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Associations of Body Mass Index-Metabolic Phenotypes with Cognitive Decline in Parkinson's Disease

Liang Zhang[a] Lu-Yan Gu[a] Shao-bing Dai[b] Ran Zheng[a] Chong-Yao Jin[a] Yi Fang[a] Wen-Yi Yang[a] Jun Tian[a] Xin-Zhen Yin[a] Guo-Hua Zhao[a] Jia-Li Pu[a] Bao-Rong Zhang[a] Ya-Ping Yan[a] Ying Chen[a]

[a]Department of Neurology, Second Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China;
[b]Department of Anesthesiology, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China

Keywords
Parkinson's disease · Body mass index · Metabolic status · Cognitive decline

Abstract
Background: Growing evidence suggests important effects of body mass index (BMI) and metabolic status on neurodegenerative diseases. However, the roles of BMI and metabolic status on cognitive outcomes in Parkinson's disease (PD) may vary and are yet to be determined. ***Methods:*** In total, 139 PD patients from the whole PD cohort in Parkinson's Progression Markers Initiative database underwent complete laboratory measurements, demographic and anthropometric parameters at baseline, and were enrolled in this study. Further, they were categorized into 4 different BMI-metabolic status phenotypes using Adult Treatment Panel-III criteria. Motor and cognition scales at baseline and longitudinal changes after a 48-month follow-up were compared among the 4 groups. Repeated-measure linear mixed models were performed to compare PD-related biomarkers among BMI-metabolic status phenotypes across time. ***Results:*** We found that PD patients in the metabolically unhealthy normal weight group showed more cognitive decline in global cognition and visuospatial perception after a 48-month follow-up than those in the other 3 groups ($p < 0.05$). No difference was found in motor scales among different BMI-metabolic status phenotypes. Finally, compared to the metabolically healthy normal weight group, the metabolically healthy obesity group had lower CSF Aβ42 and serum neurofilament levels in repeated-measure linear mixed models adjusting for age, gender, APOE e4 carrier status, and years of education ($p = 0.031$ and 0.046, respectively). ***Conclusion:*** The MUNW phenotype was associated with a rapid cognitive decline in PD.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder that affects 1% of persons older than 65 years and 3% of those older than 80 years [1]. However, the etiology of PD is still elusive. In addition to genetics, the influence of obesity and metabolic syndrome (Mets)-related factors such as hypertension, type 2 diabetes mellitus, and dyslipidemia on PD has begun to be emphasized [2].

L.Z. and L.-Y.G. have contributed equally to this work.

karger@karger.com
www.karger.com/ene

Correspondence to:
Ya-Ping Yan, yanyaping@zju.edu.cn
Ying Chen, chenying0218@zju.edu.cn

Recently, evidence suggests that neurological diseases such as PD and Alzheimer's disease could be initiated by various metabolic changes caused by obesity [3]. These metabolic changes could cause damage to the central nervous system and affect cognition through several mechanistic pathways (such as oxidative stress, lipid pathway alteration, and increased inflammation related to abnormal protein deposition) [4]. Thus, we hypothesized that neurodegenerative diseases and metabolic abnormalities are linked due to their shared mechanistic pathophysiology. However, not all obese subjects are at a higher risk of morbidity and mortality, which suggests that there is a subgroup of body mass index (BMI-metabolic status phenotypes called metabolically healthy obesity (MHO) [5]. MHO is characterized by the absence of metabolic abnormalities such as dyslipidemia, insulin resistance, hypertension, and an unfavorable inflammatory profile [6]. Several studies have shown that MHO individuals are at a lower risk of cardiovascular disease and mortality than metabolically unhealthy obesity (MUO) individuals and are not at elevated risk compared with normal weight individuals [7]. In addition, MHO individuals showed high insulin sensitivity as well as favorable lipid, inflammation, hormones, liver enzymes, and immune status which are associated with protective factors for neurodegenerative diseases [8]. Thus, the study of BMI-metabolic status phenotypes has focused on neurodegenerative diseases in recent years. Several studies have suggested that MHO individuals reduce the risk of Alzheimer's disease in a longitudinal follow-up [9, 10]. However, research has rarely involved in PD and longitudinal studies of the association between BMI-metabolic phenotypes and the development of PD are limited. In this study, we assessed the correlations of BMI-metabolic phenotypes with the disease progression of PD and explored the differences in PD biomarkers among those groups to explore possible mechanisms whereby BMI-metabolic phenotypes affect PD progression.

Materials and Methods

Participants

Data used in this study were obtained from the Parkinson's Progression Markers Initiative (PPMI) database, which is a prospective, longitudinal, multicenter study and aims to assess whether serial PET, MRI, biological markers, and other clinical, genetic markers can be identified to measure the progression of PD. The PPMI-PD cohort recruited patients who were diagnosed with PD within 2 years, drug naïve, Hoehn & Yahr (H&Y) stage 1 or 2 at baseline, age 30 years or older, and had striatal dopaminergic dysfunction on SPECT. To update, over 400 patients were enrolled in the PPMI-PD cohort, among whom 152 cases underwent laboratory measurements and anthropometric parameters at baseline and were included in this study. Since APOE genotype plays an important role on cognition, APOE e4-carrying state was included as a covariate in further analysis, and 13 patients were excluded due to a lack of APOE genotype result. In total, 139 PD patients were enrolled in this study.

Definition of BMI-Metabolic Status

Laboratory measurement data, anthropometric parameters, and medical history were downloaded from the PPMI database. Triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and fasting venous blood glucose were measured. BMI was calculated by dividing body weight (in kg) by height squared (in m^2). Arterial blood pressure was measured, while participants were seated with their forearms placed horizontally in the 4 rib spaces of the sternum.

Adult Treatment Panel-III components were used to define metabolic status [11]. Participants who met ≥2 of the following 4 parameters were defined as metabolically unhealthy: (1) elevated systolic blood pressure (≥130 mm Hg) or diastolic blood pressure (≥85 mm Hg) or antihypertensive treatment; (2) elevated fasting plasma glucose (≥100 mg/dL) or antidiabetic treatment; (3) elevated TG (≥1.7 mmol/L); and (4) reduced HDL-C (<1.0 mmol/L for men and <1.3 mmol/L for women). Obese phenotypes were determined by the BMI value according to World Health Organization criteria [12]: obese ≥25 kg/m^2 and normal weight <25 kg/m^2. Based on the metabolic and obese status, participants were categorized into the following 4 groups: (1) metabolically unhealthy normal weight (MUNW): BMI <25 kg/m^2 and ≥2 metabolic risk factors; (2) MUO: BMI ≥25 kg/m^2 and ≥2 metabolic risk factors; (3) metabolically healthy normal weight (MHNW): BMI <25 kg/m^2 and <2 metabolic risk factors; and (4) MHO: BMI ≥25 kg/m^2 and <2 metabolic risk factors.

Clinical Assessment

Demographic and clinical features including age, gender, disease duration, years of education, and APOE e4-carrying state were downloaded from the PPMI database. Data on disease severity and cognition status at baseline and 48-month follow-up were obtained. Movement Disorder Society Unified Parkinson's Disease Rating Scale part 3 (MDS-UPDRS 3) and H&Y stage were used to assess motor function. Cognitive tests included the Montreal Cognitive Assessment (MoCA) for global cognition; the Hopkins Verbal Learning Test for memory; the Benton Judgment of Line Orientation Test (BJLOT) for visuospatial perception; the Letter-Number Sequencing and Semantic Fluency Test for working memory and executive function; and the Symbol Digit Modality Test for attention-processing speed.

Dopamine Transporter Imaging

Dopamine imaging was performed by dopamine transporter (DAT) scan. The mean of bilateral quantitative DAT scan measures in striatal binding ratio of caudate and putamen uptake values (Ave-DAT) at baseline and 12-month follow-up were downloaded.

CSF and Serum Sample Collection and Protein Measurement

CSF samples were collected at baseline, 6 months, 12 months, 24 months, and 36 months. Serum samples were collected at baseline, 6 months, 12 months, 24 months, 36 months, and 48 months. CSF Aβ42, total tau (t-tau), and phosphorylated tau (p-tau) at threonine 181 position, α-synuclein, and serum neurofilament light chain (NfL) were measured and systematically assessed according to the PPMI study protocol.

Table 1. Demographic characteristics of study participants at baseline

	Total (*n* = 139)	MUNW (*n* = 19)	MUO (*n* = 45)	MHNW (*n* = 34)	MHO (*n* = 41)	*p* value
Age, year	62.97±9.44	65.09±9.09	61.81±9.32	64.66±10.27	61.87±8.61	0.356
Gender, male/female	98/41	10/9	37/8	19/15	32/9	0.015
Disease duration, year	2.07±2.09	1.47±0.82	2.42±3.10	2.10±2.55	1.93±1.27	0.395
Education, year	15.52±2.93	15.42±2.18	15.09±3.32	15.41±2.65	16.12±2.92	0.438
APOE e4 carrier, *n* (%)	37 (26.6)	5 (26.3)	13 (28.9)	8 (23.5)	11 (26.8)	0.962
BMI, kg/m2	26.88±4.45	22.84±1.30	29.86±3.56	22.50±1.86	29.12±3.37	<0.0001
HDL-C, mg/dL	56.32±17.13	59.74±21.10	46.73±15.67	65.65±13.79	57.54±13.48	<0.0001
Triglycerides, mg/dL	114.66±55.03	125.16±42.66	136.84±71.14	99.94±47.22	97.66±30.96	0.002
Fasting glucose, mmol/L	5.62±0.86	5.95±0.80	6.04±0.88	5.33±0.67	5.25±0.74	<0.0001
Systolic BP, mm Hg	125.14±17.64	129.10±15.24	134.04±17.14	116.85±18.50	120.39±12.92	<0.0001
Diastolic BP, mm Hg	78.59±11.70	81.21±8.85	83.84±9.85	74.68±13.46	74.85±10.55	0.003

MUNW, metabolic unhealthy normal weight; MUO, metabolic unhealthy obesity; MHNW, metabolic healthy normal weight; MHO, metabolic healthy obesity; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure.

Table 2. Baseline clinical features of PD patients in different BMI-metabolic status phenotypes

	MUNW (*n* = 19)	MUO (*n* = 45)	MHNW (*n* = 34)	MHO (*n* = 41)	*p* value
Ave-DAT caudate	2.10±0.30	2.14±0.58	2.06±0.49	1.98±0.54	0.555
Ave-DAT putamen	0.84±0.20	0.90±0.35	0.83±0.26	0.77±0.25	0.263
MDS-UPDRS 3	21.63±8.00	19.89±7.93	20.09±7.18	21.63±7.92	0.774
MDS-UPDRS total	30.05±11.38	30.75±14.00	32.20±11.47	32.63±11.09	0.838
H&Y stage	1.47±0.50	1.49±0.50	1.62±0.48	1.58±0.49	0.590
MoCA	26.84±2.39	26.78±2.38	27.15±1.91	27.53±1.96	0.226
Line orientation test	13.00±2.41	12.84±2.01	13.24±2.07	13.32±2.03	0.738
Letter-number sequencing	10.21±2.19	10.67±2.67	10.88±2.01	11.22±2.61	0.494
Semantic fluency test	45.95±8.60	46.98±11.41	47.12±9.71	50.58±9.34	0.219
Symbol digit modality test	45.95±8.60	41.27±7.92	40.00±8.29	41.20±11.37	0.163
HVLT-total recall	24.32±2.36	24.36±4.92	24.65±4.46	24.27±4.25	0.984
HVLT-delayed recall	8.37±2.50	8.09±2.69	8.41±2.21	8.15±2.38	0.935
HVLT-discrimination recognition	9.95±1.05	9.82±1.77	10.38±1.51	9.98±1.40	0.444

MUNW, metabolic unhealthy normal weight; MUO, metabolic unhealthy obesity; MHNW, metabolic healthy normal weight; MHO, metabolic healthy obesity; BMI, body mass index; DAT, dopamine transporter; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; H&Y, Hoehn & Yahr; MoCA, Montreal Cognitive Assessment; HVLT, Hopkins Verbal Learning Test; PD, Parkinson's disease.

Statistical Analysis

Demographic data, clinical scales, and imaging characteristics at baseline were compared between the 4 groups by using the analysis of variance (ANOVA) test (for continuous variables) or the χ^2 test (for categorical data). The rates of longitudinal changes of clinical scales and Ave-DAT were compared using the ANOVA test. To calculate the rate of change, the difference between the baseline and follow-up values was divided by the absolute baseline value. Repeated-measure linear mixed models were used to compare the concentrations of CSF or serum biomarkers among BMI-metabolic status phenotypes across time. For cognition tests and CSF or serum biomarkers, age, gender, APOE e4 carrier status, and years of education were adjusted for the analysis. Statistical analysis was performed using SPSS software (SPSS, Armonk, NY: IBM Corp.) and graphs were plotted using GraphPad (San Diego, CA; GraphPad Inc.). The significance level was set at a p value <0.05.

Results

Demographic Characteristics and Clinical Features at Baseline

Demographic characteristics are listed in Table 1. Among the 139 participants, 64 (46%) were defined as metabolically unhealthy with significantly higher TG, LDL-C, fasting glucose, and lower HDL-C. No difference was found in age, disease duration, years of education, and APOE e4-carrying status among different BMI-metabolic status phenotypes. Table 2 shows the baseline clinical features of the participants. There was no difference in Ave-DAT, motor, or cognition scales among the 4 groups at baseline.

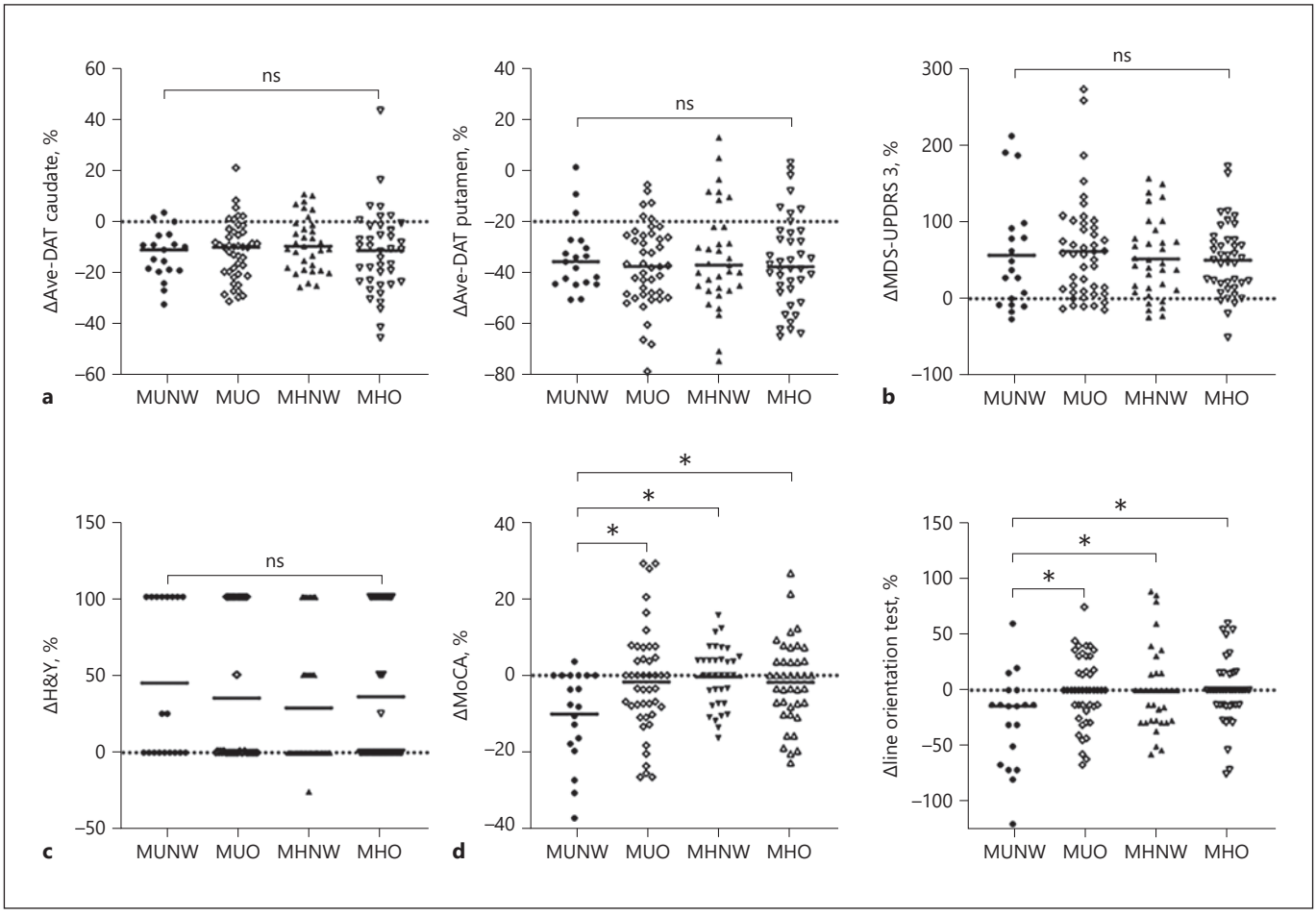

Fig. 1. Longitudinal changes of Ave-DAT and clinical scales in PD patients with different BMI-metabolic phenotypes. **a–c** No significant difference was found with longitudinal changes of Ave-DAT, MDS-UPDRS part 3 score, or H&Y stage among 4 groups. **d** PD patients in the MUNW group showed a larger decrease in MoCA and BJLOT scores than those in other 3 groups. △, the rate of longitudinal changes, dividing the difference between the baseline and follow-up values by the absolute baseline value. *$p < 0.05$. MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; H&Y, Hoehn & Yahr; PD, Parkinson's disease; BJLOT, Benton Judgment of Line Orientation Test; MoCA, Montreal Cognitive Assessment; BMI, body mass index; MUNW, metabolic unhealthy normal weight; MHNW, metabolic healthy normal weight; MUO, metabolic unhealthy obesity; MHO, metabolic healthy obesity; DAT, dopamine transporter.

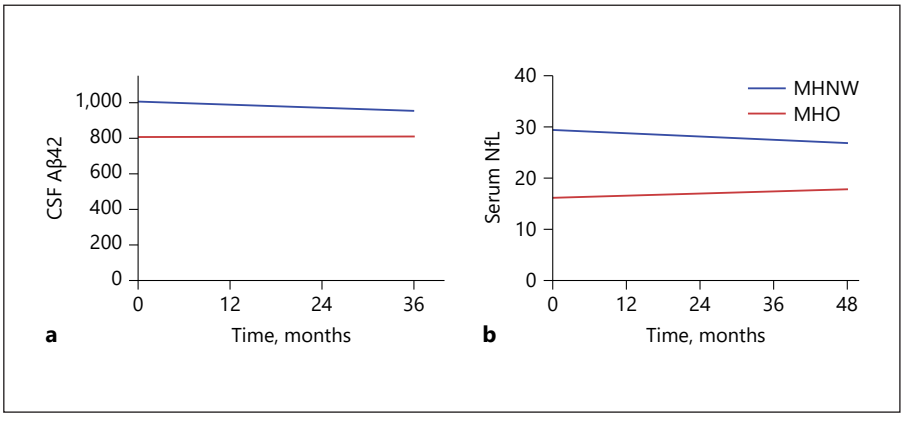

Fig. 2. Longitudinal levels of CSF Aβ42 (**a**) and serum NfL (**b**) in MHNW and MHO groups. MHO, metabolic healthy obesity; MHNW, metabolic healthy normal weight; CSF, cerebrospinal fluid; NfL, neurofilament light chain.

Longitudinal Changes of Ave-DAT and Clinical Scales

No significant difference was found in the longitudinal changes of Ave-DAT, MDS-UPDRS 3 score, or H&Y stage (shown in Fig. 1a–c, respectively) among the 4 BMI-metabolic status phenotypes. The means of absolute changed MoCA scores after 48-month follow-up were −2.62, −0.60, −0.12, and −0.51, respectively, for MUNW, MUO, MHNW, and MHO groups; and those of BJLOT scores were −3.26, −0.27, −0.47, and −0.10, respectively. The patients in the MUNW group experienced more longitudinal cognitive decline with a larger decrease in MoCA and BJLOT scores than those in the other 3 groups after a 48-month follow-up ($p < 0.05$, shown in Fig. 1d). There was no difference in longitudinal changes of other cognition scales between the 4 groups (shown in online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000517538).

BMI-Metabolic Status and PD Biomarkers

Between the metabolically healthy groups, there were significant correlations of MHO with lower CSF Aβ42 and serum NfL in repeated-measure linear mixed models adjusting for age, gender, APOE e4 carrier status, and years of education ($p = 0.031$ and 0.046, shown in Table 3; Fig. 2). No statistical differences were observed in CSF α-synuclein, t-tau, or p-tau between the 2 groups. As for the metabolically unhealthy groups, there was no difference in CSF or serum biomarkers between MUO and MUNW groups (Table 3).

Table 3. Associations between BMI-metabolic phenotypes and PD-related biomarkers

	MHO versus MHNW		MUO versus MUNW	
	estimate	*p* value	estimate	*p* value
CSF α-synuclein	71.73	0.893	−120.42	0.473
CSF Aβ42	170.32	0.031	−1.00	0.993
CSF t-tau	10.71	0.324	−15.91	0.381
CSF p-tau	0.678	0.493	−0.94	0.595
Serum NfL	8.414	0.046	0.53	0.949

MUNW, metabolic unhealthy normal weight; MUO, metabolic unhealthy obesity; MHNW, metabolic healthy normal weight; MHO, metabolic healthy obesity; BMI, body mass index; CSF, cerebrospinal fluid; t-tau, total tau; p-tau, phosphorylated tau at threonine 181 position; NfL, neurofilament light chain; PD, Parkinson's disease.

Discussion

In the present study, we examined the associations between BMI-metabolic status phenotypes and disease progression in PD patients using the longitudinal data from the PPMI database. Our results revealed that PD patients in the MUNW group showed more cognitive decline in global cognition and visuospatial perception after a 48-month follow-up than those in the other 3 groups.

The associations of Mets or BMI with cognitive impairment have been assessed in previous studies. It was reported that individuals with Mets were at an increased likelihood of being cognitive impaired and progression to dementia [13–15]. Moreover, a longitudinal neuroimaging study by Gomez et al. [16] revealed that Mets, particularly elevated fasting glucose and blood pressure, were linked with accelerated Aβ accumulation in the aging brains, which may be an important factor in the progression of cognitive impairment. The contributing effect of BMI on cognitive impairment has been inconsistent. Several studies suggested that a lower late-life BMI is correlated with an increased risk of incident dementia [17, 18], while other studies have reported that late-life obesity is associated with smaller brain volumes in patients with mild cognitive impairment and AD [19, 20]. Since Mets and obesity are often related but can exist independently, it is necessary to examine the effects of different BMI-metabolic status phenotypes on cognitive impairment [21]. Two longitudinal studies have investigated the risk of incident dementia according to metabolic health and obesity status [9, 10] and reported a protective effect of MHO phenotype on AD. In our study, PD patients in the MUNW group experienced more cognitive impairment than those in the other 3 groups. We did not find evidence for the protective effect of MHO on cognitive impairment in PD. Considering cognitive decline, especially dementia, normally appears in the advanced stages of PD [22]; the most likely explanation for this result is that participants enrolled in the current study were in the early disease stage and experienced little progression in cognitive decline during the follow-up. Further studies with advanced patients and a longer follow-up are needed to investigate the effect of other 3 BMI-metabolic status phenotypes on cognitive impairment in PD. Besides, it is interesting that in our study, a significant cognitive decline was seen only in the MUNW group, but not in the MUO group, suggesting that obesity may serve as a protective factor in the cognitive progression of PD patients with an unhealthy metabolically status. Further studies with larger sample sizes are warranted to incorporate these findings.

In our study, no difference was found in the progression of motor function among 4 BMI-metabolic status phenotypes in PD patients. Previous studies have assessed the impacts of Mets or BMI on motor functional outcomes in PD separately. It was reported that PD patients with Mets experienced a greater increase in total and motor MDS-UPDRS scores [23]. However, the effect of BMI remains unclear. A large-scale longitudinal study previously reported that the change in BMI was inversely associated with the change in motor and total MDS-UPDRS scores [24], while another recent study found that obesity was related to an increased risk of functional dependency and rapid motor progression in PD [25]. The impacts of metabolic health status were missed in both studies, which may lead to the controversial results. Therefore, examining the effects of BMI on motor function in PD with different metabolic health statuses may help to understand better.

In addition, we evaluated the associations of BMI-metabolic status phenotypes with PD-related biomarkers and demonstrated a negative correlation between MHO group and CSF Aβ42 or serum NfL levels in comparison with MHNW group. Serum NfL levels were found to be elevated in PD patients compared with those in controls and correlated with disease severity and progression in terms of both motor and cognitive functions [26]. Our results showed that the MHO group was linked with lower serum NfL levels than the MHNW group, to some extent, indicating a protective effect of MHO phenotype on the progression of PD.

This study has some limitations. First, only a moderate number of patients were included. Further studies with a larger sample size are needed to confirm our findings. Additionally, BMI or metabolic status may change over time in some individuals. However, we only analyzed baseline data and did not include longitudinal changes during the follow-up. Besides, as mentioned above, this study included PD patients in the early stage who experienced little progression of cognitive decline during the follow-up. To understand better the impacts of BMI and metabolic status on cognitive decline in PD, further studies with advanced patients are warranted.

Conclusions

In conclusion, we demonstrated the associations of different BMI-metabolic status phenotypes with PD progression and found that the MUNW group was linked with more cognitive impairment than the other 3 groups. The protective effect of MHO was not found in clinical features, but was indicated by its correlation with lower serum NfL levels than the MHNW group. Further studies in other populations are needed to better understand the effects of obesity and metabolic status on PD progression.

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Statement of Ethics

Regional ethical committees of all participating institutions approved the PPMI and all study participants provided written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

L.Z., L.-Y.G., Y.-P.Y., and Y.C.: conceptualization. L.Z., S.-B.D., R.Z., and C.-Y.J.: performance of experiments. L.Z., L.-Y.G., Y.F., and W.-Y.Y.: data analysis. B.-R.Z. and J.-L.P.: funding acquisition. J.T., X.-Z.Y., and G.-H.Z.: project administration. B.-R.Z., Y.-P.Y., and Y.C.: supervision. L.Z., L.-Y.G., and Y.C.: writing – original draft. L.Z., L.-Y.G., J.-L.P., B.-R.Z., Y.-P.Y., and Y.C.: writing – review and editing. All authors have approved the final article.

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