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Progressive and accelerated weight and body fat loss in Parkinson's disease: A three-year prospective longitudinal study

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ABSTRACT

Introduction: Although weight loss is common in Parkinson's disease (PD), longitudinal studies assessing weight and body composition changes are limited.
Methods: In this three-year longitudinal study, 125 subjects (77 PD patients and 48 spousal/sibling controls) underwent clinical, biochemical and body composition assessments using dual-energy X-ray absorptiometry.
Results: Patients were older than controls (65.6 ± 8.9 vs. 62.6 ± 7.1, P = 0.049), with no significant differences in gender, comorbidities, dietary intake and physical activity. Clinically significant weight loss (≥5% from baseline weight) was recorded in 41.6% of patients, with a doubling of cases (6.5 to 13.0%) classified as underweight at study end. Over three years, patients demonstrated greater reductions in BMI (mean −1.2 kg/m^2, 95%CI-2.0 to −0.4), whole-body fat percentage (−2.5% points, 95%CI-3.9 to −1.0), fat mass index (FMI) (−0.9 kg/m^2, 95%CI-1.4 to −0.4), visceral fat mass (−0.1 kg, 95%CI-0.2 to 0.0), and subcutaneous fat mass (−1.9 kg, 95%CI-3.4 to −0.5) than in controls, with significant group-by-time interactions after adjusting for age and gender. Notably, 31.2% and 53.3% of patients had FMI < 3rd (severe fat deficit) and < 10th centiles, respectively. Muscle mass indices decreased over time in both groups, without significant group-by-time interactions. Multiple linear regression models showed that loss of body weight and fat mass in patients were associated with age, dyskinesia, psychosis and constipation.
Conclusions: We found progressive loss of weight in PD patients, with greater loss of both visceral and subcutaneous fat, but not muscle, compared to controls. Several associated factors (motor and non-motor disease features) were identified for these changes, providing insights on possible mechanisms and therapeutic targets.

1. Introduction

Unintended weight loss is highly prevalent in PD [1], sometimes preceding diagnosis and often becoming pronounced over the disease course [2,3]. The literature so far suggests that it manifests primarily from mid-stages of the disease [2–4]. Importantly, weight loss is associated with negative outcomes including worse quality of life, more severe parkinsonism, osteoporosis and fractures, pressure ulceration, dementia, dependency, and death [1,3–8]. The condition is challenging to manage, given that underlying etiological factors are poorly understood. Contributing factors include gastrointestinal dysfunction (e.g., nausea, anorexia, and dysphagia), hyposmia, depression, altered reward processing, psychosis, cognitive impairment, loss of functional ability (e.g., preparing meals or self-feeding), increased energy expenditure due to muscular rigidity or involuntary movements, pain, and treatment-related factors; disruption of complex interactions between hypothalamic and peripheral mechanisms of feeding regulation also play an important role [5–10].

Body weight and composition are known to change with age, generally with reductions in body weight and skeletal muscle and bone mass, but increases in fat, especially visceral fat [11,12]. Preliminary research suggested that weight loss in PD may predominantly be due to

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fat rather than muscle loss [6,13]. However, most studies on body composition in PD have been limited by small sample sizes, lack of clinical correlation, and cross-sectional design providing limited insight into the temporal evolution of body composition alterations in PD [13–18]. To our knowledge, only three small studies evaluated body composition changes using a longitudinal design, with conflicting results. Patients were recruited at different disease phases, followed for variable periods (1–3 years), and studied using bioelectrical impedance (BIA) (n = 58) or more precise body imaging methods, i.e. dual-energy X-ray absorptiometry (DXA) and magnetic resonance imaging (n = 25–26) [15–17].

Our objectives were to: (1) describe the changes in body weight and composition in a consecutively-recruited cohort of patients over a three-year period, and compare these with non-PD spousal/sibling controls; and (2) determine the factors associated with body weight and composition alterations in PD.

2. Methods

2.1. Subjects

Patients and corresponding controls from a previous cross-sectional study in 2015 [13] were invited to return for repeat assessments three years later, in 2018. Inclusion and exclusion criteria for patients and controls were as previously described [13]. Briefly, patients fulfilling standard clinical diagnostic criteria for PD and able to reliably complete study assessments were consecutively recruited. Two patients on apomorphine infusion who were not included in the 2015 report were included in this study. The study was approved by the Ethics Committee, University of Malaya Medical Centre and written informed consent was obtained from all subjects.

2.2. Clinical assessments

Detailed demographic and clinical data were collected as previously described [13]. Habitual dietary intake was assessed using a locally-developed Food Frequency Questionnaire (FFQ) with 136 food items and physical activity using the International Physical Activity Questionnaire (IPAQ). PD severity (motor, non-motor and motor response complications) was graded using the International Parkinson and Movement Disorder Society-Unified PD Rating Scale (MDS-UPDRS) and Hoehn and Yahr staging, during the patients' usual “On”-medication state in the morning. For consistency, the MDS-UPDRS part III was scored by a single Movement Disorders neurologist (AHT). Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA).

2.3. Body weight and composition assessments

Body weight was measured with participants wearing light, indoor clothes without shoes and using a calibrated digital scale. Height was measured using a calibrated, wall-mounted stadiometer. Clinically significant weight loss or weight gain was defined as ≥5% decrease/increase in baseline weight over three years [7]. Body composition was evaluated using whole-body DXA (Lunar iDXA, GE Healthcare, Wisconsin, USA), with the same machine and protocol used in 2015, in a quality-controlled facility certified for routine clinical use. Measurements of fat and lean muscle in the total body and in specifically-defined regions (trunk, arm, leg, android and gynoid) were obtained. Total fat mass was divided by height(m)^2 to obtain the fat mass index (FMI). In view of the paucity of normative data on body composition in the Asian population, FMI values in our study were compared to corresponding age- and gender-specific GE-Lunar DXA reference curves of a Caucasian population, derived from the large National Health and Nutrition Examination Survey (NHANES, United States, 1999–2004) [13], and categorized into five groups (< 3rd, 3rd-10th, 10th-90th, 90th-97th, and > 97th centiles). Visceral fat mass (VFM) was calculated based on android fat mass by the CoreScan application [19]. Subcutaneous fat mass (SFM) was calculated by subtraction of VFM from total fat mass. Total lean muscle mass was divided by height(m)^2 to obtain the lean muscle mass index (LMMI). The muscle masses of the four limbs were summated to calculate the appendicular skeletal muscle mass and adjusted for height to obtain the skeletal muscle mass index (SMMI).

2.4. Serum biochemical analysis

Fasting bloods were drawn at follow-up to measure albumin, insulin-like growth factor-1 (IGF-1), glucose, and insulin, using validated assays certified for routine clinical care. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score was calculated (Fasting insulin [microU/L]xFasting glucose[nmol/L]/22.5).

2.5. Statistical analysis

Data were analyzed using SPSS for Macintosh Version 24.0 (SPSS, Inc., Chicago, IL, USA). Qualitative variables were described as frequencies and percentages while quantitative variables were described as means and standard deviations or medians and interquartile ranges (IQR). In testing the differences in baseline and clinical characteristics between the patients and controls, either Chi-square, t or Mann-Whitney U tests were used. In testing the differences in these characteristics over time in each group, either ANOVA with repeated measures, Wilcoxon signed-ranked test or McNemar's test was used. In comparing the changes in body composition parameters between 2015 and 2018, the Generalized Estimating Equations (GEE) procedure was used to analyse the effect of time and group (between patients and controls), and the interaction effect of time and group, controlling for age and gender, with Bonferroni correction for pairwise comparisons. To determine the factors associated with changes in weight and fat mass, multiple linear regression analyses with forward selection method (using probability of F-to-enter < 0.1) were performed. Factors for possible inclusion as independent variables in the regression models were baseline age, gender, and disease duration; and baseline and changes in: levodopa equivalent daily dosage, physical activity (iPAQ), total calorie intake per day, disease (motor) severity (MDS-UPDRS part III), severity of motor fluctuations (based on the sum of scores for MDS-UPDRS items 4.3, 4.4, 4.5 and 4.6), severity of dyskinesia (based on the sum of scores for MDS-UPDRS items 4.1 and 4.2), swallowing difficulty (based on MDS-UPDRS item 2.3), constipation severity (based on MDS-UPDRS item 1.11), cognitive function (MoCA), and psychosis severity (based on MDS-UPDRS item 1.2). Spearman's correlations were used to test the association between selected variables. For all tests, the level of significance was set as 0.05. Bonferroni correction was used to adjust for multiplicity.

3. Results

3.1. Patient characteristics and study flow

Patient flow is depicted in Supplementary Fig. 1. There were 95 patients at baseline, of whom 77 completed three-year follow-up. Reasons for dropout were deaths (n = 9, i.e., 6/37 = 16% of those with FMI < 10th centile at baseline and 3/58 = 5.2% of those with FMI ≥ 10th centile at baseline), severe disability (n = 3), diagnosis reassigned (to progressive supranuclear palsy; n = 2) and treatment with deep brain stimulation (DBS) (n = 4; these patients were excluded due to the well-recognized potential for DBS to cause significant weight gain post-operatively [6,20,21]).

Demographic, clinical and lifestyle characteristics are summarized in Table 1. The mean age of patients was slightly higher compared to controls (P = 0.049). There were no significant differences in other

Table 1
Demographic, clinical, and lifestyle characteristics of patients and controls.

	Patients (n = 77)			Controls (n = 48)		
	Baseline (2015)	Follow-up (2018)	Within-group P value	Baseline (2015)	Follow-up (2018)	Within-group P value
Demographics						
Age	65.6 ± 8.9			62.6 ± 7.1[c]		
Gender, n (%) male	43 (55.8)			21 (43.8)		
Ethnicity, n (%)						
Chinese	55 (71.4)			32 (66.7)		
Indian	13 (16.9)			8 (16.7)		
Malay	6 (7.8)			5 (10.4)		
Others	3 (3.9)			3 (6.3)		
Comorbidities, n (%)						
Diabetes mellitus	9 (11.5)			8 (16.7)		
Hypertension	32 (41.0)			18 (38.1)		
Heart failure	1 (1.6)			0 (0)		
Stroke	1 (1.6)			1 (2.4)		
Respiratory disease	9 (11.5)			3 (7.1)		
Peptic disease	19 (24.6)			7 (14.3)		
Thyroid disease	10 (13.1)			2 (4.8)		
Arthritis	24 (31.1)			15 (31.0)		
Cancer	0 (0)			2 (4.8)		
Dietary intake						
Total calorie (kcal/day)	2556.5 [1796.4]	2434.9 [1532.3]	0.417	2285.9 [1230.1]	2310.0 [1445.8]	0.478
Total protein (g/day)	117.5 [90.0]	107.3 [75.2]	0.172	99.6 [59.5]	102.0 [80.5]	0.204
Total fat (g/day)	96.6 [72.9]	92.5 [67.1]	0.318	83.4 [59.3]	88.9 [68.1]	0.899
Total carbohydrate (g/day)	312.8 [232.3]	343.4 [216.9]	**0.023**	260.9 [154.8]	280.7 [168.9]	**0.043**
Physical Activity						
Low physical activity[a], n (%)	33 (42.9)	29 (37.7)	0.607	30 (39.6)	19 (25.0)	0.118
Disease Severity						
Disease duration (years)	8.4 ± 5.5					
Hoehn and Yahr, n (%)						
Stage 1	1 (1.3)	1 (1.3)	< **0.001**			
Stage 2	50 (64.5)	25 (52.6)				
Stage 3	25 (32.9)	15 (30.3)				
Stage 4	0 (0.0)	4 (9.2)				
Stage 5	1 (1.3)	3 (5.3)				
MDS-UPDRS part III score	32.9 ± 12.5	39.3 ± 13.8	< **0.001**			
With motor complications[b], n (%)	48.1	66.2	**0.001**			
MoCA	26.0 [5.0]	26.5 [7.0]	0.611			
	25.3 ± 3.5	24.7 ± 5.5				
LEDD (mg/day)	600.0 [648.5]	500.0 [751.5]	< **0.001**			
	551.4 ± 382.0	749.2 ± 475.2				
DA-only LEDD (mg/day)	150.0 [100.0]	150.0 [101.0]	0.772			
	171.5 ± 109.1	182.4 ± 121.7				

Normally distributed data are presented as mean ± standard deviation, while non-normally distributed data are presented as median [interquartile range]. DA = Dopamine agonist; LEDD = Levodopa equivalent daily dosage; MDS-UPDRS = International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale, higher scores indicate worse severity; MoCA = Montreal Cognitive Assessment, lower scores indicate worse cognitive function.

[a] Based on the International Physical Activity Questionnaire (iPAQ).

[b] Score of ≥1 on MDS-UPDRS part IV.

[c] Denotes statistically significant between-group difference (p = 0.049). There were no significant between-group differences at baseline or at follow-up in other demographic, comorbidity, dietary or physical activity variables.

variables between the groups at baseline. There were also no significant between-group differences in dietary intake (total calories, protein, fat and carbohydrate) and physical activity at baseline and three-year follow up. Among the patients, the mean age and PD duration at baseline were 65.6 ± 8.9 and 8.4 ± 5.5 years, respectively. As expected, indices of disease severity (MDS-UPDRS part III and percentage of patients with motor response complications) increased significantly over three years, reflecting disease progression.

3.2. Progression of body weight and fat loss in PD over three years

Although self-reported total caloric intake and physical activity were similar over three years (Table 1), weight loss was recorded in 41.6% of patients, weight gain in 16.9%, and 41.6% remaining stable (within 5% of baseline weight) (Fig. 1). The mean BMI reduced significantly from 24.3 to 23.1 kg/m^2 (P < 0.001) (Table 2) and the proportion of underweight patients (BMI < 18.5 kg/m^2) doubled from 6.5 to 13.0% (Fig. 1). Similarly, all indices of body fat (FMI, whole-body fat percentage, SFM and VFM) reduced significantly over the three-year follow-up, including a reduction in whole-body fat by 2.5% points (Table 2). Notably, more than half (53.3%) the patients had FMI < 10th centile at three years and nearly a third (31.2%) had severe fat deficit with FMI < 3rd centile (Fig. 1). In the group classified at baseline with FMI < 10th centile, only one patient increased in fat mass, while 14/49 (28.6%) patients with FMI ≥ 10th centile at baseline showed reduction in fat mass to < 10th centile (Supplementary Fig. 1). Regarding muscle mass indices, there was a significant reduction in SMMI but not LMMI (Table 2).

3.3. Body composition comparison with controls

At baseline, patients had lower BMI and body fat parameters (FMI, whole-body fat percentage, SFM, and VFM), but not muscle mass indices, compared to controls (Table 2). A lower proportion of control subjects recorded weight loss compared to the patients (18.8% vs. 41.6%) (Fig. 1). Over the three-year follow-up, controls had significant

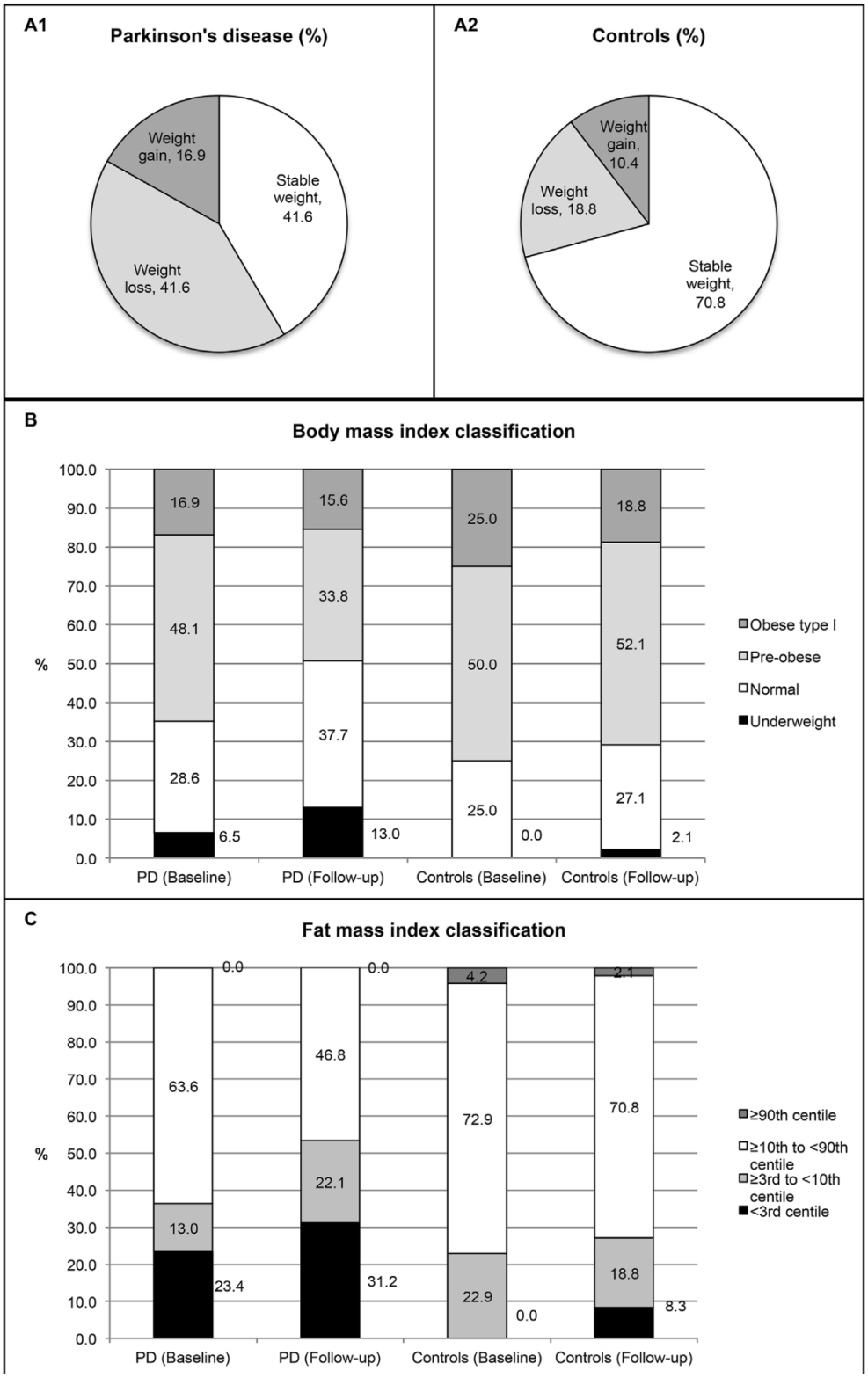

Fig. 1. Pattern of weight, body mass index and fat mass index change in patients with Parkinson's disease and controls. Figure A1, A2: Weight changes were categorized based on cut-off of ≥5% change from baseline weight in 2015. Figure B: Body mass indices were classified according to the Malaysian Clinical Practice Guidelines on Management of Obesity 2004. Figure C: Fat mass indices were classified according to age- and gender-specific centiles, based on the National Health and Nutrition Examination Survey (NHANES) reference curves (Fan B et al., J Clin Densitom 2014).

reductions in FMI and SMMI only, however, the magnitude of reduction in these parameters was smaller compared to the reductions seen in patients (Table 2). There were significant group-by-time interactions for BMI and all body fat parameters (meaning the change over time differed between the two groups), but not for LMMI and SMMI (Table 2), after controlling for age and gender. After Bonferroni correction for multiple comparisons, only whole-body fat percentage and visceral fat mass were found to have significant group-by-time

Table 2
Comparison of body composition parameters between 2015 and 2018, controlled for age and gender.

Body composition parameters	Group	2015	2018	Mean difference (95% CI)	Within-group P value (Time)	Between-group P value (Time*Group)
		Mean (95% CI)	Mean (95% CI)			
Body mass index (kg/m^2)	Patient	24.3 (23.4, 25.1)	23.1 (22.2, 23.9)	−1.2 (−2.0, −0.4)	< **0.001**	**0.038**
	Control	25.7 (24.7, 26.8)	25.3 (24.2, 26.3)	−0.5 (−1.0, 0.1)	0.150	
Fat mass index (kg/m^2)	Patient	7.6 (7.0, 8.2)	6.7 (6.0, 7.3)	−0.9 (−1.4, −0.4)	< **0.001**	**0.025**
	Control	9.3 (8.5, 10.1)	8.9 (8.1, 9.7)	−0.4 (−0.7, 0.0)	**0.041**	
Whole-body fat percentage (%)	Patient	31.4 (30.0, 33.2)	29.0 (27.0, 30.9)	−2.5 (−3.9, −1.0)	< **0.001**	**0.005**[a]
	Control	37.0 (34.7, 39.2)	36.4 (34.2, 38.5)	−0.6 (−1.5, 0.2)	0.268	
Subcutaneous fat mass (kg)	Patient	18.3 (16.7, 19.8)	16.4 (14.8, 17.9)	−1.9 (−3.4, −0.5)	**0.002**	0.050
	Control	22.6 (20.5, 24.6)	22.0 (20.0, 24.0)	−0.5 (−1.7, 0.6)	0.999	
Visceral fat mass (kg)	Patient	0.9 (0.7, 1.0)	0.7 (0.6, 0.9)	−0.1 (−0.2, 0.0)	**0.004**	**0.004**[a]
	Control	1.0 (0.7, 1.1)	1.0 (0.9, 1.2)	0.1 (−0.1, 0.2)	0.287	
Lean muscle mass index (kg/m^2)	Patient	15.9 (15.5, 16.4)	15.7 (15.2, 16.1)	−0.3 (−0.5, 0.0)	0.092	0.922
	Control	15.4 (14.9, 16.0)	15.2 (14.5, 15.8)	−0.3 (−0.6, 0.1)	0.164	
Skeletal muscle mass index (kg/m^2)	Patient	7.1 (6.9, 7.4)	6.9 (6.6, 7.2)	−0.3 (−0.5, −0.1)	**0.004**	0.573
	Control	7.1 (6.8, 7.4)	6.9 (6.6, 7.2)	−0.2 (−0.4, −0.1)	**0.004**	

Analyses were performed using Generalized Estimating Equations (GEE) procedure with robust estimation method and Bonferroni correction for pairwise comparisons. In the analyses, the effect of time and group and the interaction effect of time and group were tested, controlling for age and gender.
[a] Denotes statistical significance after adjustment for multiplicity using Bonferroni-adjusted alpha level of 0.0071 (=0.05/7).

interactions.

3.4. Factors associated with changes in weight and body fat mass in PD patients

Multiple linear regression models showed that change (worsening) in psychosis severity from baseline to follow-up was the only factor significantly associated with weight change, with an estimate of −1.3 kg (weight loss) over three years (95%CI: −3.8 to −0.5, p = 0.011) (Table 3). Baseline constipation severity and change (worsening) in dyskinesia severity were significantly associated with reduction in body fat mass, with fat loss estimates of −1.7 kg (95%CI: 2.9 to −0.5, p = 0.007) and −1.1 kg (95%CI: 1.9 to −0.3, p = 0.007) over three years, respectively. Although baseline age was found to be a significant factor for fat mass change in PD, the associated fat loss estimate was very small (−0.1 kg, 95%CI: 0.3 to 0.0, p = 0.028).

3.5. Factors correlated with subcutaneous and visceral fat mass in PD at three-year follow-up

HOMA-IR showed a significant and moderate-sized positive correlation with both subcutaneous (Spearman's r = 0.381, p = 0.001) and visceral fat mass (Spearman's r = 0.374, p = 0.001) (Supplementary Table 1). Worse constipation correlated moderately with reduced

Table 3
Factors associated with changes in weight and fat mass in Parkinson's disease.

Independent variables	Change in weight (kg)		Change in fat mass (kg)	
	B (95% CI)	P value	B (95% CI)	P value
Change in psychosis severity[a]	−1.3 (−3.8, −0.5)	**0.011**		
Baseline dyskinesia severity[b]	−2.2 (−2.7, 0.0)	0.052		
Baseline constipation severity[c]			−1.7 (−2.9, −0.5)	**0.007**
Change in dyskinesia severity[b]			−1.1 (−1.9, −0.3)	**0.007**
Baseline age			−0.1 (−0.3, 0.0)	**0.028**
Change in constipation severity[c]			−1.0 (−2.1, 0.1)	0.084

Analyses were performed using multiple linear regression models with forward selection method for possible inclusion of 23 independent variables for each dependent variable. Other variables that were excluded for both models were gender, baseline disease duration, and baseline psychosis severity[a]; as well as baseline and changes in: levodopa equivalent daily dosage, physical activity (iPAQ), total calorie intake per day, disease (motor) severity (MDS-UPDRS part III), severity of motor fluctuations (based on the sum of scores for MDS-UPDRS items 4.3, 4.4, 4.5 and 4.6), swallowing difficulty (based on MDS-UPDRS item 2.3), and cognitive function (MoCA).
[a] Based on MDS-UPDRS item 1.2.
[b] Based on the sum of scores for MDS-UPDRS items 4.1 and 4.2.
[c] Based on MDS-UPDRS item 1.11. B = Regression coefficient.

subcutaneous fat mass (Spearman's r = −0.345, p = 0.002), and female gender correlated moderately with reduced visceral fat mass (Spearman's r = −0.427, p < 0.001).

4. Discussion

In this three-year longitudinal prospective study, patients with primarily moderately-advanced PD showed progressive and greater loss of body weight and fat (in both visceral and subcutaneous compartments), but not of muscle mass, compared to non-PD controls. Clinically significant weight loss (≥5% from baseline weight) was recorded in 41.6% of patients, with a doubling of cases classified as underweight (BMI < 18.5 kg/m^2) in 2018. Notably, at three years, nearly one-third and more than one-half of patients had FMI under the 3rd (i.e., a severe fat deficit) and 10th centiles, respectively. These changes occurred in the face of stable self-reported total caloric intake and physical activity level.

Our findings are in agreement with previous cross-sectional case-control studies (n = 22–51) reporting lower body fat mass in PD [14], and a previous longitudinal study in Sweden (n = 26) which recruited a mixed sample of newly diagnosed unmedicated patients as well as more advanced patients, showing (using DXA) loss of body weight and fat over two years follow-up [15]. In contrast, another study of newly-diagnosed patients in Sweden using BIA found significant weight and fat mass increases after three years follow-up [16], and a study from Germany using MRI found numerically higher (albeit not statistically significant) fat volumes after one year (mean disease duration at baseline was not stated; 16/25 (64%) patients were also recorded to gain weight over this period [17]). These observations, taken together with the results of prior studies observing that weight loss in parkinsonism is associated with increasing disease duration or severity and age [2–4], suggest that PD patients may undergo different patterns and directions of body weight/composition alterations according to disease phase, with weight and fat loss featuring more prominently from mid-stages of the disease. Another potentially important source of heterogeneity in PD clinical manifestations and body weight/composition is the effect of ethnicity; for example, studies in the general non-PD population found that Asians had lower BMI but higher percent body fat compared to whites [12,22,23]. To our knowledge, this study is the only one on body composition in Asian PD so far, and further work is needed to make meaningful comparisons between different ethnicities or geographic regions.

In terms of the topology of fat loss, our patients showed loss of both SFM as well as VFM over time. Lower subcutaneous fat in PD compared to controls has been reported in cross-sectional studies [13,17]. The observed loss of VFM in our patients is noteworthy since this is opposite in direction to what normally occurs during ageing [11,12]. The clinical implications of VFM loss in PD are currently unknown. On the one hand, visceral fat is the most diabetogenic and atherogenic fat depot [23], and visceral adiposity is associated with metabolic syndrome (e.g., as expected, in our study VFM correlated with insulin resistance, as measured by HOMA-IR), type 2 diabetes, and cardiovascular disease in the general population [23]. Several of these factors are known to substantially impact on PD risk and progression [22]. On the other hand, a recent report found an association between reduced fat mass and worse motor performance in relatively early-stage PD that appeared to be particularly driven by low android fat mass (a surrogate marker for VFM) [18]. In our study, longer disease duration tended to be correlate with reduced VFM, and further studies are warranted to determine whether this aspect of altered body composition accelerates during the disease course, and the clinical implications of such change. Previous work found an association between female gender and loss of body weight [6]; in our study, female gender was moderately correlated with reduced VFM, suggesting that while monitoring of weight and nutritional status should become a routine part of PD management [1], this group of patients may deserve particular attention. Gender differences in weight and fat loss could be due to differences in hormonal or metabolic regulation, but so far few biochemical studies have investigated these issues in PD [6,9,15].

Constipation is the most frequent clinical manifestation of gastrointestinal dysfunction in PD with prevalence of up to 70% [24]. Contributing factors include reduced fluid intake, sedentary lifestyle, pathological involvement of the enteric nervous system, and medication treatment [22,24]. In this study, baseline constipation severity was independently associated with loss of fat mass, and constipation severity at three-year follow-up showed a moderate correlation with reduced subcutaneous fat. To our knowledge, this has not been reported previously, and builds on previous work associating presence [25] or severity [26] of constipation with poorer nutritional status. While the association between constipation and weight/fat loss could simply be a reflection of greater disease burden (e.g., more extensive neuropathology in the enteric nervous system and hypothalamus, respectively [9]), other explanations (not mutually exclusive) are possible. For example, constipated patients may restrict dietary intake to alleviate abdominal discomfort or bloating [9]. Recently, the role of the colonic microbiome and metabolome in health and disease has gained interest, with possible effects on bowel motility and dietary metabolism that may influence body weight and composition [27]. Importantly, constipation is amenable to treatment [24,28] and thus could potentially be a target for preventing and managing weight/fat loss in PD.

Worsening psychosis and dyskinesia in our patients were also independently associated with loss of body weight and fat mass, respectively; in addition, dyskinesia severity at three-year follow-up correlated with reduced subcutaneous and visceral fat mass. The most parsimonious explanation for these observations is that psychosis and dyskinesia cause weight/fat loss due to reduced food intake (e.g., because of patient preoccupation with hallucinations/delusions to the exclusion of eating, or delusional fear of food being poisoned), and increased energy expenditure (due to involuntary movements). On the other hand, for a given amount of dopaminergic medication administered, reduced body weight/fat can result in disproportionately larger concentrations of drug reaching the brain, which can worsen psychosis and dyskinesia in a dose-dependent fashion. The association between all of these features, which typically occur in more advanced stages of disease, could also reflect increasing disease burden. A number of treatments exist for psychosis and dyskinesia, although these strategies are often only partially successful [22,28].

An inverse relationship between serum IGF-1 and FMI was previously reported in our cross-sectional study [13], as well as in a small study showing higher serum IGF-1 in patients experiencing weight loss; accordingly, IGF-1 has been postulated to contribute to lipolysis and weight loss in PD [13]. We were however unable to find any significant association between serum IGF-1 and body weight or fat parameters in this study. Future studies should examine alterations in other lipolytic factors such as metabolic lipases, cytokines (e.g., IL-6 or TNFα) and hormones (e.g., catecholamines or natriuretic peptides), which have been described in cachexia, a wasting condition associated with cancer but also seen in a variety of non-malignant diseases including neurological disorders [10]. Interestingly, loss of body fat was found to be more rapid than skeletal muscle loss in the early phases of cachexia [10,29], akin to our findings in PD patients. The extent to which poor outcomes associated with weight loss in PD are driven by fat loss, including reduced survival [3] (as observed in cancer cachexia [30]) also warrants further study.

The main limitation of our study was limited sample size from a single centre, although this is currently the largest cohort of PD patients undergoing longitudinal analysis of body composition. Because we did not want to impose a heavy burden on patients, and to avoid participant fatigue, not all clinical factors that could potentially have an impact on weight and body composition changes were studied, such as hyposmia [6]. The list of comorbidities studied was not exhaustive and use of a comprehensive scale for measurement of overall comorbidity burden,

such as the Charlson Comorbidity Index (CCI) [31], should be considered in future studies. Although using spouses or siblings as controls has certain advantages (to a large extent they share with patients the same ethnicity, living environment, dietary pattern, and lifestyle - factors which may significantly influence body composition) [13], this recruitment method resulted in some imbalance in age and gender between the patient and control groups. These effects were statistically adjusted for, but these differences may still bias the results in our study. Finally, using reference curves derived from a Caucasian population for FMI categorization was not ideal [13], but reliable normative data on body composition from the Asian population are currently lacking.

Study strengths include high (> 80%) patient retention for a three-year study with broad recruitment eligibility criteria involving primarily moderately-advanced patients from a real-world clinic setting. We used DXA, a preferred, simple, and reliable method to assess body composition, which also enabled analysis of different body compartments (e.g., SFM vs. VFM) [23]. Clinical-demographic data were carefully collected (e.g., detailed dietary history was obtained, and all MDS-UPDRS motor ratings were administered by a single expert rater), and adjusted for potential confounding in the analysis.

Although not powered to examine mortality outcomes, it was notable in our study that the three-year patient mortality was 16% for those with FMI < 10th centile at baseline, which was 3-fold higher than those with FMI ≥ 10th centile. Given the numerous serious negative outcomes associated with weight loss highlighted by other investigators [1,3–8], further research efforts into this area are urgently needed, particularly interventional studies. It will be important to determine, for example, whether personalized nutritional advice and/or administration of fat-, carbohydrate- or protein-enriched supplements can improve nutritional status, function, quality of life, and survival in PD. The future may see testing of agents acting on appetite-stimulating, sex hormone, growth hormone/IGF-1, metabolic lipase and/or inflammatory pathways [10,12,32]. Different approaches may need to be adapted to different patients, at different points in their disease course. Meanwhile, monitoring weight and nutritional status, and better education and engagement of patients and families regarding these aspects, should become part of the total care of people with PD [1,28].

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Authors' contribution

Conception and design of the study: AH Tan, SY Lim, M Grossmann, NM Ramli.

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Analysis and interpretation of data: AH Tan, VW Yong, SY Lim, K Chinna, MNM Shah, RRAR Aman, NM Ramli, M Grossmann, FM Moy.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

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