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Original article

Low cardiometabolic risk in Parkinson's disease is independent of nutritional status, body composition and fat distribution☆

Emanuele Cereda [a,b,*], Erica Cassani [a], Michela Barichella [a], Angela Spadafranca [c], Riccardo Caccialanza [b], Simona Bertoli [a,b], Alberto Battezzati [a,b], Gianni Pezzoli [a]

[a] Parkinson Institute, Istituti Clinici di Perfezionamento, Milano, Italy
[b] Nutrition and Dietetics Service, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[c] International Center for the Assessment of Nutritional Status (ICANS), Dipartimento di Scienze e Tecnologie Alimentari e Microbiologiche (DISTAM), Università degli Studi di Milano, Milano, Italy

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SUMMARY

Background & aims: To investigate if the reduced cardiometabolic risk in Parkinson's disease (PD) is independent of nutritional status, body composition and fat distribution.
Methods: We designed a case–control study comparing 80 non underweight PD patients with 80 controls matched for sex, age and body mass index (BMI). Nutritional assessment included: anthropometry (BMI and waist circumference [WC]), body composition estimated by impedance and biochemistry (fasting glucose, serum lipids and transaminases). The presence of arterial hypertension, diabetes mellitus and metabolic syndrome (MetS) were noted.
Results: Compared to controls and independently of gender, PD patients showed lower percentage of body fat ($P < 0.001$) and biochemical parameters (glucose, $P < 0.001$; total cholesterol, $P < 0.001$; LDL, $P < 0.001$; triglycerides, $P = 0.002$; alanine aminotransferase, $P < 0.001$ and aspartate aminotransferase, $P = 0.015$) but similar WC ($P = 0.324$). The prevalence of hypertension and MetS was similar in the two groups, as well as the frequency and the number of MetS criteria. The relationship between PD and low cardiometabolic profile was independent of age, gender, current smoking and BMI. After adjusting for WC and body fat, most of the associations remained significant.
Conclusions: PD patients seem to have a more favorable cardiometabolic risk profile, independently of nutritional status, body composition and fat distribution.

1. Introduction

Parkinson's disease (PD) is a chronic neurodegenerative motor disorder affecting 1 out of 800 people all over the world.[1]

Typical motor symptoms (bradykinesia, resting tremor, rigidity and postural instability), together with complications or consequences of both pharmacological and non-pharmacological treatments may cause changes in food intake, lifestyle and energy requirements associated with weight loss or weight gain.[2] Previous studies have reported that the prevalence of overweight and obesity among PD patients changes during the course of disease.[2–4] An Italian population study has shown that the prevalence of obesity among PD patients is about 50% higher than that in the general reference population.[3] However, it has also been observed that body mass index (BMI) progressively decreases during the course of the disease and that undernutrition may also occur.[3] Indeed, the limited literature available suggests that fluctuations in body weight are mainly due to changes in fat mass, which are gender-specific to some extent.[5–7]

Cardiovascular disease (CVD) still remains the main cause of mortality in the general population and the occurrence has been linked to body weight excess through the adverse effect of adipose-tissue-related complications such as hypertension, diabetes and dylipiudemia.[8,9] Despite the higher prevalence of overweight and obesity, PD patients appear to be less susceptible to CVD,[10,11] but the mechanisms behind this protection have been scantily investigated. In a previous retrospective case–control study[12] it was found that the prevalence of CV risk factors in PD patients is significantly lower than in sex and age-matched controls and the

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* Corresponding author. Nutrition and Dietetics Service, Fondazione IRCCS Policlinico San Matteo, Viale Golgi 19, 27100 Pavia, Italy. Tel.: +39 0382 501615; fax: +39 0382 502801.
E-mail address: e.cereda@smatteo.pv.it (E. Cereda).

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reduced autonomic activity has been fingered as one of the potential explanations for the phenomenon.[12,13] However, the effect of other confounders, such as nutritional status, adiposity and its distribution over the body, has not been investigated. This is particularly intriguing because not only total and abdominal adiposity have been associated with cardiometabolic risk and the risk of death[14,15] but also because body fat mass, particularly visceral adipose tissue (VAT), have been associated also with chronic neurodegeneration.[16]

Aim of our case–control study was to evaluate the relationship between low cardiometabolic risk in PD and nutritional status, body composition and body fat distribution.

2. Methods and procedures

The study was performed in agreement with the principles of the Declaration of Helsinki. The protocol was approved by the local Ethics Committees and written informed consent was obtained from every patient recruited. All patients underwent a complete nutritional assessment and medical examination, including blood pressure measurement. Information on smoking history and pharmacological treatment was also collected.

All the evaluations were performed early in the morning and in fasting conditions. PD patients were assessed after taking PD medications in order to avoid any bias due to movement disorders (e.g. rigidity or resting tremor) which could theoretically affect some evaluations (e.g. height and body composition).

The exclusion criteria were: refusal to give informed consent, use of lipid-lowering medications, thyroid disease, viral hepatitis (B or C; by appropriate serological markers), body weight changes in the previous 6 months, neurosurgical procedure for PD (deep brain stimulation or pallidotomy). Patients who were overtly underweight (BMI < 18.5 kg/m^2)[17] were also excluded, because they are obviously less likely to present an adverse cardiometabolic risk profile. Along with this, low body weight or malnutrition in PD patients is likely to be due to the combination of increased energy expenditure produced by dyskinetic movements and inadequate food intake,[3,18] while in the general population it usually is the result of disease-related inflammatory disorders and inadequate food intake.[19]

2.1. PD patients

From January 2008 to January 2010, eighty patients with a diagnosis of PD according to UK Brain Bank criteria[20] living in the community, who were admitted to the Parkinson Institute for periodic disease reassessment (elective hospital stay), and fullfilled the inclusion criteria, were consecutively recruited.

2.2. Controls

During the same period, sedentary controls ($n = 80$) matched in pairs for age (± 3 years), gender and BMI (± 1 kg/m^2) were recruited among the population of subjects attending the International Center for the Assessment of Nutritional Status for weight concerns.

2.3. Nutritional assessment

The procedures included were:

Anthropometry. Subjects were wearing only underwear. Height (to the nearest 0.5 cm) and body weight (to the nearest 0.1 kg) were measured by the same calibrated scale equipped with a telescopic vertical steel stadiometer (SECA 711; Germany). For those patients with evident spinal cord deformities height was derived by validated equations.[21] Afterward, the body mass index (BMI) was calculated as the ratio between weight [kg] and height [m] squared (kg/m^2).[17] Waist circumference (WC; to the nearest 0.5 cm) was measured through plastic flexible tape-measures at the midpoint between the lowest rib and the iliac crest, placing the tape perpendicular to the long axis of the body and parallel to the floor.[17,22] Also skinfold thickness (SFT; by a Holtain caliper to the nearest 0.2 mm – Holtain LTD, Crymych, UK) was measured at four sites (biceps, triceps, subscapular and suprailiac) to better evaluate subcutaneous fat deposition. The sum of all skinfolds was considered in the analysis. All anthropometric measurements were performed in triplicate according to standard procedures[17] and the mean of three values was considered in the analysis.

Biochemistry. Venous blood samples were drawn after 8–12 h of fasting and the following parameters were assessed using conventional automated analyzers: glucose, total cholesterol, high and low density lipoprotein cholesterol (HDL and LDL, respectively), triglycerides, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values.

Body composition. Whole-body resistance was measured at frequencies of 50 kHz (R_{50}), following international guidelines and using four-polar impedance meters (Tanita Segmental Multifrequency Body Composition Monitor, MC 180 MA, Sensormedics, Milan, Italy [at the Parkinson Institute] or Human IM Scan, DS-Medigroup, Milan, Italy [at the International Center for the Assessment of Nutritional Status]). Fat-free mass (FFM; kg) was then calculated using R_{50} values according to the formula for healthy adults proposed by Deurenberg et al.[23] FFM was then normalized for height to calculate the FFM index (FFMI; FFM [kg] and height [m] squared [kg/m^2]) according to Pichard et al.[24] Percentage of body fat mass (BF%) was also derived.

2.4. Cardiometabolic profile

The cardiometabolic profile was based on biochemical parameters (total cholesterol, HDL, LDL, triglycerides, glucose, ALT and AST), established comorbidities (arterial hypertension and diabetes mellitus) and the presence of metabolic syndrome (MetS+). Comorbidities were defined as follows: arterial hypertension as repeated blood pressure measurements $\geq$140/90 mmHg or the reported use of antihypertensive medications; diabetes as at least two blood glucose measurements $\geq$126 mg/dL or reported antidiabetic treatment. The National Cholesterol Education Program's Adult Treatment Panel III criteria[25] were used to define MetS+. Accordingly, subjects had to have $\geq$3 of the following: (1) WC $>$102 cm in men and $>$88 cm in women; (2) serum triglycerides $\geq$150 mg/dL; (3) HDL cholesterol $<$40 mg/dL in men and $<$50 mg/dL in women; (4) blood pressure $\geq$130/85 mmHg; and (5) fasting plasma glucose level $\geq$110 mg/dL. The total number of criteria was also considered in the analyses.

2.5. Statistical analysis

Statistical analyses were performed by MEDCALC® for Windows Version 11.3.0.0 (MedCalc Software, Mariakerke, Belgium), setting the level of significance at a two-tailed P-value <0.05.

Continuous variables are reported as mean and standard deviation (in case of normal distribution), or median and interquartile range (25th–75th percentile; in case of non normal distribution). The Kolmogorov–Smirnov test was used to test for normal distribution of the data. Categorical variables were presented as counts and percentages.

Descriptive and parametric statistics were initially considered before and after categorizing both PD patients and controls on the basis of:

- gender;
- nutritional status by thresholds of BMI (kg/m^2; normal weight, 18.5 ≤ BMI < 25; overweight, 25 ≤ BMI < 30; obesity, BMI ≥ 30)[11].

Categorical variables were compared by the Chi-square test (when expected counts >10) or Fisher's exact test (when expected counts <10), while between-group comparisons for continuous variables were performed by Student's *t*-test (two groups) and ANOVA analysis (multiple groups). In particular, ANOVA was used for cardiometabolic parameters (continuous variables) set as dependent variables, and BMI groups and PD and their 2-way interactions as independent variables. Bonferroni's correction was used for post-hoc comparisons.

Multivariable regression models were constructed to fully evaluate the relationship between cardiometabolic risk parameters and PD. Linear and logistic regression analyses were considered for the evaluation of continuous (glucose, total cholesterol, HDL, LDL, triglycerides, and the number of MetS criteria) and categorical variables (hypertension, diabetes and MetS+), respectively. Accordingly, data were presented as coefficient of regression (linear model) or odds ratio (OR) and their 95% confidence intervals (95% CI). Prior to inclusion in the models, collinearity between variables was assessed through the Pearson's statistic. Analyses were initially adjusted for age, gender, smoking and BMI. Therefore, BF% and WC were included as additional confounders in secondary analyses.

3. Results

In total, 107 PD patients were admitted to the Parkinson Institute consecutively and were screened for study inclusion. In agreement with previous studies,[3,4] the distribution of patients among nutritional status categories was as follows: underweight, 5.6%; normal weight, 40.2%; overweight, 35.5%; obesity, 18.7%. We excluded 27 patients for the following reasons: underweight ($n = 6$), thyroid disease ($n = 7$), use of lipid-lowering drugs ($n = 6$), previous neurosurgical procedure ($n = 2$), body weight change over the last 6 months ($n = 4$), viral hepatitis ($n = 2$).

Median duration of disease in our PD population was 9 years [25th–75th, 4–13 years]. Most PD patients were taking levodopa (90%; dose, mean ± SD: 542 ± 272 mg [range: 150–1350 mg]), either alone (27.8%) or in combination with other therapies. The proportions of patients who were taking other pharmacological treatment were: dopamine agonists (53.8%; pramipexole, ropinirole or apomorphine), MAO inhibitors (20%; rasagiline or selegiline), COMT inhibitors (13.8%; entacapone), amantadine (5%), anticholinergic drugs (2.5%; biperidene).

The features of the study population are presented in Table 1. Compared to controls, PD patients were characterized by a more favorable body composition, with reduced BF% and total SFT, and higher FFMI, even in the presence of comparable WC. PD patients also had lower blood levels of glucose, total and LDL cholesterol, triglycerides, AST and ALT than controls, while the prevalence of diabetes, hypertension and MetS, as well as the frequency and the mean number of MetS criteria were similar. Only the prevalence of increased triglyceride values (>150 mg/dL) was significantly lower (11.3% vs. 30%; $P < 0.01$). The prevalence of other MetS criteria in PD patients and controls were: large WC, 65% vs. 60%; high fasting plasma glucose or diabetes, 7.5% vs. 10%; low HDL, 20% vs. 12.5% ($P > 0.05$ for all), respectively.

Gender-specific analyses showed that the differences in body composition and biochemical variables between PD patients and controls were observed in both genders, except for triglycerides and AST blood levels in women, which were similar in the two groups, even in the presence of larger WC (Table 1).

3.1. Nutritonal status and cardiometabolic profile (Table 2)

According to WHO criteria, the prevalence of overweight and obesity in both groups was 47.5% and 25% (moderate-to-severe obesity [BMI ≥ 35 kg/m^2], 8.8%), respectively. ANOVA analyses for the effect of BMI and PD on cardiometabolic parameters showed that, regardless of nutritional status, PD patients are characterized by lower blood levels of fasting glucose, total and LDL cholesterol, triglycerides, AST and ALT, even in the presence of higher WC. No effect of PD was found on the prevalence of hypertension, diabetes and MetS. Moreover, nutritional status in PD patients was related only to plasma glucose and MetS criteria, while in controls BMI categorization enabled us to detect differences in HDL, LDL and the number of MetS criteria.

Table 1
Features of Parkinson's disease patients and controls by gender.

	Overall			Males			Females		
	PD ($n = 80$)	Controls ($n = 80$)	P^a	PD ($n = 42$)	Controls ($n = 42$)	P^a	PD ($n = 38$)	Controls ($n = 38$)	P^a
Age (years)	61.5 ± 10.2	58.6 ± 9.1	0.063	62.2 ± 10.1	59.9 ± 9.8	0.285	60.7 ± 10.4	57.3 ± 8.2	0.113
Current smoking (*n*, [%])	5 [6.3]	20 [25]	0.002	2 [4.7]	10 [23.8]	0.029	3 [7.9]	10 [26.3]	0.033
Body mass index (Kg/m^2)	27.6 ± 5.1	28.3 ± 4.6	0.381	27.9 ± 4.3	28.9 ± 4.3	0.185	27.6 ± 6.0	27.6 ± 4.8	0.977
Fat-free mass index (kg/m^2)	19.9 ± 2.7	18.3 ± 2.4	<0.001	21.2 ± 1.8	19.7 ± 1.8	<0.001	16.7 ± 2.7	18.3 ± 1.8	0.005
Body fat mass (%)	26.6 ± 9.8	34.8 ± 8.0	<0.001	21.2 ± 6.8	31.0 ± 7.3	<0.001	31.8 ± 10.3	38.8 ± 6.8	0.002
Sum of skinfolds (mm)	86.8 ± 35.2	98.0 ± 31.3	0.038	81.6 ± 32.5	88.4 ± 26.7	0.300	93.1 ± 37.7	108.6 ± 32.9	0.067
Waist circumference (cm)	98.0 ± 13.8	100.1 ± 13.2	0.324	103.9 ± 13.4	101.6 ± 12.0	0.415	98.4 ± 14.1	91.4 ± 11.3	0.022
Glucose (mg/dL)	86.5 ± 12.6	96.6 ± 18.6	<0.001	89.5 ± 14.6	100.0 ± 23.2	0.016	82.3 ± 7.6	92.7 ± 10.6	<0.001
Total cholesterol (mg/dL)	186.1 ± 30.9	220.8 ± 34.8	<0.001	182.1 ± 29.6	221.5 ± 38.8	<0.001	191.3 ± 32.3	220.1 ± 30.3	<0.001
HDL cholesterol (mg/dL)	52.9 ± 15.3	55.9 ± 12.7	0.206	48.4 ± 15.3	50.0 ± 12.7	0.489	59.3 ± 17.2	62.3 ± 13.6	0.429
LDL cholesterol (mg/dL)	113.0 ± 30.0	139.2 ± 31.8	<0.001	113.3 ± 27.6	141.8 ± 34.7	<0.001	112.7 ± 33.5	136.1 ± 28.2	0.004
Triglycerides (mg/dL)	102.1 ± 38.1	128.3 ± 60.8	0.002	105.5 ± 43.6	148.3 ± 69.3	0.002	97.4 ± 29.2	104.9 ± 38.3	0.400
AST (UI/dL)	18.1 ± 6.4	21.8 ± 10.2	0.015	18.8 ± 7.1	24.5 ± 11.9	0.012	17.1 ± 5.3	17.6 ± 4.5	0.766
ALT (UI/dL)	15.1 ± 7.4	25.3 ± 14.9	<0.001	15.9 ± 7.9	29.2 ± 17.9	<0.001	14.1 ± 6.7	20.8 ± 8.8	0.002
Diabetes (*n*, [%])	2 [2.5]	4 [5]	0.439	1 [2.4]	3 [7.1]	0.608	12 [2.6]	1 [2.6]	1.0
Hypertension (*n*, [%])	25 [31.3]	31 [38.8]	0.320	13 [30.9]	16 [38.1]	0.491	12 [31.6]	15 [39.5]	0.472
MetS+ (*n*, [%])	15 [18.8]	22 [27.5]	0.189	10 [23.8]	16 [38.1]	0.157	5 [13.1]	6 [15.8]	1.0
MetS criteria (n)	1.6 ± 1.0	1.7 ± 1.3	0.405	1.7 ± 1.0	2.0 ± 1.3	0.167	1.4 ± 1.0	1.3 ± 1.1	0.741

Data are reported as mean ± standard deviation or counts [%].
Abbreviations: **PD**, Parkinson's disease; **HDL**, high density lipoprotein; **LDL**, low density lipoprotein; **AST**, aspartate aminotransferase; **ALT**, alanine aminotransferase; **MetS**, metabolic syndrome.
[a] *P*-values according to Student's *t*-test or Chi-square test or Fisher's exact test.

Table 2
Features of Parkinson's disease patients and controls by nutritional status expressed as body mass index.

	Parkinson's disease			Controls			*P*-values		
	NW ($n = 22$)	OW ($n = 38$)	OB ($n = 20$)	NW ($n = 22$)	OW ($n = 38$)	OB ($n = 20$)	P^a	P^b	P^c
Males (n, [%])	9 [40.9]	20 [52.6]	13 [65]	9 [40.9]	20 [52.6]	13 [65]	0.956		
Age (years)	56.8 ± 7.5	65.4 ± 9.1[d]	59.4 ± 12.4	53.3 ± 7.4	62.5 ± 8.0[d]	57.1 ± 9.5	<0.001	0.052	0.958
Body mass index (kg/m^2)	22.3 ± 1.9[d]	27.3 ± 1.3[d]	34.7 ± 4.3[d]	23.3 ± 1.6[d]	27.9 ± 1.2[d]	34.6 ± 3.1[d]	<0.001	0.190	0.516
Fat-free mass index (kg/m^2)	17.8 ± 1.8[d]	19.7 ± 2.3[d]	23.1 ± 1.2[d]	16.6 ± 1.8[d]	17.9 ± 1.8[d]	20.8 ± 1.8[d]	<0.001	<0.001	0.418
Body fat mass (%)	19.4 ± 8.5[d]	27.9 ± 8.7	33.2 ± 7.7	28.3 ± 7.5[d]	35.9 ± 6.6[d]	39.5 ± 6.9[d]	<0.001	<0.001	0.731
Sum of skinfolds (mm)	58.7 ± 24.7[d]	86.4 ± 29.9[d]	118.8 ± 26.6[d]	72.1 ± 19.8[d]	99.1 ± 29.5[d]	124.4 ± 20.9[d]	<0.001	0.018	0.753
Waist circumference (cm)	87.3 ± 9.6	98.9 ± 7.2	117.8 ± 8.0	84.0 ± 7.3	98.3 ± 8.7	112.8 ± 7.4	<0.001	0.026	0.357
Glucose (mg/dL)	79.7 ± 6.2[d]	88.1 ± 14.0	92.1 ± 12.6	91.4 ± 13.0	101.2 ± 23.7	93.4 ± 8.5	0.013	0.002	0.184
Total cholesterol (mg/dL)	184.0 ± 35.0	186.4 ± 29.6	188.3 ± 129.6	212.3 ± 29.6	227.6 ± 34.9	217.5 ± 39.0	0.400	<0.001	0.529
HDL cholesterol (mg/dL)	55.3 ± 15.3	53.3 ± 16.8	49.0 ± 12.2	65.4 ± 14.4[d]	52.5 ± 8.9	51.8 ± 11.9	0.003	0.083	0.124
LDL cholesterol (mg/dL)	109.3 ± 31.3	112.3 ± 29.7	119.7 ± 29.9	126.1 ± 25.5	147.5 ± 30.7[d]	137.5 ± 36.0	0.120	<0.001	0.228
Triglycerides (mg/dL)	96.6 ± 41.0	102.1 ± 32.3	110.0 ± 46.2	104.9 ± 44.3	134.8 ± 60.8	140.6 ± 71.1	0.096	0.009	0.459
AST (UI/dL)	17.1 ± 5.0	18.8 ± 7.8	17.9 ± 4.5	19.0 ± 4.7	22.9 ± 13.3	23.9 ± 5.0	0.229	0.016	0.646
ALT (UI/dL)	14.7 ± 8.1	15.2 ± 8.0	15.6 ± 5.2	20.6 ± 8.5	26.3 ± 16.6	30.1 ± 17.2	0.185	<0.001	0.314
Hypertension (n, [%])	4 [18.2]	14 [36.8]	7 [35]	4 [18.2]	15 [39.5]	12 [60]	0.699		
MetS+ (n, [%])	0 [0][d]	6 [15.8]	9 [45]	0 [0][d]	13 [34.2]	9 [45]	0.254		
MetS criteria (n)	1.0 ± 0.8	1.6 ± 0.9	2.3 ± 0.8[d]	0.7 ± 0.7[d]	1.9 ± 1.2	2.5 ± 1.1	<0.001	0.619	0.133

Data are reported as mean ± standard deviation or counts [%].
Abbreviations: **NW**, normal weight; **OW**, overweight; **OB**, obesity; **HDL**, high density lipoprotein; **LDL**, low density lipoprotein; **AST**, aspartate aminotransferase; **ALT**, alanine aminotransferase; **MetS**, metabolic syndrome.
[a] *P*-values according to body mass index categories by two-way ANOVA or test for independence according to body mass index categories and PD (Chi-square or Fisher's tests).
[b] Effect for Parkinson's disease according to two-way ANOVA.
[c] Effect for interaction (Parkinson's disease × body mass index) according to two-way ANOVA.
[d] Significantly different from the other BMI categories within the same population group by post-hoc comparison or association test (Chi-square or Fisher's tests).

3.2. Multivariable regression analyses

Primary analyses showed that PD patients are characterized by lower blood levels of fasting glucose, total and LDL cholesterol, triglycerides, AST and ALT (Table 3). Also the lack of association between PD and hypertension (OR = 0.83 [95% CI, 0.30–2.28], $P = 0.714$), diabetes (OR = 0.11 [95% CI, 0.01–2.11], $P = 0.141$) and MetS+ (OR = 0.22 [95% CI, 0.75–2.55], $P = 0.644$) were confirmed. Analyses were additionally adjusted for BF% and WC due to their slight collinearity ($r = 0.36$). BMI was removed from the models, because it was too highly correlated with BF% ($r = 0.60$) and WC ($r = 0.84$). All the associations found remained significant, with the exception of the association with HDL. The results of logistic regression analyses were consistent with the findings described above.

4. Discussion

In the present study, we confirmed previous findings[5,6] showing that PD patients are characterized by lower BF% than healthy controls, mainly due to reduced subcutaneous adipose tissue. We also demonstrated for the first time that this occurs regardless of nutritional status. It could be argued that low BF mass should result in a healthier cardiometabolic profile[9,14] but the main finding of our study was that the better cardiometabolic profile of PD is unrelated to nutritional status, body composition and fat distribution, even in the presence of comparable degrees of abdominal weight accumulation. Nonetheless, the prevalence of hypertension, diabetes and MetS was similar.

It should be recognized from the outset that the strength of our results is partly limited by the case–control design. However, although a cautious interpretation is suggested, the magnitude of the effect of PD on cardiometabolic profile and previous literature allow supporting and substantiating our findings.

Adipose tissue, especially in the abdominal region, is associated with an increase in the risk of several disorders, such as insulin resistance up to diabetes, hyperlipidemia, hypertension, fatty liver disease, chronic low-grade inflammation and, ultimately, CVD.[15,26–28] Cytokine over-production and release by the VAT and sympathetic over-activity within this fat compartment have been invoked as major promoters of overweight-related complications.[9,14,29,30]

Table 3
Multivariable linear regression models testing the association between Parkinson's disease (independent variable) and cardiometabolic risk factors (dependent variables).

Dependent variable	Model 1[a]		Model 2[b]	
	Effect for PD		Effect for PD	
	Coefficient [95% CI]	*P*-value	Coefficient [95% CI]	*P*-value
Glucose (mg/dL)	−9.6 [−15.0, −4.4]	<0.001	−8.1 [−15.1, −1.1]	0.027
Total cholesterol (mg/dL)	−32.1 [−43.6, −20.6]	<0.001	−30.7 [−45.3, −16.1]	<0.001
HDL cholesterol (mg/dL)	−4.1 [−8.3, 0.1]	0.053	−3.1 [−8.5, 2.3]	0.272
LDL cholesterol (mg/dL)	−22.7 [−33.6, −11.8]	<0.001	−23.1 [−36.9, −9.3]	0.001
Triglycerides (mg/dL)	−20.9 [−38.2, −3.6]	0.017	−16.4 [−32.1, −0.7]	0.048
AST (UI/dL)	−4.3 [−7.3, −1.3]	0.006	−4.0 [−7.7, −0.3]	0.050
ALT (UI/dL)	−10.5 [−14.7, −6.4]	<0.001	−9.1 [−14.5, −3.7]	0.001
MetS criteria (n)	−0.1 [−0.3, 0.1]	0.605	−0.1 [−0.5, 0.3]	0.448

Abbreviations: **PD**, Parkinson's disease; **Coeff.**, coefficient (change for PD); **95% CI**, 95% confidence interval; **HDL**, high density lipoprotein; **LDL**, low density lipoprotein; **AST**, aspartate aminotransferase; **ALT**, alanine aminotransferase; **MetS**, metabolic syndrome.
[a] Models adjusted for sex, age, smoking status and body mass index.
[b] Models adjusted for sex, age, smoking status, percentage of body fat and waist circumference.

It seems likely that VAT is less metabolically active in PD. Scigliano et al. have reported a reduced prevalence of vascular risk factors, supporting the hypothesis that idiopathic PD is a natural model of generalized sympathetic denervation,[12,13] associated with decreased catecholamine availability in the adrenal medulla.[31,32] Sympathetic modulation could be also a consequence of levodopa treatment.[13] It has been suggested that dopamine may inhibit catecholamine release by the peripheral nervous system in levodopa-treated patients,[33,34] thus reducing a number of catecholamine effects, such as inhibition of insulin secretion and stimulation of glucagon release resulting in hyperglycemia,[14,35,36] altered glucose uptake by the skeletal muscle[25,26] and free fatty acid mobilization from VAT.[14,35] Levodopa induces also the secretion of growth hormone (GH).[37] Visceral obesity is associated with impaired GH and IGF-1 secretions, which have been associated with an abnormal metabolic phenotype, inflammation and pronounced vascular disease that could be significantly improved by GH replacement therapy.[14,38–40] Along with this, it cannot be excluded that dyskinesias induced by long-term levodopa treatment contribute to the improvement in both lipid profile and insulin resistance via physical activity.[41] Unfortunately, we did not assess insulin resistance, inflammatory markers, the GH- IGF-1 axis and urinary catecholamines. These parameters would have contributed to make stronger the results. Also physical activity was not evaluated. However, it is unlikely that this variable differed between patients and controls, because controls were sedentary and PD patients become progressively disabled during the course of the disease.

We observed a similar prevalence of hypertension among PD patients and controls, a result that appears inconsistent with previous findings.[12] Dopaminergic activity should result in vasodilatation and reduced vascular tone.[33,34,42] However, levodopa treatment is not associated with lower blood pressure.[13] In their first case–control study, Scigliano et al. acknowledged that hospital controls were unwell and might have had an abnormally high prevalence of vascular risk factors.[12] However, analyses were not adjusted for BMI and in our study underweight patients were excluded. A similar explanation could also account for the similar prevalence of diabetes, although it could be argued that the small sample size may account for the lack of a significant difference.

Finally, the finding of a similar prevalence of MetS could be partly explained by the fact that large waist and hypertension were the most frequent criteria in our study groups. Nonetheless, also the prevalence of MetS was low. However, we do not know how useful the current thresholds for CV risk factors (large waist, fasting glucose, low HDL, etc.) and diagnosing MetS really are in the PD patient population. Prospective studies may provide more exhaustive indications for clinical practice.

In interpreting the results of this study, other limitations should be considered. First, the PD group considered was not representative of the whole patient population. However, we believe that the exclusion of several confounders through strict inclusion criteria should be considered a strength from a pathophysiological point of view. Along with this, in most case–control studies, it is not possible to rule out inclusion bias. In our study the controls were subjects admitted to a medical center because of excessive body weight, a condition that often is associated with other disorders. However, the comorbidity rates were similar to those in the general population.[43] Second, the assessment of body composition by BIA may be associated with estimation errors (both over- or underestimation) which relate to variations in hydration status that occur with aging and moderate-to-severe weight excess.[44] However, few patients included in our study had BMI $\geq$ 35 kg/m^2. Third, the use of WC as a surrogate of VAT is also a potential limitation. However, its effect should be small, as VAT has been found to be robustly correlated with WC measurements using reliable imaging techniques.[45,46] Finally, we did not evaluate dietary factors, which are also potentially involved in plasma glucose and lipid abnormalities.[47] However, the bias deriving from this factor may be reasonably excluded, because the diet of PD patients is similar to that of the general population.[48]

In conclusion, PD patients seem to have a more favorable cardiometabolic risk profile, independently of nutritional status, body composition and fat distribution. This suggests that metabolic activity within adipose tissue is low. Future research should focus on other adipose tissue-related variables such as insulin resistance and inflammatory markers. Finally, the implications of this profile for health outcomes deserve further investigation.

Statement of authorship

All authors significantly contributed to the work, and read and approved the final version of the manuscript. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. In particular, contributions were as follows:

Study design: E. Cereda, M.B., G.P.

Data collection: E. Cereda, E. Cassani, A.S., M.B., S.B., A.B.

Data analyses: E. Cereda, A.S.

Data interpretation: E. Cereda, M.B., R.C., G.P.

Manuscript drafting: E. Cereda.

Critical revision of the manuscript: E. Cereda, M.B., R.C., S.B., A.B., G.P.

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Conflict of interest

All the Authors certify that there are no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript.

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References

1. Lees AJ, Hardy J, Revesz T. Parkinson’s disease. *Lancet* 2009;**373**:2055–66.
2. Barichella M, Cereda E, Pezzoli G. Major nutritional issues in the management of Parkinson’s disease. *Mov Disord* 2009;**24**:1881–92.
3. Barichella M, Marczewska A, Vairo A, Canesi M, Pezzoli G. Is underweightness still a major problem in Parkinson’s disease patients? *Eur J Clin Nutr* 2003;**57**:543–7.
4. Barichella M, Villa MC, Massarotto A, Cordara SE, Marczewska A, Vairo A, et al. Mini nutritional assessment in patients with Parkinson’s disease: correlation between worsening of the malnutrition and increasing number of disease-years. *Nutr Neurosci* 2008;**11**:128–34.
5. Markus HS, Tomkins AM, Stern GM. Increased prevalence of undernutrition in Parkinson’s disease and its relationship to clinical disease parameters. *J Neural Transm Park Dis Dement Sect* 1993;**5**:117–25.
6. Beyer PL, Palarino MY, Michalek D, Busenbark K, Koller WC. Weight change and body composition in patients with Parkinson’s disease. *J Am Diet Assoc* 1995;**95**:979–83.
7. Montaurier C, Morio B, Bannier S, Derost P, Arnaud P, Brandolini-Bunlon M, et al. Mechanisms of body weight gain in patients with Parkinson’s disease after subthalamic stimulation. *Brain* 2007;**130**(Pt 7):1808–18.
8. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the

Identification, Evaluation, and Treatment of Overweight in Adults. *Am J Clin Nutr* 1998;**68**:899–917.
9. The obesity epidemic: strategies in reducing cardiometabolic risk. *Am J Med* 2009;**122**(4 Suppl. 1):S1–52.
10. Fall PA, Saleh A, Fredrickson M, Olsson JE, Granérus AK. Survival time, mortality, and cause of death in elderly patients with Parkinson's disease: a 9-year follow-up. *Mov Disord* 2003;**18**:1312–6.
11. Beyer MK, Herlofson K, Arsland D, Larsen JP. Causes of death in a community-based study of Parkinson's disease. *Acta Neurol Scand* 2001;**103**:7–11.
12. Scigliano G, Musicco M, Soliveri P, Piccolo I, Ronchetti G, Girotti F. Reduced risk factors for vascular disorders in Parkinson disease patients: a case-control study. *Stroke* 2006;**37**:1184–8.
13. Scigliano G, Ronchetti G, Girotti F, Musicco M. Sympathetic modulation by levodopa reduces vascular risk factors in Parkinson disease. *Parkinsonism Relat Disord* 2009;**15**:138–43.
14. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. *Endocr Rev* 2000;**21**:697–738.
15. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med* 2008;**359**:2105–20.
16. Cereda E, Sansone V, Meola G, Malavazos AE. Increased visceral adipose tissue rather than BMI as a risk factor for dementia. *Age Ageing* 2007;**36**:488–91.
17. World Health Organization. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser* 1995;**854**:1–452.
18. Cereda E, Pezzoli G, Barichella M. Role of an electronic armband in motor function monitoring in patients with Parkinson's disease. *Nutrition* 2010;**26**:240–2.
19. Cereda E, Pedrolli C. The geriatric nutritional risk index. *Curr Opin Clin Nutr Metab Care* 2009;**12**:1–7.
20. Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improves the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. *Neurology* 2001;**57**(Suppl. 3):S34–8.
21. Cereda E, Bertoli S, Battezzati A. Height prediction formula for middle-aged (30–55 y). *Caucasians Nutr* 2010;**26**:1075–81.
22. Wang J, Thornton JC, Bari S, Williamson B, Gallagher D, Heymsfield SB, et al. Comparisons of waist circumferences measured at 4 sites. *Am J Clin Nutr* 2003;**77**:379–84.
23. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al, Composition of the ESPEN Working Group. Bioelectrical impedance analysis–part I: review of principles and methods. *Clin Nutr* 2004;**23**:1226–43.
24. Pichard C, Kyle UG, Morabia A, Perrier A, Vermeulen B, Unger P. Nutritional assessment: lean body mass depletion at hospital admission is associated with an increased length of stay. *Am J Clin Nutr* 2004;**79**:613–8.
25. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCPE) Expert Panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001:2486–97.
26. Stump CS, Henriksen EJ, Wei Y, Sowers JR. The metabolic syndrome: role of skeletal muscle metabolism. *Ann Med* 2006;**38**:389–402.
27. Ritchie SA, Connell JMC. The link between abdominal obesity, metabolic syndrome and cardiovascular disease. *Nutr Metab Cardiovasc Dis* 2007;**17**:319–26.
28. Malavazos AE, Gobbo G, Zelaschi RF, Cereda E. Lifestyle intervention and fatty liver disease: the importance of both disrupting inflammation and reducing visceral fat. *Hepatology* 2010;**51**:1091–2.
29. Rahmouni K, Correia ML, Haynes WG, Mark AL. Obesity-associated hypertension: new insights into mechanisms. *Hypertension* 2005;**45**:9–14.
30. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* 2003;**112**:1821–30.
31. Wakabayashi K, Takahashi H. Neuropathology of autonomic nervous system in Parkinson's disease. *Eur Neurol* 1997;**38**(Suppl. 2):2–7.
32. Carmichael SW, Wilson RJ, Brimijoin WS, Melton LJ, Okazaki H, Yaksh TL, et al. Decreased catecholamines in the adrenal medulla of patients with parkinsonism. *N Engl J Med* 1988;**28**:254.
33. Whitsett TL, Halushka PV, Goldberg LI. Attenuation of postganglionic sympathetic nerve activity by L-dopa. *Circ Res* 1970;**27**:561–70.
34. Murphy MB. Dopamine: a role in the pathogenesis and treatment of hypertension. *J Hum Hypertens* 2000;**14**:S47–50.
35. Nonogaki K. New insights into sympathetic regulation of glucose and fat metabolism. *Diabetologia* 2000;**43**:533–49.
36. Leblanc H, Lachelin GC, Abu-Fadil S, Yen SS. The effect of dopamine infusion on insulin and glucagon secretion in man. *J Clin Endocrinol Metab* 1977;**44**:196–8.
37. Sirtori CR, Bolme P, Azarnoff DL. Metabolic responses to acute and chronic L-dopa administration in patients with parkinsonism. *N Engl J Med* 1972;**287**:729–33.
38. Møller N, Jørgensen JO. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. *Endocr Rev* 2009;**30**:152–77.
39. Makimura H, Stanley T, Mun D, Chen C, Wei J, Connelly JM, et al. Reduced growth hormone secretion is associated with increased carotid intima-media thickness in obesity. *J Clin Endocrinol Metab* 2009;**94**:5131–8.
40. Mekala KC, Tritos NA. Effects of recombinant human growth hormone therapy in obesity in adults: a meta analysis. *J Clin Endocrinol Metab* 2009;**94**:130–7.
41. Janiszewski PM, Ross R. The utility of physical activity in the management of global cardiometabolic risk. *Obesity (Silver Spring)* 2009 Dec;**17**(Suppl. 3):S3–14.
42. Goldberg LI, Rajfer SI. Dopamine receptors: applications in clinical cardiology. *Circulation* 1985;**72**:245–8.
43. Calza S, Decarli A, Ferraroni M. Obesity and prevalence of chronic diseases in the 1999–2000 Italian National health Survey. *BMC Public Health* 2008;**8**:140.
44. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gómez J, et al, ESPEN. Bioelectrical impedance analysis-part II: utilization in clinical practice. *Clin Nutr* 2004;**23**:1430–53.
45. Rankinen T, Kim SY, Pérusse L, Després JP, Bouchard C. The prediction of abdominal visceral fat level from body composition and anthropometry: ROC analysis. *Int J Obes Relat Metab Disord* 1999;**23**:801–9.
46. Taylor RW, Jones IE, Williams SM, Goulding A. Evaluation of waist circumference, waist-to-hip ratio, and the conicity index as screening tools for high trunk fat mass, as measured by dual-energy X-ray absorptiometry, in children aged 3–19 y. *Am J Clin Nutr* 2000;**72**:490–5.
47. Sofi F, Gori AM, Marcucci R, Innocenti G, Dini C, Genise S, et al. Adherence to a healthful life attenuates lipid parameters among a healthy Italian population. *Nutr Metab Cardiovasc Dis* 2007;**17**:642–8.
48. Marczewska A, De Notaris R, Sieri S, Barichella M, Fusconi E, Pezzoli G. Protein intake in parkinsonian patients using the EPIC food frequency questionnaire. *Mov Disord* 2006;**21**:1229–31.