



# Energy expenditure, body composition and dietary habits in progressive supranuclear palsy

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## Abstract

**Introduction** Little is known about metabolic changes in progressive supranuclear palsy. Goals of the present study are to: (1) investigate whether early progressive supranuclear palsy is associated with changes in energy expenditure, body composition and dietary intake compared with Parkinson's disease and healthy controls; (2) assess the accuracy of the Harris–Benedict equation to predict measured rest energy expenditure in progressive supranuclear palsy; (3) verify differences according to sex, phenotypes, disease severity and presence of dysphagia in progressive supranuclear palsy.

**Methods** Twenty-one progressive supranuclear palsy, 41 Parkinson's disease and nine healthy controls were included. Rest energy expenditure was assessed with indirect calorimeter, body composition with bio-impedance analysis and physical activity and dietary intake were estimated with a validated frequency questionnaire. Parametric testing was used to analyze differences between groups.

**Results** Progressive supranuclear palsy showed reduced total daily energy expenditure and physical activity compared to both other cohorts ( $p < 0.001$ ) and a tendency toward lower fat-free mass compared to Parkinson's disease ( $p > 0.05$ ). Limited accuracy was shown for the Harris–Benedict equation (accurate prediction frequency  $< 60\%$ ). Greater disease severity was associated with lower rest energy expenditure ( $p = 0.030$ ), fat-free mass ( $p = 0.026$ ) and muscle mass ( $p = 0.029$ ).

**Conclusion** Greater disease severity is associated with reduction in rest energy expenditure likely due to the reduction in lean mass and muscle mass. Such data may pave the way to clinical trials evaluating the efficacy of muscle-targeted nutritional support and physical therapy in preserving muscle mass and improving motor performances in progressive supranuclear palsy at early stages.

**Keywords** Progressive supranuclear palsy · Rest energy expenditure · Body composition · Diet · Parkinson

## Introduction

Recent evidence suggests that neurodegenerative diseases are associated with a wide spectrum of metabolic changes [1–6]. Furthermore, alterations in eating behaviors and dietary habits often feature patients with Parkinson's disease (PD) and behavioral variant of Frontotemporal dementia (bvFTD) since the earliest stages [3, 4].

While PD and Alzheimer's disease have been associated with weight loss, bvFTD has been linked to weight gain [4]. However, the nature of these metabolic changes and how they can affect the disease progression are largely unknown [4].

Scant of data is available on progressive supranuclear palsy (PSP), a rapidly progressive 4-R tauopathy classified within the spectrum of Frontotemporal lobar degeneration (FTLD) with bvFTD and Amyotrophic Lateral Sclerosis (ALS). Studies on limited number of PSP patients report a tendency toward weight loss since the earliest phase of the disease and a decreased muscle energy metabolism [7, 8].

Aim of the present case–control study was to investigate whether PSP at early stages is associated with changes in energy expenditure, body composition and dietary intake compared with PD patients and healthy controls (HC)

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matched for age, sex and body mass index (BMI) (and disease duration for PD). Additional objectives were to (1) assess the accuracy of the equation of Harris–Benedict, constructed to estimate rest energy expenditure in healthy individuals, to predict measured in PSP; (2) verify differences in the above-mentioned variables according to pre-specified categories in the PSP cohort (sex, phenotypes, disease severity and presence of clinically significant dysphagia).

## Methods

### Participants

Consecutive patients with PSP diagnosed with the Movement Disorder Society (MDS) criteria and referred to the Center for Neurodegenerative diseases (CEMAND) of the University of Salerno, Italy, were approached to take part to the present study between June 2018 and April 2021 [9]. Detailed information on enrollment and application of the PSP diagnostic criteria and phenotyping is available elsewhere [10–13]. Specific inclusion criteria for the present study were: ability to walk with for at least 10 steps with or without unilateral support, ability to complete the proposed assessments based on current physical and cognitive conditions, availability of a caregiver supporting the compilation of the dietary habit questionnaire.

A cohort of patients with idiopathic PD, diagnosed according to the MDS criteria [14], was recruited matched by gender, age, disease duration and BMI (PSP:PD = 1:2) (Flow chart showing enrollment in Supplemental File 1).

Finally, a cohort of HC matched for age, sex and BMI was recruited among spouses and caregivers of patients attending the outpatient clinic (PSP:HC = 1:0.5).

Based on previous literature [3], the following exclusion criteria were considered for all enrolled cohorts: inclusion in any intervention trial, history of significant weight loss (> 5 kg) in the previous 3 months, uncontrolled diabetes, major respiratory diseases, hepatic and renal failure, thyroid diseases, and all other conditions/diseases that can affect energy expenditure, body composition or dietary intake (e.g., fever, infections, cancer). In addition, PSP and PD patients with changes in dopaminergic medications during the previous three months as well as PD patients with motor fluctuations and dyskinesia were excluded.

### Assessments

#### Anthropometry

Body weight (to the nearest 0.5 kg) was measured using the same calibrated flat scale (SECA GMBH 7997021099;

Germany) according to standard procedure. Height was measured in cm (to the nearest 0.5 cm) and BMI was derived as the ratio between weight [kg] and height [m] squared ( $\text{kg}/\text{m}^2$ ) [15]. Measurement of waist circumference was performed with an elastic tape measure at the midpoint between the last rib and the iliac crest [15].

### Energy expenditure

Rest energy expenditure was measured, based on oxygen consumption ( $\text{VO}_2$ ), with the portable FitMate® (Cosmed, Rome, Italy) calorimeter and estimated according to the validated and widely used gender-specific predictive equation of Harris–Benedict for healthy people based on weight, height and age. Details on rest energy expenditure evaluation as well as computation of the total daily energy expenditure and physical activity level are given in Supplemental file 1.

### Body composition

Bio-impedance analysis (BIA Akern 101) was used to measure body composition. The following parameters were retrieved from the output of the BIA instrument: Fat-Free Mass (Kg), Fat-Free Mass index ( $\text{kg}/\text{m}$ ), Fat Mass (Kg), Fat Mass index ( $\text{Kg}/\text{m}$ ), Body Cellular Mass (Kg), Body Cellular Mass index ( $\text{Kg}/\text{m}$ ), Total Body Water (L), Total Body Water index ( $\text{L}/\text{m}$ ), Extracellular Water (L). Furthermore, whole-body Skeletal Muscle Mass was estimated from impedance parameters using the equation provided by Janssen et al. [16]. Then, Skeletal Muscle Mass was normalized for height (muscle mass [kg]/height [m]<sup>2</sup>) and skeletal muscle mass index (Skeletal Muscle Mass/height [m]<sup>2</sup>) was calculated to define low muscle mass as follows: men < 8.87  $\text{kg}/\text{m}^2$  and women < 6.42  $\text{kg}/\text{m}^2$  [17].

### Dietary habits

Dietary habits were estimated with specific questions from a validated online software freeware (Supplemental File 1).

### Disease-specific features

Severity of disease was assessed with the Movement Disorder Society-sponsored version of the Unified Parkinson's disease part III (MDS-UPDRS-III) [18] in both PSP and PD and with the PSP rating scale (PSP-rs) in PSP [19]. PSP patients were divided in two groups according to the median PSP-rs total score (less severe disease < 36; more severe disease  $\geq 36$ ).

Only for PSP, severity of dysphagia was derived from the item 13 of the PSP-rs and a score equal or greater than 2 was considered a proxy for clinical significant dysphagia [19]. None of the PD patients reported clinically significant

dysphagia (no cough or choking episodes or need to modify the food consistency).

Dopaminergic therapy was reported as Levodopa Equivalent Daily Dose (LEDD).

### Statistical analysis

Kolmogorov–Smirnov tests were run to determine suitability of variables for parametric analyses. Between-groups comparisons were performed with the Student's *t* test, ANOVA, ANCOVA or with the Fisher's exact test, as appropriate. Post hoc analyses were performed with the Bonferroni test. As for the PSP cohort, pre-specified sub-group analyses by sex, phenotypes, disease severity (PSP-rs < 36 versus ≥ 36) and clinically significant dysphagia (PSP-rs item 13 < 2 versus ≥ 2) were also considered.

The agreement between measured and estimated rest energy expenditure in PSP was investigated through calculation of bias and the limits of agreement by the method of Bland and Altman, and the Lin's concordance correlation coefficient [20, 21]. The accuracy of predictive equations was also described as the proportion of patients outside the threshold of accurate prediction of ± 10% [21].

All analyses were performed using SPSS 27.0 (SPSS Inc., Chicago, Illinois). All statistical tests were two-tailed, and a *p* < 0.05 was deemed as statistically significant.

## Results

Upon exclusion of 13 patients (7 PSP for physical and cognitive conditions preventing completion of study assessments, 3 PSP for lack of caregiver, 1 PSP for uncontrolled diabetes, 1 PSP for thyroid problems and 1 PD for uncontrolled diabetes) and 1 HC for incomplete data, 21 PSP, 41 PD and 9 HC were included in the present study. Table 1 shows demographic, clinical and anthropometric features of the study cohorts. Two out of 21 (9.5%) PSP and 11/41 (26.8%) PD were not taking any dopaminergic medication. As expected, given the greater disease severity, PSP patients presented higher LEDD and MDS-UPDRS-III compared to PD.

Seventeen PSP patients (80.9%) presented a Richardson's syndrome (PSP-RS), two PSP with predominant parkinsonism and two PSP with progressive gait freezing. Twelve PSP patients (57.1%) reported clinically significant dysphagia.

Table 2 details comparisons between groups for energy expenditure, body composition and dietary intake.

### Energy expenditure and accuracy of Harris–Benedict equation

No significant differences in either measured or estimated rest energy expenditure were observed between cohorts. However, total daily energy expenditure was significantly lower in PSP compared to both PD and HC, due to lower physical activity level and physical activity intensity levels (*p* < 0.001). Of note, the difference between PSP and PD remained significant after correction for LEDD (*p* < 0.001). Such results were confirmed when comparing PSP men with

**Table 1** Demographic, clinical and anthropometric features of the study cohorts

	PSP (21)	PD (41)	HC (9)	<i>p</i>
Age, years	67.05 (6.31)	63.54 (10.58)	62.22 (6.47)	0.270
Sex, men, <i>N</i> (%)	12 (57.1)	30 (73.1)	5 (55.5)	0.347
Disease duration from onset of symptoms	3.14 (2)	2.49 (2.16)	–	0.255
LEDD, mg	501.84 (255.84)	265.12 (326.86)	–	<b>0.007</b>
PSP-rs	39.29 (15.93)	–	–	–
MDS-UPDRS-III	35.9 (15.11)	26.34 (8.89)	–	<b>0.003</b>
Weight, Kg	72.12 (12.66)	79.8 (14.22)	84 (27.95)	0.109
BMI, kg/m <sup>2</sup>	27.91 (4.76)	28.48 (4.22)	27.84 (5.46)	0.865
BMI categories				0.860
Normal weight, <i>n</i> (%)	5 (26.3)	8 (21.6)	3 (33.3)	
Overweight, <i>n</i> (%)	10 (52.6)	19 (51.4)	3 (33.3)	
Obese, <i>n</i> (%)	4 (21.1)	10 (27)	3 (33.3)	
Waist circumference, cm	97.57 (11.24)	101.78 (17.6)	93.78 (8.75)	0.284

Significant differences are highlighted in bold

All data are expressed in mean (standard deviation), unless otherwise specified

*BMI* body mass index; *HC* healthy controls; *LEDD* levodopa equivalent daily dose; *MDS-UPDRS-III* the Movement Disorder Society version of the Unified Parkinson's disease part III; *PD* Parkinson's disease; *PSP* Progressive supranuclear palsy (PSP); *PSP-rs* Progressive supranuclear palsy rating scale

**Table 2** Study assessments in PSP, PD and HC

	PSP (21)	PD (41)	HC (9)	<i>p</i>
<b>Energy Expenditure</b>				
Measured rest energy expenditure, Kcal/day	1696.43 (425.59)	1702.76 (439.54)	1635.56 (494.05)	0.917
Estimated rest energy expenditure, Kcal/day	1439.96 (317.74)	1562.5 (264.12)	1430.99 (225.18)	0.177
Total daily energy expenditure, Kcal/day	2721.96 (603.23)	3614.87 (932.22)	3652.6 (674.96)	<b>&lt; 0.001*</b>
Physical activity level	1.61 (0.17)	2.17 (0.48)	2.38 (0.67)	<b>&lt; 0.001<sup>§</sup></b>
Physical activity intensity levels, <i>n</i> (%)				<b>&lt; 0.001<sup>°</sup></b>
1.40–1.69 low	13 (68.4)	6 (15.4)	2 (22.2)	
1.70–1.99 moderate	5 (26.3)	10 (25.6)	1 (11.1)	
2.00–2.40 high	1 (5.3)	23 (59)	6 (66.7)	
<b>Body composition</b>				
Free Fat Mass, Kg	54.31 (9.11)	59.49 (10.06)	51.11 (8.18)	<b>0.026<sup>+</sup></b>
Free Fat Mass index, Kg/m	33.59 (4.15)	35.54 (4.69)	31.43 (3.76)	<b>0.031<sup>+</sup></b>
Skeletal Muscle Mass Index, Kg/m <sup>2</sup>	9.76 (1.55)	10.34 (1.69)	8.91 (1.52)	0.053
Pathologic Skeletal Muscle Mass Index, <i>n</i> (%)	2 (9.5)	2 (5)	2 (22.2)	0.245
Fat Mass, Kg	17.77 (9.64)	19.58 (8.91)	21.73 (9.86)	0.544
Fat Mass index, Kg/m	11.17 (6.32)	11.81 (5.53)	13.48 (6.45)	0.618
Body Cellular Mass, Kg	27.41 (7)	31.3 (7.38)	25.98 (4.73)	<b>0.039<sup>+</sup></b>
Body Cellular Mass index, Kg/m	16.93 (3.89)	18.67 (3.8)	15.95 (2)	0.064
Total Body Water, L	40.12 (6.93)	44.45 (7.68)	37.76 (6.48)	<b>0.017<sup>^</sup></b>
Total body Water index, L/m	24.81 (3.19)	26.55 (3.63)	23.23 (3.13)	<b>0.019<sup>#</sup></b>
Extracellular water, L	19.66 (3.54)	20.87 (3.82)	18.27 (3.02)	0.125
<b>Dietary intake</b>				
Calorie intake, Kcal/day	2081.8 (447.28)	2376.63 (687.16)	2043.11 (481.71)	0.119
Protein intake, g/day	79.84 (19.92)	84.66 (22.31)	76.09 (23.85)	0.486
Carbohydrates intake, %	51.05 (5.08)	49.56 (8.92)	47.44 (3.81)	0.484
Sugars, %	17.9 (4.22)	19.12 (4.75)	17.56 (6.48)	0.524
Lipid intake, %	31.3 (5.31)	32.54 (7.42)	31.67 (4.92)	0.776
SFA, %	10.25 (2.1)	9.76 (2.42)	11 (2.55)	0.335
PUFA, %	4.1 (0.96)	4.61 (1.28)	4.56 (1.13)	0.284
Water intake, mL/day	1240 (439.37)	1219.51 (498.1)	1177.77 (263.52)	0.945
Fibers intake, g/day	28.25 (8.91)	32.41 (8.02)	25.31 (9.64)	<b>0.039<sup>^</sup></b>
Calcium intake, mg/day	879.45 (241.89)	970.71 (326.64)	906.11 (300.5)	0.517
Iron intake, intake, mg/day	12.93 (3.66)	14.32 (3.19)	12.55 (3.32)	0.180
Zinc intake, mg/day	11.32 (2.81)	12.27 (2.94)	10.87 (3.27)	0.298
Vitamin A intake, µg/day	1172.85 (377.43)	1375.8 (500.46)	1146 (507.07)	0.185
Vitamin D intake, µg/day	2.69 (1.25)	2.68 (1.22)	2.62 (1.29)	0.989
Vitamin E intake, mg/day	12.67 (2.95)	16.54 (5.6)	12.07 (3.82)	<b>0.004<sup>x</sup></b>
Vitamin B12 intake, mg/day	4.96 (1.91)	7.74 (17.9)	4.6 (1.49)	0.692
Vitamin C intake, mg/day	156.5 (74.34)	192.68 (62.21)	147.11 (72.7)	0.060
Folate intake, µg/day	347.59 (104.41)	416.24 (112.02)	321 (112.48)	<b>0.017<sup>^</sup></b>
Alcohol intake, g/day	6.6 (6.45)	12.76 (21.93)	17.18 (17.68)	0.295

Significant differences are highlighted in bold

Data are expressed in mean (standard deviation), unless otherwise specified

HC healthy controls; PD Parkinson's disease; PSP Progressive supranuclear palsy; PUFA Poly-unsaturated fatty acids; SFA Saturated fatty acids

\*Difference between PSP and PD  $p=0.001$ ; difference between PSP and HC  $p=0.019$

<sup>§</sup>Difference between PSP and PD  $p<0.001$ ; difference between PSP and HC  $p<0.001$

<sup>°</sup>Difference PSP and PD  $p<0.001$ ; difference between PSP and HC  $p=0.002$

<sup>+</sup>Post hoc did not show significant differences between groups ( $p>0.05$ )

<sup>^</sup>Difference between PD and HC  $p=0.048$

<sup>#</sup>Difference between PD and HC  $p=0.033$

<sup>x</sup>Difference between PSP and PD  $p=0.013$ ; difference between PD and HC  $p=0.041$

PD men and PSP women with PD women (Supplemental File 2).

Estimated rest energy expenditure was lower than measured rest energy expenditure. Mean (standard deviation, 95% confidence intervals) difference between measured and estimated rest energy expenditure was 256.46 in the whole PSP cohort (341.58, 100.97–411.95) ( $p=0.003$ ), 51.88 in women (305.52, – 117.31–221.07) ( $p<0.001$ ) and 194.66 in men (340.42, 77.72–311.6) ( $p<0.001$ ).

In general, the Harris–Benedict formula tended to underestimate rest energy expenditure in PSP by 15.1%. The Lin's concordance correlation coefficient (95% confidence intervals) was 0.471 (0.164–0.695) showing only moderate agreement between measured and estimated rest energy expenditure. The proportion of accurate prediction ( $\pm 10\%$  difference between measured and estimated rest energy expenditure) in the whole population was 42.8%. In general, the equation was likely to underestimate rest energy expenditure ( $< 10\%$  in 47.6% of cases;  $> 10\%$  in 9.5% of cases).

## Body composition

PSP tended to present lower Free Fat Mass and Free Fat Mass index compared to PD without reaching the threshold for a significant difference ( $p > 0.05$ ). When dividing the patients by sex, such trend was confirmed in men ( $p > 0.05$ ) (Supplemental File 2). Pathologic skeletal muscle mass index had a low prevalence in both PSP and PD cohorts (9.5% and 5%, respectively). No significant differences in pathological skeletal muscle mass were shown when dividing the patients by sex (Supplemental File 2).

## Dietary intake

PSP patients had lower vitamin E intake compared to PD ( $p < 0.05$ ). No other significant differences in dietary intake for PSP were shown.

## Differences according to pre-specified categories in the PSP cohort

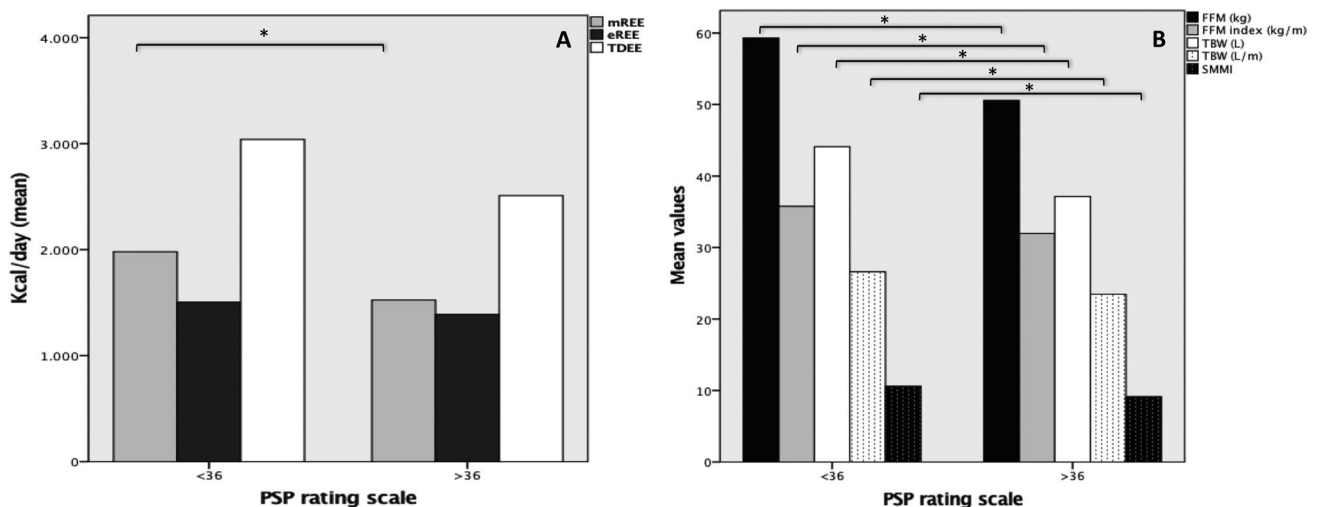
Supplemental File 2 provides details for differences according to pre-specified categories in the PSP cohort.

As for sex differences, in line with data available in healthy controls, rest energy expenditure, Free Fat Mass and skeletal muscle mass index, Total Body Water and Extracellular water were higher in men, while Fat Mass index was higher in women.

No significant differences were shown according to diseases phenotypes.

As for disease severity, patients with higher PSP-rs showed lower rest energy expenditure, Free Fat Mass, Free Fat Mass index, skeletal muscle mass index, Total Body Water and Total Body Water index compared to patients with lower PSP-rs. Furthermore, patients with a more severe form of disease showed a tendency toward lower total daily energy expenditure (Fig. 1A, B). No significant differences were present for either anthropometric data or dietary habits.

No significant differences were shown in patients with clinically relevant dysphagia except for a lower intake of saturated fatty acid and a tendency for lower water intake compared to patients without clinically relevant dysphagia.



**Fig. 1** Differences in energy expenditure (A) and body composition (B) according to disease severity in PSP. \*:  $p < 0.05$ ; eREE estimated Rest Energy Expenditure; FFM Free Fat Mass; mREE measured Rest

Energy Expenditure; SMMI Skeletal Muscle Mass Index; TBW Total Body Water

## Discussion

Using an extensive set of instrumental assessments and validated questionnaires, we investigated energy expenditure, body composition and dietary intake in PSP at early stages in comparison with age-, sex- and BMI-matched PD patients and HC.

PSP disclosed similar measured and estimated rest energy expenditure, but lower total daily energy expenditure compared to PD and HC. The significant reduction in total daily energy expenditure in PSP was likely due to the significant contraction of physical activity demonstrated by the reduction of both physical activity level and physical activity intensity levels. Indeed, such reduced mobility is likely due to the high motor disability and risk of falls experienced by PSP patients since the earliest stages of disease [22]. In keeping with this speculation, motor disability of the PSP cohort is supported by the mean (standard deviation) scores with the Fall, Gait and Postural Instability items of the PSP-rs [2.29 (1.19), 1.9 (0.89), 2.24 (1.14), respectively]. Differently from PSP, bvFTD and ALS have been associated with a hypermetabolic status with increased resting energy expenditure [5, 23]. Yet, although PSP belongs to the FTL spectrum as bvFTD and ALS, our data would suggest that PSP at early stages is not associated with major changes in rest energy expenditure as compared with PD and HC.

Our data also demonstrated that the Harris–Benedict equation does not provide a reliable estimation of rest energy expenditure in PSP. Although extensively validated in healthy controls, in the present study, the Harris–Benedict equation underestimated measured energy expenditure also in PD and healthy controls. Limited accuracy of such equation in PSP is also supported by the scarce agreement between measured and estimated rest energy expenditure shown by the Lin's concordance correlation coefficient. As a consequence, the Harris–Benedict equation should not be considered as a valid proxy of indirect calorimeter assessment in PSP in routine practice. Reliability of the other available equations should be tested in PSP to verify their validity in the estimation of measured rest energy expenditure. Alternatively, new prediction equations should be designed by future studies taking into account the predictors of estimation bias [3].

As for body composition, we showed PSP did not have major significant differences compared with PD and HC. In keeping with the discrepancy observed for energy expenditure, also body composition changes in PSP differ from those observed in bvFTD [6]. Ahmed et al. reported an increase in both total lean and fat mass in bvFTD compared to both Alzheimer's disease and HC [6]. Differently from Ahmed et al., we only observed a tendency toward

a reduction of Free Fat Mass and skeletal muscle mass index in PSP compared with PD. On the other hand, we confirmed the low prevalence of pathologic skeletal muscle mass index in PD and parkinsonism [2].

All our results on basal metabolism and body composition were confirmed when dividing PSP and PD cohorts by sex. Takamatsu et al. found lower basal metabolism only in women with PSP compared to age-matched healthy women [24]. Such discrepancy with our data may be explained by few methodological differences. First, Takamatsu et al. performed a retrospective estimation of body metabolism with a body composition analyzer while we measured it with a calorimeter in a prospective study. Furthermore, Takamatsu et al. also included in their study inpatients performing rehabilitation, while our cohort only included outpatients. Finally, due to the small number of healthy controls in our study, we run comparisons by sex between PSP and PD only.

As for dietary intake and in keeping with similar anthropometric data, we failed to find major differences in caloric intake, macronutrients and micronutrients assumptions in PSP compared to both PD and HC, except for a lower intake of vitamin E compared to PD. Such findings may suggest dietary intake does not have a major role in the differences observed for energy expenditure and body composition.

As for the evaluation of energy expenditure, body composition and dietary intake according to pre-specified PSP subgroups, we confirmed men with PSP have higher rest energy expenditure and Fat-Free Mass and lower Fat Mass compared to women with PSP in line with sex differences in the general population.

When dividing the PSP cohort according with disease phenotypes, we failed to show major differences. However, the PSP cohort was mainly represented by PSP-RS (80.9%), thus, our study lacks of the necessary power to demonstrate any differences at the sub-group level [10, 11].

Interestingly and differently from bvFTD [5], we showed that disease severity, as measured with the PSP rating scale, was associated with lower measured but not estimated rest energy expenditure, further supporting the scarce agreement between these two measures. As a significant contraction in physical activity was lacking, such reduction in rest energy expenditure in PSP patients with a more severe form of disease was likely responsible for a trend toward significance for lower total daily energy expenditure. As for body composition, differently from bvFTD and in spite of similar anthropometric measures (i.e., weight, BMI, waist circumference) [6], greater disease severity was associated with lower Fat-Free Mass and Fat-Free Mass index, skeletal muscle mass index, Total Body Water, and Total Body Water index. Based on available literature on healthy individuals [25], we cannot exclude reduced muscle mass may be associated with a reduction in rest energy expenditure in patients with greater severity of disease. Given the lack of difference

in protein intake, we hypothesize the tendency toward a reduced mobility might play a role in body composition changes affecting the PSP patients with disease progression.

Indeed, skeletal muscle mass index reduction has a key role in determining sarcopenia, which in turn is linked to loss of muscle strength (dynapenia), further contributing to reduction in mobility and increasing motor difficulties in elderly patients [2, 26]. Recent randomized clinical trials have shown that in sarcopenic older adults oral nutritional support with muscle-targeted whey protein-based formula enriched with essential amino acids may improve muscle mass, strength and physical function, especially in combination with physical therapy [27–29]. Recently, Barichella et al. showed the efficacy of a whey protein-based nutritional formula associated with physical rehabilitation in preserving muscle mass and improving motor performances in patients with parkinsonism [30]. Although few PSP patients were included in this study (8–9%) [30], strong evidence for efficacy of muscle-targeted nutritional support on disease severity in PSP is not available yet. Indeed, the data of the present study would support the rationale for the design of such a clinical trial in PSP patients at early stages.

Given such changes in energy expenditure and body composition with disease severity can only be detected with objective instrumental assessments (i.e., indirect calorimeter and bio-impedance analysis) and are not associated to change in anthropometric measures or dietary intake, they are at high risk of being unrecognized by clinicians and, thus, undertreated.

Finally, we failed to detect major differences in any of the administered assessments in relation with the presence of clinically significant dysphagia. Since we recruited a population of early PSP, we speculate dysphagia was not severe enough yet to determine significant changes in patients' metabolism.

A complementary or alternative explanation for the change in energy expenditure and body composition observed in PSP patients with greater disease severity is autonomic dysfunction. The presence of autonomic dysfunction in PSP is increasingly recognized with a length-dependent loss of sensory and autonomic nerve fibers associated with functional impairment related to autonomic dysfunction paralleling disease severity [31]. Such hypothesis requires further studies as we did not evaluate autonomic function in the present study.

Our study has limitations. We are aware a limited number of HC was included in the present study. The main reason for low enrollment of HC was COVID-19 pandemic which limited the access and the time spent into the health care facility for spouses and caregivers. Future studies should enroll a larger healthy control group with no direct link to the patient population. Also, we cannot exclude the COVID-19 pandemic may have had an impact on measurements performed

in the present study. Lockdown restrictions may have contributed to decreased daily energy expenditure and physical activity levels, particularly in the PSP group. However, we failed to find significant differences in the outcome measures between patients enrolled before and after the COVID-19 pandemic (data not shown). Furthermore, we acknowledge a possible assessment bias, with either under- or over-reporting, associated with the method used in the ascertainment of dietary habits as well as with physical activity level [1]. Notwithstanding, all questionnaires and equations used in the present work have been validated and extensively applied to the general population and to PD patients in Italy and worldwide [1–3]. Furthermore, we decided to use the cut-off for sarcopenia recommended by the European consensus and used in previous works including Italian parkinsonian subjects [2, 26, 30]. Notwithstanding, we are aware the cut-off for sarcopenia relies on the measurement method and on the population involved. Also, all the patients included in the present study were recruited in a single center in the South of Italy. Thus, we recognize dietary habits and anthropometric data may not necessarily reflect those from the general population of PSP patients. Another drawback is the cross-sectional design of our study. Further longitudinal studies are required to confirm the relationship between changes in energy expenditure and body composition and disease progression and the effect on overall survival in PSP. Finally, our study only provides a first extensive description of energy expenditure, body composition and dietary habits in PSP. Future studies will also apply neuroimaging techniques to explore the pathophysiological correlates of such metabolic changes in PSP at early stages.

In conclusion, we provide data on an extensive set of assessments evaluating energy expenditure, body composition and dietary intake in PSP at early stages. We showed lower total daily energy expenditure possibly linked to reduced mobility in PSP compared with age-, sex-, BMI-matched PD and HC associated with trend for a reduction in lean mass. Furthermore, we demonstrated the Harris–Benedict equation, a validated method to estimate rest energy expenditure in healthy controls, does not provide a reliable estimation of measured rest energy expenditure in PSP. Finally, we showed disease severity in PSP is linked with a reduction in rest energy expenditure possibly due to the significant reduction in lean and muscle mass. If confirmed by larger and longitudinal studies, such data may pave the way to future clinical trials evaluating the efficacy of muscle-targeted nutritional support with or without physical therapy in preserving muscle mass and improving measures of disease severity in PSP at early stages.

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**Author contributions** MP: Research project: conception, organization; Statistical analysis: design, execution; Manuscript: writing of the first draft. MFT, MCR, FA, MS, ADS: Research project: execution; Manuscript: review and critique. RE, MTP, PB: Statistical analysis: review and critique; Manuscript: review and critique.

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## Declarations

**Conflict of interest** The authors declare that they have no conflict of interests. Statistical analysis was conducted by Marina Picillo, MD, PhD. Disclosures from the past two years: Dr Marina Picillo is supported by the Michael J Fox Foundation for Parkinson's research; Prof Paolo Barone received consultancies as a member of the advisory board for Zambon, Lundbeck, UCB, Chiesi, Abbvie and Acorda; Dr Roberto Erro received consultancies from Zambon and honoraria from TEVA; the other authors report no financial disclosures.

**Ethical approval** The study was approved by the institutional Ethics Committee (N. 101, 19 October 2017) and was carried out in accordance with the principles laid down in the 1964 Declaration of Helsinki and later amendments. Subjects were recruited upon signature of the written consent form.

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