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ORIGINAL COMMUNICATION

Predictors of weight loss in early treated Parkinson's disease from the NET-PD LS-1 cohort

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Abstract Weight loss is a common symptom of Parkinson's disease and is associated with impaired quality of life. Predictors of weight loss have not been studied in large clinical cohorts. We previously observed an association between change in body mass index and change in Unified Parkinson's Disease Rating Scale (UPDRS) motor and total scores. In this study, we performed a secondary analysis of longitudinal data (1–6 years) from 1619 participants in the NINDS Exploratory Trials in PD Long-term Study-1 (NET-PD LS1) to explore predictors of weight loss in a large prospective clinical trial cohort of early treated Parkinson's disease. The NET-PD LS1 study was a double-blind randomized placebo controlled clinical trial of creatine monohydrate 10 gm/day in early treated PD (within 5 years of diagnosis and within 2 years of starting dopaminergic medications). Linear mixed models were used to estimate the effect of baseline clinical covariates on weight change over time. On average, participants lost only 0.6 kg per year. Higher age, baseline weight, female gender, higher baseline UPDRS scores, greater postural instability, difficulty eating and drinking, lower cognitive scores and baseline levodopa use (compared to dopamine agonists) were all associated with weight loss. Surprisingly baseline difficulty swallowing, dyskinesia, depression, intestinal hypomotility (constipation) and self-reported nausea/vomiting/anorexia were not significantly associated with weight loss in this cohort of early treated Parkinson's disease patients. On average, participants with Parkinson's disease experience little weight loss during the first 1–6 years after starting dopaminergic replacement therapy, however levodopa use and postural instability were both predictors of early weight loss.

Trial Registration clinicaltrials.gov identifier# NCT00449865.

Keywords BMI · Weight loss · Dysphagia · Nausea · Parkinson's disease

Introduction

Weight loss is a common symptom of Parkinson's disease (PD) and is associated with a reduction in health related quality of life [1]. Using the NINDS Exploratory Trials in PD Long-term Study-1 (NET-PD LS-1) clinical trial, we recently found that changes in body mass index (BMI) early in Parkinson's disease are associated with changes in motor and total UPDRS scores [2]. Participants who experienced a decline in BMI (and decline in weight) also experienced a more rapid increase (worsening) in motor and total UPDRS scores compared to those whose BMI was stable, while participants whose BMI increased during the study experienced a slower increase in UPDRS.

Weight loss in Parkinson's disease has been hypothesized to be due to multiple factors including hyposmia, difficulty self-feeding, dysphagia, intestinal hypomotility,

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depression, anorexia, nausea, and increased energy requirements due to muscular rigidity and increased involuntary movements such as dyskinesia and tremors (reviewed [3]). Few clinical cohort studies have examined predictors of weight loss in a prospective manner. One cross-sectional analysis of Parkinson's disease patients' BMI and anthropomorphic measurements found disease duration and dyskinesia to correlate with BMI [4]. Another cross-sectional study found that age, UPDRS III scores, levodopa equivalent daily dose (LEDD)/body weight (mg/kg), anxiety scores and beck depression inventory (BDI) scores were significantly associated with malnourishment as measured using the Scored Patient-Generated Subjective Global Assessment (PG-SGA) [5]. Uc et al. followed a cohort of 49 Parkinson's disease patients over time and found only Hoehn and Yahr stage to be predictive of change in body weight, although the presence of hallucinations reached borderline significance [6]. By contrast, one clinical cohort study reported weight gain and increased fat mass in the first 3 years after diagnosis [8].

In the present study we wished to examine predictors of weight loss in the large prospective NET-PD LS-1 cohort of 1741 early treated PD participants for whom weights were measured repeatedly in 1619 participants.

Methods

Participants

NET-PD LS-1 was a large, randomized, multicenter, double blind, placebo-controlled trial of 10 g/day of creatine monohydrate. The institutional review boards of the 45 participating sites approved the study, the study protocol, and the informed consent process and documentation in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All patients provided written informed consent. Participants had early, treated PD (within 5 years of diagnosis and between 90 days to maximum two years of starting dopaminergic therapy). On average, participants were enrolled 1.5 years since diagnosis, 3.3 years since the onset of symptoms, and 0.8 years after starting dopaminergic replacement therapy [7]. The study design and characteristics at randomization of this clinical trial have been previously published [7]. A total of 1741 participants were enrolled (2007–2010). Follow-up time was defined as the time between the randomization study visit until the loss to follow-up, death, or 17 July 2013, when the clinical trial was terminated early [8]. Out of the 1741 participants, 1619 were included in this analysis having at least 1 year of repeated body weights. Participants who had less than 1 year of follow-up and/or no repeated body weights (122) were excluded from the analysis.

Outcome measures

Weight change from baseline, measured at yearly visits scheduled at 12, 24, 36, 48, 60, and 72 months from baseline [7].

Covariate variables

The following baseline covariates were analyzed: treatment assignment (creatine vs. placebo), age, disease duration, gender, weight, UPDRS motor (part III) score, presence of dyskinesia (defined as positive if participants answered greater than 0 on any of UPDRS questions 32–34 from UPDRS part IV complications of therapy), bulbar symptoms (the sum of UPDRS part II questions 5, 6, 7 addressing speech, saliva and difficulty swallowing), tremor symptoms (calculated as the average of the sum of questions 16, 20, and 21), postural instability symptoms (calculated as the average of the sum of questions 13–15 and questions 29–30), the Beck Depression Inventory II total score (BDI-II), the scales for outcomes in Parkinson's disease-COGnition (SCOPA-COG) score, and the symbol digit modalities test (SDMT) score. The following individual questions were included due to their particular relevance: UPDRS part II question 9 ("cutting food and handling utensils"), Parkinson's Disease Questionnaire-39 (PDQ-39) questions 15, 16, and 24 ("Due to having Parkinson's Disease, how often in the last month have you had difficulty cutting up your food", "had difficulty holding a drink without spilling it", and "avoided situations which involve eating or drinking in public"), UPDRS part IV question 40 ("Does the patient have anorexia, nausea or vomiting") and self-reported constipation based upon a baseline diagnostic features questionnaire. PDQ-39 questions 15 and 16 were combined and treated as a dichotomous variable 0 vs $\geq$1 due to the severely skewed distribution of these variables (most participants answered 0 or no difficulty). Baseline medications were examined including antidepressant medications, the type of symptomatic PD medications (i.e., levodopa only, dopamine agonist only or more than one dopaminergic therapy), and the total levodopa equivalent daily dose (LEDD) in mg.

Statistical methods

The linear mixed model (LMM) for repeated measurements was used to examine the relationship between baseline covariates and the longitudinal weight change from baseline. Missing data in LS-1 were mainly administrative, caused by early termination of the study [8]. The declining number of participants at each year is shown at the bottom of Fig. 1. The missing

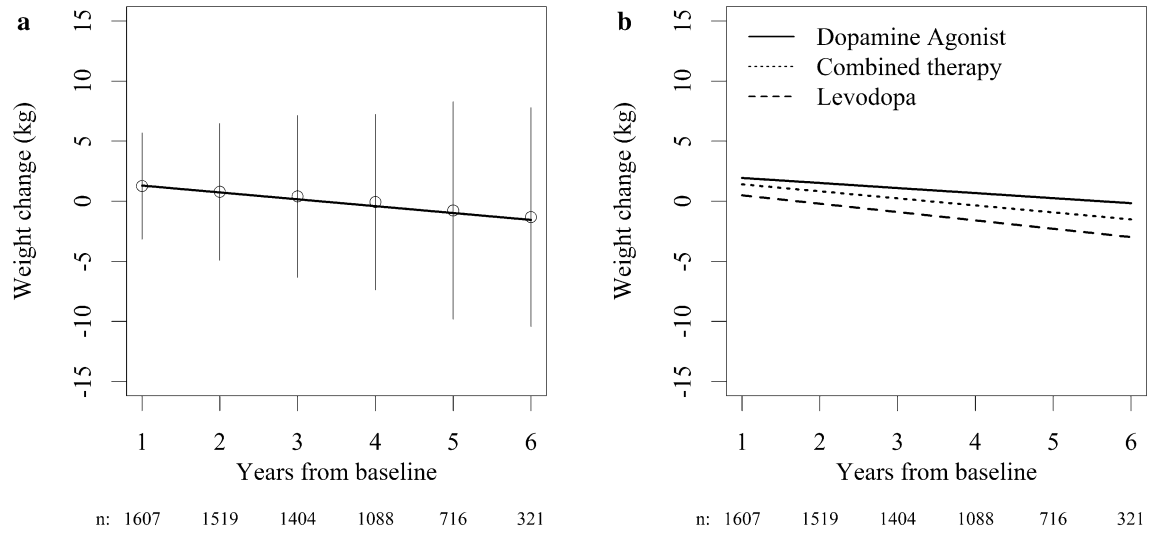

Fig. 1 Mean weight change over time, overall and by baseline dopaminergic therapy. In **a**, *gray circles and bars* correspond to sample mean ± sample standard deviation at each visit year. The *black line* represents the estimated mean from the linear mixed model. In **b** the *lines* represent the estimated mean from the linear mixed model by baseline dopaminergic replacement therapy, where other baseline covariates were fixed at the overall mean. *Solid line* dopamine agonist therapy only, *dotted line* combined therapy (dopamine agonist and levodopa), *dashed line* levodopa therapy only

data mechanism was assumed to be missing at random (MAR) [9], which is a flexible assumption that allows the missing data mechanism to depend on the observed covariates and outcomes and the amount of missingness is below 10%. The LMM offers unbiased results in the presence of MAR. In all models, we adjusted for visit time (years), and baseline weight (kg). We also included subject-specific and site-specific random intercepts to account for within-subject and within-site correlations. To identify baseline factors that are associated with weight change, we conducted stepwise model selection with entry criteria of $p \leq 0.2$ and stay criteria of $p \leq 0.1$. Given the a priori importance of UPDRS question 40, it was forced into the multivariable model regardless of its p value. To account for the possibility that the effects of some covariates may be time-varying, we also considered covariate by time interactions in the model selection procedure. Since weight change data in this analysis were first measured at year 1 visit, we centered the time variable at 1 year, such that the main effects in the LMM correspond to covariate effects on weight change from baseline to year 1, and the covariate by time interactions reflect covariate effects on the *rate* of weight change in subsequent years.

Given the number of covariates tested in this secondary analysis, a type I error level of 0.01 was used to determine statistical significance. All statistical analyses were conducted using SAS Statistical Software (Version 9.4; SAS Institute Inc.).

Results

The baseline characteristics of the included participants are shown in Table 1. Almost half of participants reported at least occasional difficulty eating or drinking and 11% of participants reported anorexia, nausea or vomiting (UPDRS#40). On average there was little weight change over time (Fig. 1 shows the mean change from baseline and sample size at each annual visit). After an initial increase, participants lost on average 0.6 kg/year. Weight loss after the first year was quite linear in all participants. Only 7.8% of participants lost at least 5% of their baseline body weight during the first 12 months of the study (clinically important weight loss [10]). While the average amount of weight loss was small in this clinical trial, several variables were found to significantly predict weight changes.

The final multivariable regression model is shown in Table 2. The estimates for each of the regression coefficients are positive or negative depending on whether they are associated with weight gain or weight loss during the study. Besides the main effects, several covariate by time interactions also entered the model, suggesting differences in the rate of weight loss based upon covariates of interest.

Few factors were associated with weight gain: males had a tendency to gain weight over females at an average of 0.33 kg/year ($p < 0.001$). Each unit increase in average tremor score was associated with a significant increase in weight of 0.51 kg/year ($p < 0.001$). Participants randomized to the creatine arm also experienced a slight

Table 1 Baseline characteristics of the analytic sample

Baseline characteristics	Mean (std) or Freq (%)
Age in years	61.7 (9.4)
Gender (male)	1040 (64%)
Weight in kg	82.2 (17.7)
Yrs since PD diagnosis	1.5 (1.1)
Randomization group	
Placebo	799 (49%)
Creatine	820 (51%)
UPDRS total ($N = 1610$)	26.0 (11.1)
UPDRS motor (N = 1611)	17.6 (8.2)
SDMT total score	44.6 (11.5)
BDI-II total score ($N = 1614$)	6.7 (5.4)
Bulbar symptoms (sum of UPDRS #5,6,7)	1.5 (1.4)
Frequency of dysphagia (score of ≥2 on question 7)	69 (4.3)
Anorexia, nausea or vomiting (UPDRS #40, $N = 1618$)	180 (11%)
Constipation	228 (14%)
Dyskinesia ($N = 1618$)	59 (4%)
Dopaminergic medicine	
Dopamine agonist only	453 (28%)
Combined therapy	706 (44%)
Levodopa only	460 (28%)
Total Levodopa equivalent dose (mg)	377 (232)
Antidepressant medication use	386 (24%)
Cutting food and handling utensils (UPDRS #9)	
0 (normal)	911 (56%)
1+ (abnormal)	708 (44%)
Difficulty eating/drinking (PDQ-39 #15&16)	
0 (normal)	904 (56%)
1+ (abnormal)	715 (44%)
Embarrassment eating in public (PDQ-39 #24)	
0 (never)	1355 (84%)
1+ (occasionally or more)	264 (16%)

Sample size equals 1619 unless otherwise specified. For categorical questions such as anorexia/nausea/vomiting, the frequency corresponds to the number of participants who scored 1 or higher. Difficulty eating/drinking = the sum of PDQ-39 questions 15 and 16 where a score of 1 (occasionally) or more on either question was rated as abnormal

SDMT symbol digit modalities test, *BDI-II* beck depression inventory-II, *UPDRS* unified Parkinson's disease rating scale, *PDQ-39* Parkinson's Disease Questionnaire-39

(0.16 kg/year) increase in weight over time which was not significant under our stringent criteria ($p = 0.04$). Each unit increase in the baseline SDMT cognitive test was associated with a small (0.01 kg/year, $p = 0.02$) but marginally significant amount of weight gain during the study. Note that in the NET-PD LS-1 study, the SDMT was completed orally and, therefore, would not correlate with the manual ability to feed oneself. No other variables were associated with weight gain in this clinical trial.

Several baseline characteristics were associated with weight loss. There was an interaction between age and time: older participants lost weight at a faster rate as the study progressed. Baseline weight was also associated with weight loss: for every kg more that participants weighed at baseline, they lost 0.025 kg/year more per year during the study. Disease severity as measured by duration of disease and baseline UPDRS motor score were unsurprisingly associated with weight loss. For every unit increase on the baseline UPDRS motor score, participants experienced a small but significant loss of 0.016 kg/year ($p = 0.007$). Each unit increase in postural instability scores at baseline was associated with 0.53 kg more weight loss per year ($p = 0.001$) suggesting that the PIGD subtype of Parkinson's disease is associated with a greater rate of weight loss.

Type of dopaminergic therapy and the amount of levodopa daily dose were both predictive of weight loss with

Table 2 Parameter estimates of the multivariable linear mixed model for change in weight from baseline

Baseline characteristics	Estimate	SE	CI	*p*
Main effects (effects on weight change at year 1)				
Time (years)[a]	−0.61	0.11	(−0.83, −0.39)	**<0.001**
Age (years)	−0.004	0.019	(−0.039, 0.031)	0.84
Creatine	0.47	0.28	(−0.08, 1.03)	0.09
Type of dopaminergic therapy (reference is Dopamine agonist only)				
Levodopa and dopamine agonist	−0.53	0.38	(−1.27, 0.22)	0.17
Levodopa only	−1.44	0.42	(−2.26, −0.62)	**0.001**
UPDRS motor score	−0.002	0.022	(−0.045, 0.042)	0.94
SDMT score	0.009	0.014	(−0.02, 0.04)	0.51
Baseline weight (kg)	0.000	0.009	(−0.02, 0.02)	0.99
LEDD (100 mg)	0.032	0.069	(−0.10, 0.17)	0.65
Male	−0.27	0.34	(−0.94, 0.40)	0.43
Anorexia, nausea, or vomiting	0.19	0.46	(−0.70,1.09)	0.67
Difficulty eating/drinking	0.33	0.30	(−0.27, 0.92)	0.28
Duration of disease (years)	−0.32	0.12	(−0.55, −0.09)	**0.007**
Average tremor score	−0.21	0.50	(−1.18, 0.77)	0.68
Postural instability	−0.63	0.56	(−1.73, 0.48)	0.27
Interactions with time (effects on the changing slope between years 1–6)				
Age by time	−0.041	0.005	(−0.05, −0.03)	**<0.0001**
Creatine by time	0.16	0.076	(0.009, 0.31)	0.04
Type of dopaminergic therapy (reference is Dopamine agonist only)				
Levodopa and dopamine agonist by time	−0.16	0.10	(−0.36, 0.03)	0.105
Levodopa only	−0.28	0.11	(−0.50, −0.06)	0.014
UPDRS motor by time	−0.016	0.006	(−0.03, −0.004)	**0.007**
SDMT by time	0.009	0.004	(0.002, 0.02)	0.02
Baseline weight by time	−0.025	0.002	(−0.03, −0.02)	**<0.001**
LEDD (100 mg) by time	−0.075	0.02	(−0.11, −0.04)	**<0.001**
Male by time	0.33	0.09	(0.15, 0.5)	**<0.001**
Anorexia, nausea, or vomiting by time	−0.21	0.13	(−0.46, 0.04)	0.1
Difficulty eating/drinking by time	−0.22	0.08	(−0.38, −0.06)	**0.007**
Average tremor by time	0.51	0.13	(0.25, 0.77)	**<0.001**
Postural instability by time	−0.53	0.16	(−0.84, −0.22)	**0.001**

Ten subjects were excluded due to missing data

The main effect of time corresponds to the rate of weight change when baseline covariates were set at the reference level (placebo, DA only, female), and continuous covariates at the overall mean. Their main effects (top section) in the table correspond to the estimated effect of the covariates on weight change from baseline to year 1. The interaction with time variables (bottom section) correspond to the covariate effects on the rate of change between year 1 and year 6. Difficulty eating/drinking refers to the sum of PDQ-39 scores question 15 (difficulty eating) and question 16 (difficulty drinking)

P-values <0.01 are in bold

DA dopamine agonist, *LD* levodopa, *LEDD* Levodopa equivalent daily dose, *SDMT* symbol digit modalities test, *UPDRS* Unified Parkinson's Disease Rating Scale

[a]Time from baseline in years

participants on levodopa experiencing 1.44 kg weight loss at year 1 compared to those on dopamine agonists only (see Fig. 1) and 0.28 kg more weight loss per year ($p = 0.014$). In addition, for every 100 mg increase in levodopa equivalent daily dose (LEDD) at baseline, participants lost 0.075 kg more per year over time ($p < 0.001$). However, when we looked at complications of levodopa therapy to identify potential mechanisms for levodopa-induced weight loss, self-reported nausea/vomiting/anorexia did not achieve statistical significance (−0.21 kg/year, $p = 0.10$) adjusting for other model covariates. Similarly presence of dyskinesia did not enter into the model, however, only 4% of participants experienced dyskinesia at baseline.

Difficulty eating and drinking (PDQ-39 questions 15 and 16) were associated with 0.22 kg/year weight loss ($p = 0.007$) while question 24 (embarrassment about eating

in public) did not enter into the final model. Surprisingly, questions about bulbar symptoms and difficulty swallowing from UPDRS part II also did not enter into the model, even though 70% of participants answered ≥1 on at least one of these bulbar symptoms. Examining dysphagia specifically, 17% of participants answered 1 or more on question 7 of the UPDRS while only 4.3% of participants answered 2 or more ("occasional choking"). Depression as measured with the BDI-II also surprisingly did not enter into this model.

Discussion

Our study is the first to examine weight changes in a large cohort of Parkinson's disease patients longitudinally. Based upon this large cohort of early treated patients, we can conclude that people with early stage Parkinson's disease experience very little weight loss (on average about 0.6 kg/year) during the first 1–6 years after starting dopaminergic replacement therapy. This is despite the fact that Parkinson's disease has long been associated with unintentional weight loss, that PD is in the differential diagnosis for unintentional weight loss [11], and that weight loss is reported to begin well before diagnosis [12]. It is in agreement with one other published study demonstrating little weight loss in the first 3 years after diagnosis [13]. Unlike other cross-sectional studies which have been previously published, our study was not biased towards patients who are experiencing unintentional weight loss. While the majority of participants did not experience significant weight loss, a minority (7.8%) did lose at least 5% of their body weight over the first year of the study. We have previously published that participants who experience a decline in BMI also experience a more rapid worsening of the UPDRS symptoms [2]. Thus, there exists a subset of Parkinson's patients in whom weight loss is clinically important.

In our study we were able to test several hypothesized causes of weight loss including difficulty self-feeding, dysphagia, intestinal hypomotility, depression, nausea, and increased energy requirements due to muscular rigidity and increased involuntary movements such as dyskinesia and tremors (reviewed in [3]). Unfortunately hyposmia and anorexia were not measured in the NET-PD LS-1 study. Difficulty eating or drinking was significantly associated with weight loss in this cohort, as one would expect, however, dysphagia, depression, dyskinesia, constipation, nausea and vomiting did not explain the weight loss that was observed, after adjusting for other covariates. We believe that the lack of association with dyskinesia and dysphagia was due to the low frequency of patients with these symptoms this early PD population. The lack of a significant association with depression, constipation, nausea or vomiting, however, is surprising, especially given that depression, as measured by the BDI, was associated with malnourishment in a prior study [5]. We can only speculate that while participants reported these symptoms, they were not severe enough to lead to weight loss. Interestingly in a cohort of more advanced PD patients, sialorrhea, dysphagia, and constipation were also not found to predict nutritional risk as measured using the malnutrition universal screening tool [14].

In our study, higher tremor scores were interestingly associated with weight gain, arguing against tremor as a significant cause of hypermetabolism and weight loss. This appears to be confirmed by doubly labeled water experiments which have shown that tremor does not increase resting energy expenditure [15]. Interestingly, a reduction in tremor has been hypothesized to partly explain the weight gain which can occur after deep brain stimulation surgery, however, weight gain after surgery may be more due to reduction in levodopa use than to a decrease in tremor [16].

In our study, treatment with levodopa (compared to dopamine agonists) and baseline levodopa equivalent dose were both associated with more rapid weight loss. This was even after adjusting for self-reported anorexia, nausea and vomiting (which are often side effects of levodopa treatment), suggesting that levodopa is affecting weight through some other mechanism. While dopamine agonists are associated with weight gain, we also found a dose-dependent effect of levodopa, which argues in favor of a direct effect of levodopa on weight loss. This association has been observed in other cross-sectional studies [5, 17]. Because this was an observational study, it is also possible that the greater weight loss observed in participants prescribed levodopa was due to them having a more severe form of PD.

We were very interested to find that participants lost on average 0.53 kg/year for every unit increase in their postural instability score. While weight loss is commonly considered a symptom of autonomic involvement, to our knowledge, this is the first study to find a direct association between postural instability and weight loss. Postural instability is associated with other forms of autonomic involvement including anosmia [18] (which was not measured in our study) and gastrointestinal disturbance (which was only measured using self-reported constipation). This correlation might also at least in part explain the association which we previously observed between decline in BMI and more rapid change in UPDRS [2]. Alternatively, it is possible that this association was due to inclusion of atypical Parkinsonian disorders which are more frequently associated with dysphagia and weight loss [19, 20]. However, in the NET-PD LS-1 study, 94% of enrollees were deemed by the investigators to have >90% probability of a diagnosis of idiopathic Parkinson's disease, thus we do not believe atypical cases could fully account for this association.

Our study was subject to several limitations which do not allow us to generalize these findings to Parkinson's disease patients in general. First, the study enrolled only patients with early Parkinson's disease and weight loss is likely to become more significant as the disease progresses. Studying prospective predictors of weight loss in a more advanced population would be helpful for clinicians trying to manage this symptom. Second, the duration of follow-up (mean follow-up 4.1 years from baseline) may not have been adequate to capture gradual weight loss. Third, participants enrolled in the NET-PD LS-1 study were not representative of the PD population as a whole, given that participants were in general younger, healthier and better educated than average. Despite these limitations, we believe that the study will be helpful in guiding clinicians towards identifying patients at higher risk of weight loss. We believe that a follow-up study which measures dietary intake, appetite, olfaction, and other autonomic features should be performed to better understand weight loss in Parkinson's disease.

Conclusions

In the first 1–6 years after diagnosis, Parkinson's disease patients on average experience very little weight loss. Predictors of weight loss early in the course of the disease include female gender, higher body weight at baseline, older age, higher motor UPDRS scores, greater postural instability, lower SDMT cognitive scores, and use of levodopa dopaminergic replacement therapy.

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Author contributions RL carried out data management, statistical programming and biostatistical analysis. RL and AP both carried out the biostatistical analysis.

Compliance with ethical standards

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Conflicts of interest The authors declare no conflicts of interest.

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