding of the role that inflammation plays in PD. More research is needed before concrete conclusions can be drawn; however, our results provide evidence against the potential of anti-inflammatory diets in the management of nonmotor symptoms in PD. Our results contrast with the findings from a meta-analysis that reported a 1.4 increased likelihood of depressive symptoms among individuals of the general population who reported to have a pro-inflammatory rather than anti-inflammatory diet (60). The sample size in our analysis was small compared to other cross-sectional analyses that found significant associations between dietary inflammatory scores and sleep quality (25), sleep duration (26), depression (27), or cognitive functioning (61). However, our results are in line with data from 137 patients with multiple sclerosis whereas no significant associations were found between dietary inflammation (DII) scores and disability, urinary symptoms, or brain lesions (62). Karshikoff, Sundelin, and Lasselin (48) argue that fatigue is likely to be explained by separate central mechanisms and thereby advocate the need for multidimensional assessments when investigating the role of inflammation in fatigue. Future research investigating the role of dietary inflammatory potential on multiple dimensions of fatigue may, as they argue, help to unravel which, if any, specific mechanisms are involved in the relationship between fatigue and diet.

## Generalizability

The WHO guidelines are well-known worldwide dietary recommendations and understood among both clinicians and patients. However, the patient sample was predominantly White British, with the majority already reporting healthy lifestyle behaviors (nonsmokers and physically active). Only 5 patients included in our sample had UPDRS I scores indicative of severe disability (63). Most of the patients included in this study were in their mid or late 60s with mild to moderate disease severity (Hoehn and Yahr score of 2, mean (SD) of 6 (2) years from PD diagnosis). As such, the results are not generalizable to younger individuals with PD or those in whom the condition is at more severe stages. Study strengths include a relatively low number of missing data in terms of demographics, symptoms, overall habitual dietary intake, and potential modifying lifestyle factors.

This study is the first to our knowledge to investigate the role of dietary patterns on overall nonmotor symptom severity, as well as common individual nonmotor symptoms reported by patients with PD (3–5). Fatigue and depression are 2 of the most debilitating and prevalent nonmotor symptoms in PD (5). Additional research including a larger sample of patients across a larger range of disease severity is required to determine whether dietary changes that adhere to the WHO guidelines are both associated with and could provide meaningful change to symptoms of fatigue and depression among individuals with PD.

## Data availability

The data that support the findings of this study are available on request from the Oxford Parkinson's Disease Center Data Access Committee.

## Disclosure statement

The authors report that there are no competing interests to declare.

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