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Early BMI Change, Cognitive Decline, and CSF AD Biomarkers Alterations in Parkinson's Disease

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ABSTRACT

Objective: To examine the relationship of early BMI change with subsequent cognitive decline, CSF AD biomarkers alterations, and progression to dementia in patients with PD.

Methods: Study data were prospectively collected from the PPMI cohort. Weight/height data at enrollment and second-year clinical visit were utilized to calculate BMI change. Cognitive tests and CSF AD biomarkers were measured at enrollment and each visit during the 5-year follow-up. Generalized linear mixed analyses were employed to identify the impact of BMI change on the deterioration of cognitive performance and CSF AD biomarkers alterations. Cox regression analyses were employed to assess the relationship of BMI change with dementia conversion.

Results: BMI loss predicted a more rapid deterioration in global cognitive performance over time. Regarding specific cognitive domains, participants in the BMI loss group experienced a significantly more rapid decline in verbal episodic memory, language, and processing speed/attention compared with those in the stable BMI group. Additionally, patients in the BMI gain group showed a slower decline in verbal episodic memory than those in the stable BMI group. BMI loss predicted a more rapid longitudinal decrease of CSF Aβ42 over time. BMI change was not associated with the risk of progression to dementia.

Conclusions: Early BMI loss is a risk factor for faster decline in cognition and longitudinal decrease of CSF Aβ42. These findings emphasize the need to monitor early BMI change in PD patients. Attention to early BMI change may help identify those at greater risk of cognitive decline.

1 | Introduction

Parkinson's disease (PD) is a prevalent neurodegenerative disease associated with the deposition of aggregated α-synuclein [1, 2]. While PD remains classified as a paradigmatic movement disorder, it is increasingly recognized for its extensive array of non-motor symptoms [3]. Cognitive decline is a common non-motor symptom in PD, with dementia being a common complaint in the advanced stages of this disease [4]. Most PD patients are likely to develop dementia if they survive more than a decade following diagnosis [4, 5]. Cognitive decline and even conversion to dementia have significant adverse implications for functional status, quality of life, caregiver burden, and healthcare-related expenditures in PD patients [5–7]. These adverse implications highlight the urgency of a better understanding of modifiable risk factors and potential pathophysiological mechanisms for the deterioration of cognitive performance. Identifying useful predictors of cognitive decline would have major clinical benefits in PD management.

Weight change was associated with accelerated biological aging [8]. PD patients may experience weight loss and weight gain in different stages of the disease [9]. Although weight loss is an important problem encountered at any disease stage, weight gain

is always under-recognized [10–12]. In fact, weight gain is common [9]. Prior literature showed that weight change has been related to PD onset and motor progression [13, 14]. Body weight change, especially weight loss, significantly increased the risk of PD incidence [13]. Weight loss had an association with a more rapid cognitive decline, while weight gain had an association with more slowly motor progression [14]. PD patients with weight loss showed a more rapid striatal dopaminergic degeneration [11]. Furthermore, PD patients with a change in body mass index (BMI) of more than 10% had a significantly increased risk of mortality [10]. However, there is limited and conflicting information regarding the association between BMI change and subsequent deterioration in global cognition and different cognitive domains. Additionally, there is a lack of evidence on the association of BMI change, cerebrospinal fluid (CSF) Alzheimer's disease (AD) biomarkers alterations, and conversion to dementia in PD.

Thus, we aimed to determine the longitudinal associations of early BMI change with subsequent deterioration in global cognitive performance and specific cognitive domains in PD. Secondary aims were to determine whether early BMI change leads to CSF AD biomarker alterations and progression to dementia.

2 | Methods

2.1 | Participants and Study Design

All participants in the study were enrolled from the Parkinson's Progression Biomarker Initiative (PPMI) database (www.ppmi-info.org/data) [15], an ongoing prospective multi-center longitudinal study aimed at investigating reliable biomarkers for PD progression, previously described in detail [15, 16]. Data used in this study were gathered from the PPMI database in April 2023. PD patients were included according to the following criteria: are 30 years or older at diagnosis; have bradykinesia combined with resting tremor, rigidity, or only asymmetric resting tremor or bradykinesia; have no treatment for PD, particularly without medications that might interfere with dopamine transporter imaging or CSF collection; and have no dementia. Furthermore, patients were followed up for 5 years. The PPMI study was approved by the institutional review board of all PPMI sites involved, and written informed consent was provided by each participant upon enrollment. All methods were conducted according to relevant guidelines and regulations.

2.2 | Key Explanatory Variable

Weight and height data were acquired at enrollment and the second year clinical visit. BMI was calculated using height and weight data, expressed in kg/m^2. BMI change was defined as follows: [(BMI at second year visit—BMI at enrollment)/BMI at enrollment] × 100 (%). Participants with BMI change < 0 were regarded as those with BMI loss. Participants with BMI change > 0 were regarded as those with BMI gain. To distinguish between minor fluctuations and substantial changes, we classified BMI change for 2 years into three categories following a previous recommendation [9, 17]: BMI loss (> 3%), stable BMI (loss or gain ≤ 3%), and BMI gain (> 3%).

2.3 | Assessment of Other Variables

Demographic characteristics and baseline clinical data were gathered, including age, gender, education (years), age at onset, and PD duration. Additionally, the Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III was utilized to measure the motor symptoms related to daily life [18]. The clinical stage of PD was identified using the Hoehn & Yahr (H&Y) stage [19]. Apolipoprotein E (APOE) genotypes were identified using allele-specific oligonucleotide probes labeled with a fluorogenic reporter (TaqMan method) [20]. Additionally, we divided patients into two groups in accordance with the ε4 allele: APOE ε4 carriers (APOE ε4+) and non-APOEε4 carriers (APOE ε4−).

2.4 | Cognitive Assessments

Cognitive assessments were carried out to measure global cognitive performance and specific cognitive domains, including: global cognitive function (MoCA), verbal episodic memory (Hopkins Verbal Learning Test [HVLT] Total Recall, HVLT Delayed Recall, and HVLT Recognition), visuospatial ability (Judgment of Line Orientation [JoLO]), executive function/working memory (letter–number sequencing [LNS]), language (semantic fluency test), and processing speed/attention (symbol digit modalities test [SDMT]). Cognitive assessments were completed by each participant at enrollment and each clinical visit during five-year follow-up. A higher cognitive score indicates a better cognitive performance. The cognitive diagnosis of patients was made according to the criteria established in prior literature [21]. Cognitive diagnoses (normal cognition, mild cognitive impairment, or dementia) were assigned at each visit by the site investigator, a process that was fully implemented starting from study Year 3 [22]. The site investigator is provided with a guidance document for identifying dementia, which was meant to approximate PDD [23] criteria.

2.5 | CSF AD Biomarkers

Detailed information of sample collection and processing has been documented (http://www.ppmi-info.org) [24]. Levels of CSF Amyloid-β42 (Aβ42), total tau (T-tau), and phosphorylated tau (P-tau) were quantified using an Elecsys electrochemiluminescence immunoassay (ECLIA) performed on a completely automated cobas e 601 analyzer (Roche Diagnostics, Basel, Switzerland).

2.6 | Statistical Analysis

For demographic and clinical variables, descriptive statistics were described as median and interquartile range (IQR) for continuous variables and as percentage frequency for categorical variables. Mann–Whitney *U* tests and chi-square tests were employed for between-group comparisons (stable vs. gain and stable

vs. loss) of demographic and clinical variables. Generalized linear mixed analyses were employed to identify the impacts of BMI change over the first 2 years on cognitive deterioration and CSF AD biomarker alterations during 5-year follow-up. These analysis models interpreted the relationship between repeated measures and variables over time. We assessed BMI change as a potential predictor of cognitive deterioration and CSF AD biomarker alterations through interactions with visit time. Cox regression analyses were employed to assess the association of early BMI change with progression to dementia. The cumulative incidence of dementia conversion was compared between subgroups. All generalized linear mixed analyses and Cox regression analyses were adjusted for confounding factors, including age, sex, education, disease duration, APOE ε4 carrier status, and MDS-UPDRS III. Statistical analysis was conducted using SPSS 26.0, and values of $p < 0.05$ were regarded as significant.

3 | Results

A total of 406 early PD patients who underwent longitudinal cognitive tests and CSF AD biomarker measurements were included in the final analyses. Participants of this cohort had a median age of 62 years, with 34.6% being female. When using a 3% BMI change as the cutoff, 52.96% of patients exhibited BMI change (either gain or loss), while 47.04% maintained a stable BMI. Table 1 describes the demographics and features of participants across three categories of BMI change. Only the baseline MoCA score was associated with early BMI change. Patients in the BMI gain group had a lower baseline MoCA score than those in the stable BMI group ($p = 0.016$), and patients in the BMI loss group also tended to have a lower MoCA score compared with those in the stable BMI group ($p = 0.069$) but this difference was not significant.

We employed generalized linear mixed analyses to identify the predictive value of early BMI change in cognitive decline. The generalized linear mixed analyses showed that BMI loss predicted a more rapid deterioration in global cognitive function (MoCA, $\beta = -0.446$, $p = 0.003$) (Table 2) over time, and patients in the BMI loss group had a faster annual reduction of 0.446 points in MOCA score compared with those in the stable BMI group. Regarding specific-domain cognition, patients in the BMI loss group experienced a faster decline in verbal episodic memory (HVLT total recall, $\beta = -2.66$, $p < 0.001$; HVLT delayed recall, $\beta = -2.335$, $p < 0.001$; HVLT retention, $\beta = -1.268$, $p = 0.033$), language (Semantic fluency test, $\beta = -1.349$, $p = 0.017$), and processing speed/attention (SDMT, $\beta = -0.93$, $p = 0.048$) compared to those in the stable BMI group. Additionally, patients in the BMI gain group showed a slower decline in verbal episodic memory than those in the stable BMI group (HVLT retention, $\beta = 1.47$, $p = 0.004$).

We also employed generalized linear mixed analyses to identify the predictive value of early BMI change in CSF AD biomarker alterations. The generalized linear mixed analyses showed that BMI loss predicted a faster longitudinal decrease of CSF Aβ42 over time ($\beta = -53.732$, $p = 0.049$) (Table 3), and participants in the BMI loss group experienced a more rapid decrease in CSF Aβ42 level of 53.732 pg/mL per annum when compared to those in the stable BMI group. However, BMI loss was not associated with the longitudinal alterations of T-tau ($\beta = 0.747$, $p = 0.819$) and P-tau ($\beta = 0.238$, $p = 0.423$). Furthermore, associations between BMI gain and CSF AD biomarker alterations were not found.

To identify the potential predictive power of early BMI change in progression to dementia, Cox regression analyses were employed. We observed that the incidence of dementia conversion was higher in the BMI loss group compared to the stable BMI and BMI gain groups (5.47% vs. 4.32% vs. 4.82%) (Table 4). However, Cox regression analyses indicated that no significant difference existed in the risk of dementia conversion between the BMI loss and stable BMI groups (HR 1.417, 95% CI 0.508–3.961, $p = 0.505$).

4 | Discussion

In this study, we found that early BMI loss could predict a more rapid decline in global cognitive function and three specific-domain cognitions, including verbal episodic memory, language, and processing speed/attention in PD regardless of potential confounding factors. There also existed an association between early BMI gain and slower deterioration of verbal episodic memory. Meanwhile, early BMI loss was a risk factor for a more rapid longitudinal decrease of CSF Aβ42. However, there was no association between BMI change and conversion to dementia. These findings emphasize the need for monitoring BMI in early PD patients. Attention to early BMI change may help identify those at greater risk of cognitive decline.

Two recent studies used data from the PPMI cohort and conducted longitudinal analyses on the relationship between body weight change and cognitive decline [14, 25]. One study showed that longitudinal changes in body weight could predict global cognitive decline over time, but domain-specific cognitive status was not assessed [14]. Another examined the relationship between early weight change and subsequent decline in global and specific domain cognitive function, as well as other non-motor symptoms [25]. Our findings add to the existing evidence by assessing the associations between BMI change and the longitudinal alterations of CSF AD biomarkers, as well as conversion to dementia. Studies consistently found that body weight change was related to longitudinal deterioration of global cognition. However, there exist conflicting results on the relationship between weight change and longitudinal deterioration of specific cognitive domains. Kim and colleagues reported that patients with early weight loss had a more rapid deterioration in executive function, while patients with early weight gain had a slower deterioration in processing speed and attention. However, we found the association between early BMI loss and more rapid deterioration in three specific domain cognitions, including verbal episodic memory, language, and processing speed/attention in PD. Additionally, there existed an association between BMI gain and slower decline in verbal episodic memory. The previous studies methodologically differed from our study in some aspects that may lead to the conflicting findings. First, weight change was calculated using weight data at enrollment and the first-year visit in the previous study [25], and they ignored the effect of height [26]. BMI change was calculated using weight/height data at enrollment and the second-year clinical visit in our study, and we longitudinally examined BMI change during a longer time period. Second, our study had a larger sample

TABLE 1 | Differences in baseline characteristics of PD patients across the three categories of BMI change.

Variables	Total ($n=406$)	BMI gain ($n=85$)	Stable BMI ($n=191$)	BMI loss ($n=130$)	p Stable vs. gain	p Stable vs. loss
Age (years)	62 (55–69)	61 (55–67)	63 (55–69)	63 (56–69)	0.197	0.794
Gender						
Male	265 (65.4)	53 (62.4)	131 (68.6)	81 (62.3)	0.381	0.296
Female	141 (34.6)	32 (37.6)	60 (31.4)	49 (37.7)		
Education (years)	16 (14–18)	16 (13–18)	16 (14–18)	16 (14–18)	0.546	0.418
Age of onset (years)	62 (55–68)	61 (54–67)	63 (54–69)	62 (55–68)	0.208	0.735
Disease duration (months)	3 (1–7)	3 (1–7)	3 (1–7)	3 (1–8)	0.871	0.91
APOE ε4carriers	100 (24.7)	17 (20.2)	52 (27.4)	31 (23.8)	0.249	0.565
MDS-UPDRS III	20 (14–26)	20 (15–27)	19 (14–24)	20 (15–28)	0.221	0.092
HY	2 (1–2)	2 (1–2)	2 (1–2)	2 (1–2)	0.801	0.105
MoCA	27 (26–29)	27 (25–28)	28 (26–29)	27 (26–29)	**0.016**	0.069
HVLT total recall	46 (39–53)	44 (37–52)	48 (40–53)	45 (38–54)	0.387	0.233
HVLT delayed recall	45 (37–54)	44 (36–51)	45 (38–53)	48 (39–55)	0.258	0.637
HVLT recognition	45 (37–53)	45 (37–52)	45 (37–54)	47 (38–53)	0.067	0.906
JoLO	13 (11–14)	12 (10–14)	13 (11–14)	13 (11–15)	0.571	0.946
LNS	12 (10–13)	12 (10–13)	12 (10–13)	12 (10–13)	0.663	0.948
Semantic fluency test	51 (44–57)	52 (41–59)	51 (45–56)	50 (44–57)	0.616	0.873
SDMT	42 (35–48)	42 (33–47)	42 (36–49)	42 (35–47)	0.265	0.544
CSF Aβ42 (pg/mL)	844.3 (618–1125)	852.5 (634.8–1071)	844.4 (583.5–1183)	839 (664.3–1063)	0.942	0.831
CSF T-tau (pg/mL)	155.6 (124.3–199.3)	145.1 (121.8–181.4)	157.1 (119.3–205.1)	160.3 (130.6–195.9)	0.322	0.476
CSF P-tau (pg/mL)	12.95 (10.41–16.79)	12.07 (9.65–15.47)	12.85 (9.92–17.66)	13.36 (11.14–16.01)	0.264	0.543

Note: p were assessed by Mann–Whitney U tests and Chi-Square tests among the groups. The bold emphasis in the table means $p<0.05$.
Abbreviations: APOE, Apolipoprotein E; Aβ42, Amyloid-β42; BMI, body mass index; CSF, cerebrospinal fluid; HVLT, Hopkins Verbal Learning Test; HY, Hoehn and Yahr; JoLO Benton, Judgment of Line Orientation; LNS, Letter Number Sequencing; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; P-tau, Phosphorylated tau; SDMT, Symbol Digit Modality Test; T-tau, Total tau; UPDRS, Unified Parkinson's Disease Rating Scale.

size and shorter follow-up time than the previous study due to different inclusion criteria. Finally, 52.96% of patients exhibited BMI change (either gain or loss) and 47.04% maintained a stable BMI in our study. However, more than half of the patients (56.15%) were classified into the weight maintenance group in the previous study [25]. Despite the existing association between BMI change and cognitive decline, we failed to confirm the relationship of early BMI change with conversion to dementia in PD. However, there exists a tendency that patients in the BMI loss group had a higher incidence of progression to dementia compared to the BMI gain and stable BMI groups; this difference was not significant. It may be due to the follow-up period of the participants being relatively short, and the incidence of conversion to dementia was therefore relatively low. Additionally, the association between BMI loss and cognitive decline could be reverse causation, whereby individuals with a degree of cognitive impairment/AD pathology have a lower BMI and are more likely to cognitively decline over time.

The underlying pathological mechanism on the relationship between BMI loss and cognitive decline remains unknown, and there exist some plausible explanations. Prior studies indicated a longitudinal relationship between weight loss and rapid striatal dopaminergic degeneration in PD [11, 14]. It has been found that dopaminergic degeneration, PD-specific mechanisms, has a correlation with cognitive decline and posterior cortical thinning [27–29]. We found that patients in the BMI loss group were more likely to have higher MDS-UPDRS III scores than those in the stable BMI group, although there existed no significant difference($p=0.092$). The association between BMI change and cognitive decline may reflect overall

TABLE 2 | Longitudinal association of early BMI change with cognitive decline in PD.

Cognitive tests	β	95% CI	p
MoCA			
BMI gain	−0.097	−0.352 to −0.158	0.457
Stable BMI	Ref		
BMI loss	−0.446	−0.739 to −0.152	**0.003**
HVLT total recall			
BMI gain	−0.805	−1.797 to 0.188	0.112
Stable BMI	Ref		
BMI loss	−2.66	−3.801 to −1.519	< 0.001
HVLT delayed recall			
BMI gain	0.317	−0.734 to 1.368	0.555
Stable BMI	Ref		
BMI loss	−2.335	−3.543 to −1.128	< 0.001
HVLT recognition			
BMI gain	1.47	0.458 to 2.483	**0.004**
Stable BMI	Ref		
BMI loss	−1.268	−2.431 to −0.104	**0.033**
JoLO			
BMI gain	0.028	−0.237 to −0.292	0.838
Stable BMI	Ref		
BMI loss	−0.245	−0.548 to 0.059	0.114
LNS			
BMI gain	0.138	−0.125 to 0.401	0.303
Stable BMI	Ref		
BMI loss	−0.2	−0.502 to 0.103	0.195
Semantic fluency test			
BMI gain	−0.082	−1.044 to −0.88	0.868
Stable BMI	Ref		
BMI loss	−1.349	−2.455 to −0.244	**0.017**
SDMT			
BMI gain	−0.676	−1.737 to 0.384	0.211
Stable BMI	Ref		
BMI loss	−0.93	−1.853 to −0.006	**0.048**

Note: In these models, BMI change is the independent variable, and the cognitive score is the dependent variable, age, gender, education, disease duration, APOE ε4 carrier status, and MDS-UPDRS III are covariates. The regression coefficients (β) and adjusted *p* values were assessed by generalized linear mixed models. The bold emphasis in the table means $p < 0.05$.
Abbreviations: β, regression coefficient; BMI, body mass index; CI, confidence interval; HVLT, Hopkins Verbal Learning Test; JoLO Benton, Judgment of Line Orientation; LNS, Letter Number Sequencing; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; SDMT, Symbol Digit Modality Test.

TABLE 3 | Longitudinal association of early BMI changes with CSF AD biomarker alterations in PD.

CSF AD biomarkers	β	95% CI	p
CSF Aβ42			
BMI gain	−34.142	−80.826 to 12.541	0.152
Stable BMI	Ref		
BMI loss	−53.732	−107.139 to −0.325	**0.049**
CSF T-tau			
BMI gain	−0.542	−6.147 to 5.063	0.85
Stable BMI	Ref		
BMI loss	0.747	−5.654 to 7.149	0.819
CSF P-tau			
BMI gain	0.209	−0.302 to 0.719	0.43
Stable BMI	Ref		
BMI loss	0.238	−0.344 to 0.821	0.423

Note: In these models, BMI change is the independent variable, and the CSF AD biomarkers alteration is the dependent variable, age, gender, education, disease duration, APOE ε4 carrier status, and MDS-UPDRS III are covariates. The regression coefficients (β) and adjusted *p* values were assessed by generalized linear mixed models. The bold emphasis in the table means $p < 0.05$.
Abbreviations: β, regression coefficient; AD, Alzheimer's disease; Aβ42, Amyloid-β42; BMI, body mass index; CI, confidence interval; CSF, cerebrospinal fluid; PD, Parkinson's disease; P-tau, Phosphorylated tau; T-tau, Total tau.

motor and disease severity rather than being specific to metabolic changes in PD. Further research is required to investigate whether the impact of BMI change on cognition is a non-specific feature of advancing disease progression. Another possible explanation is that BMI change may be related to oxidative stress, mitochondrial dysfunction, and increased inflammation that are suggested to lead to cognitive decline and dementia [30, 31]. Additionally, AD pathologies may also be involved in the link between BMI loss and cognitive decline in PD. It has been identified that CSF AD biomarkers could be used as predictors of cognitive impairment in PD patients [32]. Patients who developed weight loss had lower CSF Aβ42 at baseline [14]. We observed that early BMI loss had an association with faster longitudinal decrease of CSF Aβ42 in PD. Literature consistently provided evidence that lower CSF levels of Aβ42 are related to worse cognitive function and predict cognitive decline and transition to dementia in patients with PD [33–35]. In contrast to CSF Aβ42, biomarkers of synucleinopathy have yielded inconsistent findings when utilized as predictors of cognitive impairment [33, 35]. Thus, early BMI loss might elevate the risk of cognitive deterioration by giving rise to a rapid longitudinal decrease of CSF Aβ42.

Strengths of our study include the utilization of a large, international cohort of patients with early PD, followed for up to 5 years, along with comprehensive longitudinal cognitive test assessments and CSF AD biomarker evaluations. Different from prior literature where weight changes have been employed, here we used BMI change, which takes the role of height into account. There are, however, some limitations. First, data on potential variables associated with BMI change, such as intentional weight modification, dietary interventions, gastrointestinal motility, and physical activity, were unavailable [36]. Second, given that this was a longitudinal cohort of PD patients with

TABLE 4 | Longitudinal association of early BMI change with conversion to dementia in PD.

	Dementia incidence (%)	HR	95% CI	*p*
BMI gain	4.82%	1.562	0.453 to 5.381	0.48
Stable BMI	4.32%	Ref		
BMI loss	5.47%	1.417	0.508 to 3.961	0.505

Note: Adjusted model: age, gender, education, disease duration, APOE ε4 carrier status, and MDS-UPDRS III as covariates. The HR and adjusted p were assessed by cox regression model. The bold emphasis in the table means $p < 0.05$.
Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; PD, Parkinson's disease.

a 5-year follow-up period, some questionnaire scales and biomarker evaluations were incomplete during follow-up. We also have not log-transformed the scores of cognitive tests. Third, the current study design did not allow for an investigation into whether the influence of BMI change on cognitive performance is modified in underweight or obese PD patients, owing to the limited number of such patients. Pre-existing cognitive disparities between the BMI strata at baseline could also have contributed to the observed differences. Fourth, the incidence of conversion to dementia was relatively low in this cohort due to the short follow-up period. Finally, We only analyzed the educational level. We had no access to information on other social determinants of health, and this information may be related with BMI change [37].

In conclusion, early BMI loss is a risk factor for more rapid decline in global cognitive performance and three specific cognitive domains, including verbal episodic memory, language, and processing speed/attention in PD. There exists a relationship between BMI gain and slower decline in verbal episodic memory. Furthermore, early BMI loss predicts faster longitudinal decrease of CSF Aβ42. Attention to early BMI change may help identify those at greater risk of cognitive decline. Future study is needed to identify whether maintaining stable BMI in early PD could prevent cognitive decline.

Author Contributions

Rui Zhong: conception and design, statistical analysis, and writing of the manuscript. **Kezhong Zhang:** conception and design, review and critique of statistical analysis, and review and critique of the manuscript.

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Ethics Statement

Ethical approval was provided by each individual PPMI study site.

Consent

Informed consent was obtained from each participant.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data used in the study were gathered on April 28, 2023, from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/access-data-specimens/download-data), RRID:SCR_006431. For up-to-date information on the study, visit www.ppmi-info.org.

References

1. B. R. Bloem, M. S. Okun, and C. Klein, "Parkinson's Disease," *Lancet* 397 (2021): 2284–2303.

2. H. R. Morris, M. G. Spillantini, C. M. Sue, and C. H. Williams-Gray, "The Pathogenesis of Parkinson's Disease," *Lancet* 403 (2024): 293–304.

3. A. H. V. Schapira, K. R. Chaudhuri, and P. Jenner, "Non-Motor Features of Parkinson Disease," *Nature Reviews. Neuroscience* 18 (2017): 435–450.

4. D. Aarsland, B. Creese, M. Politis, et al., "Cognitive Decline in Parkinson Disease," *Nature Reviews. Neurology* 13 (2017): 217–231.

5. P. Svenningsson, E. Westman, C. Ballard, and D. Aarsland, "Cognitive Impairment in Patients With Parkinson's Disease: Diagnosis, Biomarkers, and Treatment," *Lancet Neurology* 11 (2012): 697–707.

6. D. Aarsland, L. Batzu, G. M. Halliday, et al., "Parkinson Disease-Associated Cognitive Impairment," *Nature Reviews. Disease Primers* 7 (2021): 47.

7. J. Wojtala, I. A. Heber, P. Neuser, et al., "Cognitive Decline in Parkinson's Disease: The Impact of the Motor Phenotype on Cognition," *Journal of Neurology, Neurosurgery, and Psychiatry* 90 (2019): 171–179.

8. X. Cao, G. Yang, X. Li, et al., "Weight Change Across Adulthood and Accelerated Biological Aging in Middle-Aged and Older Adults," *American Journal of Clinical Nutrition* 117 (2023): 1–11.

9. S. Ghourchian, A. L. Gruber-Baldini, S. Shakya, et al., "Weight Loss and Weight Gain in Parkinson Disease," *Parkinsonism & Related Disorders* 83 (2021): 31–36.

10. S. Y. Yoon, S. J. Heo, H. J. Lee, et al., "Initial BMI and Weight Loss Over Time Predict Mortality in Parkinson Disease," *Journal of the American Medical Directors Association* 23, no. 1719 (2022): e1–e1719.

11. K. Pak, H. K. Shin, E. J. Kim, et al., "Weight Loss Is Associated With Rapid Striatal Dopaminergic Degeneration in Parkinson's Disease," *Parkinsonism & Related Disorders* 51 (2018): 67–72.

12. A. M. Wills, R. Li, A. Pérez, X. Ren, J. Boyd, and NINDS NET-PD Investigators, "Predictors of Weight Loss in Early Treated Parkinson's Disease From the NET-PD LS-1 Cohort," *Journal of Neurology* 264 (2017): 1746–1753.

13. J.-H. Park, Y. Choi, H. Kim, et al., "Association Between Body Weight Variability and Incidence of Parkinson Disease: A Nationwide,

Population-Based Cohort Study," *European Journal of Neurology* 28 (2021): 3626–3633.

14. D. Urso, D. J. van Wamelen, L. Batzu, et al., "Clinical Trajectories and Biomarkers for Weight Variability in Early Parkinson's Disease," *NPJ Parkinson's Disease* 8 (2022): 95.

15. Parkinson Progression Marker Initiative, "The Parkinson Progression Marker Initiative (PPMI)," *Progress in Neurobiology* 95 (2011): 629–635.

16. K. Marek, S. Chowdhury, A. Siderowf, et al., "The Parkinson's Progression Markers Initiative (PPMI)—Establishing a PD Biomarker Cohort," *Annals of Clinical Translational Neurology* 5 (2018): 1460–1477.

17. J. Stevens, K. P. Truesdale, J. E. McClain, and J. Cai, "The Definition of Weight Maintenance," *International Journal of Obesity* 30 (2006): 391–399.

18. C. G. Goetz, B. C. Tilley, S. R. Shaftman, et al., "Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Testing Results," *Movement Disorders* 23 (2008): 2129–2170.

19. M. M. Hoehn and M. D. Yahr, "Parkinsonism: Onset, Progression and Mortality," *Neurology* 17 (1967): 427–442.

20. J.-H. Kang, B. Mollenhauer, C. S. Coffey, et al., "CSF Biomarkers Associated With Disease Heterogeneity in Early Parkinson's Disease: The Parkinson's Progression Markers Initiative Study," *Acta Neuropathologica* 131 (2016): 935–949.

21. J. Gallagher, C. Gochanour, C. Caspell-Garcia, et al., "Long-Term Dementia Risk in Parkinson Disease," *Neurology* 103 (2024): e209699.

22. D. Weintraub, C. Caspell-Garcia, T. Simuni, et al., "Neuropsychiatric Symptoms and Cognitive Abilities Over the Initial Quinquennium of Parkinson Disease," *Annals of Clinical Translational Neurology* 7 (2020): 449–461.

23. M. Emre, D. Aarsland, R. Brown, et al., "Clinical Diagnostic Criteria for Dementia Associated With Parkinson's Disease," *Movement Disorders* 22 (2007): 1689–1707.

24. J.-H. Kang, D. J. Irwin, A. S. Chen-Plotkin, et al., "Association of Cerebrospinal Fluid β-Amyloid 1-42, T-Tau, P-tau181, and α-Synuclein Levels With Clinical Features of Drug-Naive Patients With Early Parkinson Disease," *JAMA Neurology* 70 (2013): 1277–1287.

25. R. Kim, S. Choi, K. Byun, et al., "Association of Early Weight Change With Cognitive Decline in Patients With Parkinson Disease," *Neurology* 100 (2023): e232–e241.

26. B. Caballero, "Humans Against Obesity: Who Will Win?," *Advances in Nutrition* 10 (2019): S4–S9.

27. Y. Uchida, H. Kan, K. Sakurai, et al., "Magnetic Susceptibility Associates With Dopaminergic Deficits and Cognition in Parkinson's Disease," *Movement Disorders* 35 (2020): 1396–1405.

28. F. Sampedro, J. Marín-Lahoz, S. Martínez-Horta, J. Pagonabarraga, and J. Kulisevsky, "Dopaminergic Degeneration Induces Early Posterior Cortical Thinning in Parkinson's Disease," *Neurobiology of Disease* 124 (2019): 29–35.

29. F. J. Siepel, K. S. Brønnick, J. Booij, et al., "Cognitive Executive Impairment and Dopaminergic Deficits in de Novo Parkinson's Disease," *Movement Disorders* 29 (2014): 1802–1808.

30. S. García-Ptacek, G. Faxén-Irving, P. Cermáková, M. Eriksdotter, and D. Religa, "Body Mass Index in Dementia," *European Journal of Clinical Nutrition* 68 (2014): 1204–1209.

31. G. Sergi, M. de Rui, A. Coin, E. M. Inelmen, and E. Manzato, "Weight Loss and Alzheimer's Disease: Temporal and Aetiologic Connections," *Proceedings of the Nutrition Society* 72 (2013): 160–165.

32. L. Parnetti, L. Gaetani, P. Eusebi, et al., "CSF and Blood Biomarkers for Parkinson's Disease," *Lancet Neurology* 18 (2019): 573–586.

33. S. Hall, Y. Surova, A. Öhrfelt, H. Zetterberg, D. Lindqvist, and O. Hansson, "CSF Biomarkers and Clinical Progression of Parkinson Disease," *Neurology* 84 (2015): 57–63.

34. L. Parnetti, A. Castrioto, D. Chiasserini, et al., "Cerebrospinal Fluid Biomarkers in Parkinson Disease," *Nature Reviews. Neurology* 9 (2013): 131–140.

35. D. C. Bäckström, M. Eriksson Domellöf, J. Linder, et al., "Cerebrospinal Fluid Patterns and the Risk of Future Dementia in Early, Incident Parkinson Disease," *JAMA Neurology* 72 (2015): 1175–1182.

36. E. J. Dhurandhar, K. A. Kaiser, J. A. Dawson, A. S. Alcorn, K. D. Keating, and D. B. Allison, "Predicting Adult Weight Change in the Real World: A Systematic Review and Meta-Analysis Accounting for Compensatory Changes in Energy Intake or Expenditure," *International Journal of Obesity* 39 (2015): 1181–1187.

37. S. Bazzazian, G. Ozgoli, H. Riazi, Z. Mahmoodi, M. Vafa, and M. Nasiri, "The Relationship Between Social Determinants of Health and Postpartum Weight Retention Based on the World Health Organization Model: Path Analysis," *BMC Public Health* 23 (2023): 323.