Ferrusola-Pastrana, A., Davison, G., & Meadows, S. N. (2023). The therapeutic effects of multimodal exercise for people with Parkinson's: A longitudinal community-based study. Parkinsonism & Related Disorders, 105366. (DOI: https://doi.org/10.1016/j.parkreldis.2023.105366**)**

The Therapeutic Effects of Multimodal Exercise for People with Parkinson's: A Longitudinal Community-based Study

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Abstract word count: 249

Text-only word count: 3931

Abstract

Introduction: Individuals with Parkinson's Disease (PD) can develop a range of motor and non-motor symptoms due to its progressive nature and lack of effective treatments. Exercise interventions, such as multimodal (MM) programmes, may improve and sustain physical or cognitive function in PD. However, studies usually evaluate physical performance, cognition, and neuroprotective biomarkers separately and over short observation periods. **Methods:** Part one evaluates the effects of a weekly community-based MM exercise class (60 min) on physical function in people with PD (PwP). Exercise participants (MM-EX; age 65 ± 9 years; Hoehn and Yahr (H&Y) scale ≤ IV) completed a battery of functional assessments every 4 months for one (n = 27), two (n = 20) and three years (n = 15). In part two, cognition and brain-derived neurotrophic factor (BDNF) levels were assessed over 6-to-8 months and compared to aged-matched non-active PwP (na-PD, n = 16; age 68 ± 7 years; H&Y scale ≤ III) and healthy older adults (HOA, n = 18; age 61 ± 6 years). **Results:** MM-EX significantly improved walking capacity (5% improvement after 8 months), functional mobility (11% after 4 months), lower extremity strength (15% after 4 months) and bilateral grip strength (9% after 28 months), overall, maintaining physical function across 3 years. Group comparisons showed that only MM-EX significantly improved their mobility, lower extremity strength, cognition and BDNF levels. **Conclusion:** Weekly attendance to a community-based MM exercise group session can improve and maintain physical and cognitive function in PD, with the potential to promote neuroprotection.

Highlights

- Community-based multimodal exercise offers a structured, feasible and safe strategy that can effectively be maintained over multiple years for people with Parkinson's Disease (PwP).
- Weekly attendance at a community-based group exercise class, in the form of a multimodal programme, shows improvements in physical function, cognition and BDNF in PwP.
- Exercise maintains function and avoids declines in PwP's walking capacity, functional mobility, grip or leg strength across all study monitoring periods (for up to 3 years).
- Engaging with exercise may be key in order to obtain improvements in physical function, cognition and BDNF in PwP.

Introduction

Parkinson's Disease (PD) is a neurodegenerative condition in which symptoms worsen over time and medication management becomes more difficult and less effective. Non-pharmacological approaches, like exercise, have proven to be a valuable therapy to improve pathognomonic signs of PD (e.g., motor, cognitive and behavioural impairments) [1,2]. However, despite the rapid accumulation of positive evidence supporting exercise as medicine for PD, people with PD (PwP) are 30% less active than age-matched healthy controls, even in early disease stages where their capability to perform exercise is comparable to that of healthy individuals [3]. It is thus imperative to investigate and design exercise interventions specific to PwP which help to overcome barriers to exercise, promote compliance and meet their needs.

Although several exercise modalities have been investigated, it is not clear which modality and dose of exercise (i.e., type, duration, frequency and intensity) are superior to address PD symptoms and elicit a therapeutic response. Nonetheless, current advice [4] recommends working at a high intensity with goal-related exercises (mimicking activities of daily living [ADLs]); using complex and combined movements with cognitive load, posture control, and promoting symmetry and full range of motion rather than performing individual exercise modalities alone [5–9]. Multimodal (MM) exercise interventions, which include multiple components of fitness (i.e., aerobic, flexibility, resistance, and neuromotor), potentially offer great utility due to their capacity to improve physical function and reduce PD's disability [7,8,10–12]. Besides, MM training is the preferred mode of exercise for PwP [13] and seems to be the most effective intervention to improve functional outcomes in older adults [14,15]. Importantly, it can easily be implemented in real-life settings (e.g., community-based), such as circuit training, where different functional and cognitive exercises can be integrated into a single session to also promote neuroplasticity (through exercise parameters such as intensity, repetition, specificity and difficulty of practice) [5,9].

Research supports exercise-induced neuroplasticity through the enhancement of trophic factors (e.g., brain-derived neurotrophic factor [BDNF]), potentially slowing down PD progression and improving brain function [16,17]. Although there is evidence suggesting that both intervention and individual session duration may influence neurotrophic factor levels [18], brain structure and function [17], most studies in PwP have focused on short interventions (<12 weeks) without evaluating more chronic changes in BDNF, or comparing them to other populations (e.g., PwP that are non-exercisers or healthy adults) [19]. Hence, there is a need to develop long-term interventions and treatment regimes that elicit long-lasting benefits for PwP.

Accordingly, a MM exercise intervention was designed to address the following domains: physical function (e.g., postural control, range of motion, coordination, balance, strength and aerobic capacity) and cognition (e.g., executive function, dual tasking [which require the simultaneous performance of a motor and cognitive task]). The objective of the first part of this study was to evaluate the long-term

effects of a weekly MM community-based exercise class for PwP on physical function. Finally, the second part of the study compares the BDNF levels, cognition and physical function of the MM exercising group (MM-EX) with a non-active group of PwP (na-PD) and healthy older adults (HOA) to help better understand the impact of the MM exercise intervention and PD's progression on physical function, cognition and BDNF.

Methods

Expanded methodology is available in **Supplementary Material**.

Study Design

The study was approved by the Research Ethics Committee at the University of Kent (Prop 04_2016_2017, Prop 61_2017_18 and Prop 63_2018_19) and is presented in two parts. Part one, initially designed as a pilot study following an observational opportunistic design, evolved into a long-term evaluation of MM exercise on health parameters and functional capacity for up to 3 years. Part two presents a non-randomized open label quasi-experimental study that compares the MM-EX group to two comparison groups (a group of healthy older adults [HOA] and a group of non-active PwP [na-PD]). Thus, using circuit training as a multi-component exercise intervention (namely MM), part two assesses the impact of MM exercise on physical function, cognition, and BDNF levels over 6-to-8 months, in a community-based group of PwP compared to two experimental groups of participants that did not engage with the MM exercise class.

Participants

Participants involved in the studies included people with mild-to-moderate PD (Hoehn & Yahr [H&Y] stage I, II, III or IV) and healthy older adults (HOA) to better understand the normal progression and expected changes in the study parameters over time in both the HOA and PD groups. The Physical Activity Readiness Questionnaire (PAR-Q) was completed by all participants [4]. Participants were excluded if they had any other neurological disease (apart from PD), cognitive decline (i.e., delirium or dementia), and any significant physical and/or sensory impairment.

PwP were instructed to take medication before starting the exercise or assessments to perform each assessment in an "on-medication" state, except for drug naïve participants. Any dosage or medication changes during the duration of the studies were recorded and levodopa equivalent daily doses (LEDD) were calculated to estimate the total daily antiparkinsonian medication that participants were receiving.

Assessments

In part one of the study, participants that completed the MM programme for up to 3 years were a subset of the group of participants included in part two of the study (n = 30; see **Supplementary Figure 1**). The MM intervention was delivered for 3 months on a weekly basis and the assessments were completed prior to the university semester holidays (i.e., easter, summer and winter) where participants had a break for approximately 4 weeks. During this time, participants were advised to stay active and keep practicing the exercises at home.

Part two, initially aimed to compare three groups of participants (MM-EX, na-PD and HOA) throughout 1 year. However, due to the COVID-19 pandemic, the intervention and scheduled assessments were interrupted and only 3 out of the initial 5 assessments for na-PD and HOA were included in the analyses as depicted in the **Supplementary Figure 1**.

Data Collection

In both parts of the study, a battery of tests widely used in PD research and clinical settings were completed at each assessment to provide an objective real-world and familiar assessment of mobility and physical function [2]. These were the 6-minute walking test (6MWT; measure of walking capacity), 3 trials of the timed up-and-go test (TUG; measure of mobility) that were averaged, 1-minute sit-to-stand test (1-STS; measure of functional lower extremity strength), and 3 trials of bilateral grip strength (GS) that were averaged across sides.

Part two of the study included additional measures to evaluate the underlying biological mechanisms of MM exercise. Thus, finger-tip capillary blood was collected to investigate exercise-related changes in BDNF using an immunoassay (DuoSet ELISA Development System, Abingdon Science Park, UK), DNA was isolated from saliva samples collected by passive drool and assessed by Polymerase Chain Reaction (PCR) for the single nucleotide polymorphism (SNP) in the BDNF gene (variant rs6265 Val66Met polymorphism; see **Supplementary Material** for protocols), and cognitive function evaluated with the Mini Mental Parkinson's (MMP; cognitive screening tool that measures attention, conceptualisation, construction, initiation/perseveration and memory, and has a maximum score of 32), the Trail Making test A and B (TMT-A and TMT-B; tests of psychomotor speed, visual attention and task switching) and the Clock Drawing test (CDT; cognitive screening tool that measures spatial dysfunction and neglect) [20–22].

Community-based Multimodal Exercise Class

Participants joined the MM exercise class on a rolling basis, starting sometime between the end of 2016 and the beginning of 2020. The circuit-based MM programme was completed weekly in a community hall, with each session lasting one hour.

The exercises, organised in stations, were meaningful (transferable to ADLs), goal-related, with combined movement and cognitive challenges, and designed to tackle and improve PD specific characteristics, such as gait impairments, balance problems, rigidity or bradykinesia, amongst others (see **Supplementary Table 1** for further details on the structure and training components of the class). Emphasis was put on repetition and moving through a full range of motion with big, global, and multidirectional movements. The order of the stations was carefully selected and organised not only based on the symptoms that were being addressed with each exercise but also mixing aerobic exercises with strength whilst trying to alternate muscle groups (including upper and lower body).

All participants exercised together as a group but were encouraged to work "as hard as they can", according to their own perceived effort for each activity, at level 13 using the 6-20 point rating of perceived exertion (RPE) Borg scale (i.e., aiming for at least "somewhat hard") [23]. Working at higher intensities and complexity leads to greater learning and structural changes in the brain (i.e., enhanced neuroplasticity) [9]. Thus, verbal feedback, cues that drew attention to the tasks, and encouragement were provided to all participants to modify and strengthen existing motor circuits that help consolidate a learned behaviour [9]. Session RPE was obtained at the end of each exercise class, which has been validated for PwP as a valid measure of intensity [23].

All sessions were monitored by at least two exercise professionals that also invited student volunteers from the School of Sport and Exercise Sciences, University of Kent, to the class. Students were previously introduced to the particularities of this programme and instructed to work closely with participants at each station providing instructions and verbal encouragement to motivate the overall class to exercise at moderate-high intensities, maintaining large ranges of motion and completing the exercises with the appropriate technique.

Statistical Analysis

Parametric assumptions were tested for each test and raw data corrected by log-transformations if needed (i.e., for the TUG). If transformations were not successful or comparisons between small sample sized groups were required, non-parametric tests were used. In part one of the study, linear mixed-effects models (with post-hoc Bonferroni-corrected t-tests) were used with time as a fixed effect and subject as random effect. Age, disease duration (i.e., months since diagnosis), H&Y scale stage and LEDD were evaluated as covariates but only LEDD resulted in a significantly better model fit. Further details on the statistics and covariates added to the analyses can be found in the **Supplementary Material**. All data were analysed on an intention-to-treat basis [14]. In part two of the study, linear mixed-effects models were built using group (MM-EX, na-PD and HOA) and time (baseline 1st, 2nd and 3rd assessment) as a fixed effect and subjects as a random effect. BDNF group comparisons were completed using linear mixed-effects models and a one-way analysis of covariance (ANCOVA), treating the baseline

measurement as covariate. Statistical analyses were performed using SPSS 27 (IBM, Armonk, NY) and R (www.r-project.org) software packages and the level of significance was P<.05.

Results

Participants' baseline and demographic information is summarised in **Table 1** where no differences between MM-EX and both comparison groups were shown. However, the na-PD group, were significantly older than the HOA group but similar on all other demographic variables. Medication changes were recorded and no significant changes in LEDD were detected throughout the study.

Part One

There was an average of 17 MM-EX participants per exercise session (range: 8 – 24) with a high attendance rate (79%). Over more than 2200 person-hours of participation in the programme, no injuries or other adverse events were reported by participants. Mitigating measures to reduce adverse effects of exercise were weekly checks of cardiovascular health status (i.e., resting heart rate [HR] pre and post exercise expected to be similar) and any changes in PD's symptomatology and/or medication.

Intensity (RPE)

On average, participants exercised at RPE 13.3, which corresponds to a "somewhat hard" effort. This was comprised of 3% exercising at RPE 11, 18% at RPE 12, 42% at RPE 13, 24% at RPE 14, 9% at RPE 15 and 3% at RPE 16.

Health Measurements

Yearly values of body mass index (BMI) and waist circumference (WC) showed no significant changes over time (all comparisons presented P>.05).

Functional Outcomes

All functional outcome measures can be seen in **Table 2**.

Part Two

The short version of the International Physical Activity Questionnaire (IPAQ) was used to estimate the levels of total physical activity that participants were engaging with outside of the exercise class. With a non-significant interaction, group or time effects, the na-PD presented lower values of physical activity (28 MET-h/week) compared to both HOA (71 MET-h/week) and MM-EX (54 MET-h/week) levels, which were maintained throughout the study (see **Supplementary Table 2**).

Health Measurements

There were no significant BMI changes over time or between groups. Nonetheless, there was a significant decrease of WC for the HOA in both the 2nd and 3rd assessments compared to the 1st (*b*=-2.033, *t*(119)=-2.475, P=.044, and *b*=-2.528, *t*(119)=3.077, P=.008, respectively).

Functional and Cognitive Outcomes

All functional and cognitive measures are presented in **Table 3**. Given the nature of the study (i.e., opportunistic), only those MM-EX participants that completed all the baseline assessments before starting the MM exercise intervention were included in the group comparison analyses of cognitive function.

Two participants (1 MM-EX, 1 na-PD) were unable to complete the TMT-B on one occasion, and 1 participant from the MM-EX group could not complete the TMT-B on any of the assessments and could not be included in the analyses.

Descriptive statistics and a qualitative assessment of the results were used to analyse the CDT data. All the participants in the HOA group, and most of the MM-EX (n = 7) and na-PD (n = 14) participants, obtained the highest scores possible (i.e., a score of 4). As a note of interest, MM-EX participants that obtained lower CDT results, also presented higher (i.e., worse) scores in the TMT and were later diagnosed with dementia (n = 4).

BDNF Genotyping

BDNF genotype distribution did not significantly differ between groups. However, a significant association between allele frequency and group was found. Post hoc analyses revealed a significant excess of the Val allele in both MM-EX and na-PD groups compared to HOA (P=.007, see **Table 4**). Subsequently, individuals with Val/Met or Met/Met genotypes were combined (Met carriers; $BDNF_{MET}$) and BDNF levels were compared with individuals with the Val/Val genotype ($BDNF_{VAL}$). Nonetheless, based on genotype, BDNF levels did not significantly differ across groups or study assessments (all P>.05).

Finger Prick BDNF

A significant time by group interaction (F(2,34)=7.654, P=.002, η^2_p=0.310) was observed, where both HOA and na-PD BDNF values significantly decreased from baseline to the 3rd assessment, whilst MM-EX BDNF significantly increased. To account for inter-individual variability and more correctly estimate the effect of MM exercise, the mean concentration of BDNF at the 3rd assessment was adjusted for baseline BDNF levels and the ANCOVA showed that BDNF levels were significantly greater in

MM-EX (3890 pg/mL [95% CI, 2570-5888]) compared to HOA (1479 pg/mL [95% CI, 1096-2042]) and na-PD (1549 pg/mL [95% CI, 1096-2239) ($F(2,33)=7.899$, $P=.002$, $\eta^2_p=0.320$).

Discussion

The present study shows that a weekly, supervised, structured, community-based MM group exercise programme is feasible and safe for PwP. Across 1, 2 and 3 years, exercising participants showed significant improvements in walking capacity, mobility, and functional lower extremity strength. Importantly, no significant declines were observed for any of the outcomes being measured, which is particularly relevant for PwP due to the chronic progressive nature of PD.

In accordance with the present results, previous studies have demonstrated that regular structured exercise is beneficial for PwP and have provided useful reference values, such as the Minimal Clinically Important Difference (MCID), for some measures. The longitudinal evaluation of participants that engaged with the MM class for 1 year, showed significant improvements in walking capacity after 3 assessments (approximately 8 months). This improvement resulted in participants being able to walk 22 metres further during the 6MWT (note: MCID = 14.0 to 30.5 metres) [24]. Further improvements in the 6MWT were also observed in the MM-EX compared with the na-PD (15 metres). For TUG, wide variations and MCIDs of up to 3.5 sec have been reported [25]. Although our results did not meet these suggested MCIDs, MM-EX participants were able to significantly improve their TUG (functional mobility) even after 3 years. This observation is important, since previous research evaluating aerobic exercise and sensory attention focused exercise found no significant improvements in TUG [26]. Moreover, compared to the MM-EX, the na-PD group TUG scores were slower and did not significantly change from baseline. Regarding 1-STS, the MM-EX group was able to significantly improve across 1, 2 and 3 years of MM exercise. Compared to na-PD, the MM-EX significantly improved their number of repetitions by 3, whilst the na-PD scores did not change throughout the study. The 3 year MM-EX was also the only group that significantly improved their left GS after 8 assessments, which has been suggested to improve ADLs performance and overall health [27]. In all the other study lengths for up to 3 years, function was maintained and, therefore, there were not any declines in walking capacity, functional mobility, grip or leg strength.

The current study was able to show the potential of MM exercise to improve PwP's cognition and adds to the growing body of literature suggesting that physical activity may enhance cognitive function in PD [1,9]. Study comparisons showed that only the MM-EX group significantly improved their cognitive function measured with the MMP, whilst the HOA and na-PD did not present any changes after 6 months. Increases in MMP scores suggest an improved mental imagery, use of internal cues, orientation (temporal and spatial), attention, mental control (frontal abilities), verbal fluency and concept processing [20]. The lack of a differential effect of group on the CDT could be limited by a ceiling effect, with most participants obtaining the maximum score for this test. To prevent any learning effects on the

performance of cognitive tests due to exposure to them at baseline, a relative long duration between assessments (3-to-4 months) was set. The fact that none of the study groups significantly improved their scores at the second assessment suggests that any possible learning effect were minimised after baseline.

The measurement of systemic concentrations of BDNF has been proposed as a biomarker for cognitive state in PD [28]. In the present study, the MM-EX group presented an increase in their basal levels of BDNF, whilst BDNF levels of HOA and na-PD were significantly lower than MM-EX after 6 months, which is consistent with previous studies reporting that circulating levels of BDNF decline over time [29]. Thus, increased levels of this important neuroprotective factor were only observed in participants that completed the MM intervention. Interestingly, similar distributions of BDNF genotype (GG, GA, AA) were observed across the study groups. However, when looking at the allele distribution, both PD groups presented a different allele distribution (i.e., a significant excess of the Val allele) compared to the HOA group although BDNF levels of participants with the $BDNF_{MET}$ genotype did not significantly differ from those of participants with the $BDNF_{VAL}$ genotype.
It is also important to note that the MM exercise intervention was delivered in a specific social context (i.e., group setting) that may also provide psychosocial benefits, and this could be a separate contributing factor to the benefits observed here. Altogether, community-based MM exercise for PwP is a structured, feasible, safe, highly reproducible strategy that requires minimal equipment and has the potential of arresting PD's progression. Furthermore, MM-EX participants presented neuroprotective, functional, and cognitive improvements that were not observed in PwP that did not complete this exercise modality. These findings should be confirmed by future studies that, preferably, follow a structured randomised control trial (RCT) design.

As a strength of the study, the long-term duration of the MM community-based exercise class (up to 3 years), and the multidimensional assessment of participants' outcomes (biomarker levels, physical function and cognition) can be highlighted. However, given the fact that PD is a slow progressive condition (with a variable rate of progression across individuals), and that age-related declines in function take time to develop, the length of the intervention for the comparison groups (HOA and na-PD) may have been insufficient to observe any significant declines in function over time. Nonetheless, as mentioned above, the length of the intervention was sufficient to show differences in capillary BDNF levels amongst groups. A major reason for the shortened length of the intervention for the comparison groups was the COVID-19 pandemic, which meant that exercising groups and any data collection had to suddenly stop in March 2020.

Limitations

The design of the present study, being quasi-experimental, offers a practical option to conduct impactful interventions in real world settings and can achieve a better balance between internal and external validity than most true experiments [30]. However, it lacks participant blinding and random assignment

to the intervention group, which were not logistically possible. Thus, compared to RCTs, the conclusions made about causality in the current study must be interpreted with caution. To reduce bias for the intervention group, baseline demographic data were evaluated to ensure appropriate matching with the comparison groups. For the MM-EX group, a convenience sampling method was used where most recruited participants were members of an active PD's Local Support Group that were pro-actively seeking to engage with a specific exercise class for PwP. Therefore, this sample may not be representative of the whole PD population and would have been of great interest to include more PwP that do not engage with support groups. Although IPAQ measurements were completed, objective measures of activity (e.g., using activity trackers or accelerometers) were not obtained. This limited the researcher's abilities to accurately account participants' activity levels outside of the MM class. Nonetheless, changes over time were evaluated and participant's data showed that estimated levels of total physical activity in MET-h/week remained constant throughout the study.

Finally, due to not having a comparison group performing an exercise modality that was not MM exercise, it is not possible to corroborate whether the observed benefits arise due to a single component or other characteristics of the MM programme (i.e., synergistic effects of the combination of strength, aerobic and cognitive components). Silveira and colleagues, demonstrated that aerobic exercise was more effective than goal-based exercise in improving cognition in PwP [31]. However, we have observed improvements in both physical and cognitive function, which could be enhanced by the MM nature of the exercise programme. Moreover, a MM programme including an aerobic component as well as goal-based and cognitive exercises might be able to improve both physical and cognitive function better than practicing those modalities alone, where goal-based modalities have been successful in improving motor symptoms and aerobic exercise promoted cognitive benefits [9,31]. In the present MM study improvement in both domains were observed and our results are in line with research undertaken in older adults [8]. Nonetheless, further research is required to clarify the origin of the beneficial effects elicited with the evaluated MM intervention.

Conclusion

The results of this study show that once a week attendance to a community-based MM exercise class for up to 3 years, can benefit physical and cognitive performance in PwP. It was observed that the HOA generally outperformed the MM-EX and na-PD. However, in contrast to the na-PD, only the MM-EX group was able to significantly improve both their physical and cognitive function, which was also reflected in higher BDNF levels. It is worth highlighting that these results were observed with a session running only once a week (i.e., long-term regular sessions rather than an intensive programme over a short period [32]) and improvements were most likely seen after 4-to-8 months. The community-based MM programme described in this study presents a specific, supervised, safe, reproducible, low-cost programme with clinical applicability that has the potential to benefit many aspects of motor and cognitive dysfunction in PD. Future studies should complete larger multi-centre RCTs to build on the

encouraging results obtained in this study and provide a more complete understanding of the disease-modifying role of MM exercise for PwP.

Acknowledgments

The authors would like to thank the Medway Working Age Group (MWAG) for their critical support and involvement throughout the study. We also thank Roisin Cox, Deana Stephens, and Emma Mundy for their important involvement at the initial stages of the programme, the student volunteers from the School of Sport and Exercise Sciences, University of Kent, for their assistance during the exercise classes, Dr Chris Fullerton for his expertise and assistance with cognitive data collection, Megan Judge, Hannah Sangan, Robert Hunter, Sam Smith, Borja Martinez-Gonzalez, and Ian Farr, for their assistance with aspects of data collection, the European School of Osteopathy (ESO) for their support and use of facilities, and, last but not least, all the study participants who participated in this project.

Funding details

Parkinson's Equip provided the start-up funding for the exercise group.

Declaration of interest statement

No potential conflict of interest was reported by the authors.

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Tables

Table 1 Demographic data of MM exercise class participants (MM-EX) and comparison groups; non-active people with Parkinson's (na-PD) and Healthy Older Adults (HOA). One way ANOVA and Mann-Whitney U tests were conducted between HOA, na-PD and MM-EX participants from the group comparison analyses. Mean values ± standard deviations are listed. For all other variables, Chi-square and Fisher's exact tests were calculated and frequency counts indicate the number of participants in each category relative to their grouping with the proportion of the sample in parenthesis. [a]Significant differences between HOA and na-PD. [b]Significant differences between HOA and MM-EX. [c]Significant differences between MM-EX and na-PD. [d]No significant differences after Bonferroni adjustments. BMI, body mass index. LEDD, levodopa equivalent daily dose.

Group n	**HOA** (n=18)	**na-PD** (n=16)	**MM-EX** (n=30)	***P***
Gender				
Female	11	5	5	
Male	7	11	25	
Age (years)	61 ± 6	68 ± 7	65 ± 9	0.040[a]
BMI (kg/m^2)	27.9 ± 4.6	29.0 ± 3.9	28.5 ± 3.2	0.719
Years since PD diagnosis	N/A	4 ± 2	5 ± 6	0.933
Hoehn and Yahr Stage	N/A			0.728
Stage 1		10 (63%)	13 (43%)	Fisher's Exact
Stage 2		2 (13%)	5 (17%)	Test
Stage 3		4 (25%)	11(37%)	
Stage 4		0	1 (3%)	
PD Staging	N/A			1.000
Early		7 (44%)	13 (43%)	Fisher's exact
Moderate		9 (56%)	16 (53%)	test
Advanced		0	1 (3%)	
LEDD	N/A	494 ± 233	581 ± 483	0.501
Comorbidities				
Hypertension	2 (11%)	0	8 (28%)	
Hypotension	0	0	3 (10%)	
Arthritis	0	1 (6%)	6 (21%)	
Joint replacement	0	0	1 (3%)	
Cancer	0	1 (6%)	2 (7%)	
Epilepsy	0	0	1 (3%)	
Heart Disease	0	0	4 (14%)	
Regular exerciser at baseline?				.024[d] Fisher's exact
Yes	17 (94%)	13 (81%)	18 (60%)	test
No	1 (6%)	3 (19%)	12 (40%)	
Side Affected	N/A			.024[d]
Left		10 (63%)	7 (23%)	Fisher's exact
Right		3 (19%)	11 (37%)	test
Both		3 (19%)	5 (17%)	
N/A		0	7 (23%)	
Employment Status				0.066
Retired	7 (39%)	12 (75%)	13 (43%)	
Employed	11 (61%)	4 (25%)	17 (57%)	

Table 2 Estimated marginal means for each physical function measurement throughout the assessments (1st to 10th) and its respective 95% confidence intervals (CI). Numbers in bold represent significant improvements compared to the 1st assessment (P<.05).

Physical Outcome Measure	*1st*	*2nd*	*3rd*	*4th*	*5th*	*6th*	*7th*	*8th*	*9th*	*10th*
6MWT 1 yr (m)	425 (399-451)	426 (400-452)	**447 (421-473)**	432 (406-458)						
6MWT 2 yr (m)	421 (386-455)	412 (378-447)	436 (402-471)	418 (383-452)	415 (381-450)	426 (392-460)	408 (374-442)			
6MWT 3 yr (m)	423 (378-468)	415 (370-460)	437 (392-482)	428 (384-473)	424 (379-469)	434 (389-479)	416 (371-461)	415 (370-460)	421 (376-466)	418 (373-463)
TUG 1 yr (sec)	8.9 (8.1-9.1)	**8.1 (7.4-8.8)**	**8.2 (7.5-9.0)**	8.4 (7.7-9.2)						
TUG 2 yr (sec)	9.1 (8.2-10.1)	**8.1 (7.3-9.0)**	**8.4 (7.6-9.2)**	8.6 (7.7-9.5)	**8.4 (7.6-9.2)**	8.5 (7.7-9.4)	**8.4 (7.6-9.3)**			
TUG 3 yr (sec)	9.1 (8.0-10.5)	**8.1 (7.0-9.3)**	**8.1 (7.1-9.4)**	**8.4 (7.4-9.7)**	**8.1 (7.1-9.3)**	**8.3 (7.2-9.5)**	**8.1 (7.0-9.2)**	**7.8 (6.8-9.0)**	**8.2 (7.2-9.4)**	**8.3 (7.2-9.5)**
1-STS 1 yr (rep)	20.3 (18.0-22.6)	**22.8 (20.5-25.2)**	**22.7 (20.3-25.0)**	21.7 (19.4-24.1)						
1-STS 2 yr (rep)	20.4 (17.8-23.0)	**23.3 (20.7-25.9)**	**22.4 (19.9-25.0)**	22.2 (19.6-24.8)	21.6 (19.0-24.1)	21.2 (18.6-23.8)	22.1 (19.5-24.7)			
1-STS 3 yr (rep)	20.9 (18.3-23.4)	**23.5 (20.9-26.1)**	**24.1 (21.5-26.6)**	22.5 (19.9-25.0)	**23.1 (20.5-25.6)**	21.1 (18.5-23.6)	22.5 (19.9-25.0)	22.7 (20.2-25.3)	21.9 (19.3-24.4)	22.1 (19.5-24.6)
L-GS 1 yr (kg)	32.8 (29.0-36.6)	33.3 (29.5-37.1)	32.8 (29.0-36.6)	33.0 (29.2-36.8)						
L-GS 2 yr (kg)	33.0 (28.9-37.9)	32.3 (28.2-36.4)	31.6 (27.5-35.6)	32.4 (28.4-36.5)	32.3 (28.1-36.3)	33.0 (29.0-37.1)	33.6 (29.5-37.7)			
L-GS 3 yr (kg)	35.7 (31.6-39.8)	34.9 (30.9-39.0)	34.0 (29.9-38.1)	35.0 (31.0-39.1)	35.1 (31.0-39.1)	35.7 (31.7-39.8)	36.8 (32.7-40.8)	**38.8 (34.7-42.8)**	36.5 (32.4-40.5)	34.8 (30.7-38.8)
R-GS 1 yr (kg)	31.1 (27.9-34.4)	31.5 (28.2-34.8)	30.9 (27.6-34.2)	30.6 (27.3-33.8)						
R-GS 2 yr (kg)	32.0 (28.5-35.4)	31.4 (28.0-32.9)	30.8 (27.4-34.3)	30.3 (26.9-33.8)	32.3 (28.9-35.8)	31.8 (28.3-35.2)	30.4 (27.0-33.9)			
R-GS 3 yr (kg)	33.7 (30.1-37.3)	32.2 (28.6-35.8)	32.2 (28.6-35.8)	32.0 (28.4-35.6)	33.5 (30.0-37.1)	33.1 (29.5-36.7)	32.5 (29.0-36.1)	35.6 (32.0-39.1)	33.7 (30.1-37.3)	32.1 (28.6-35.7)

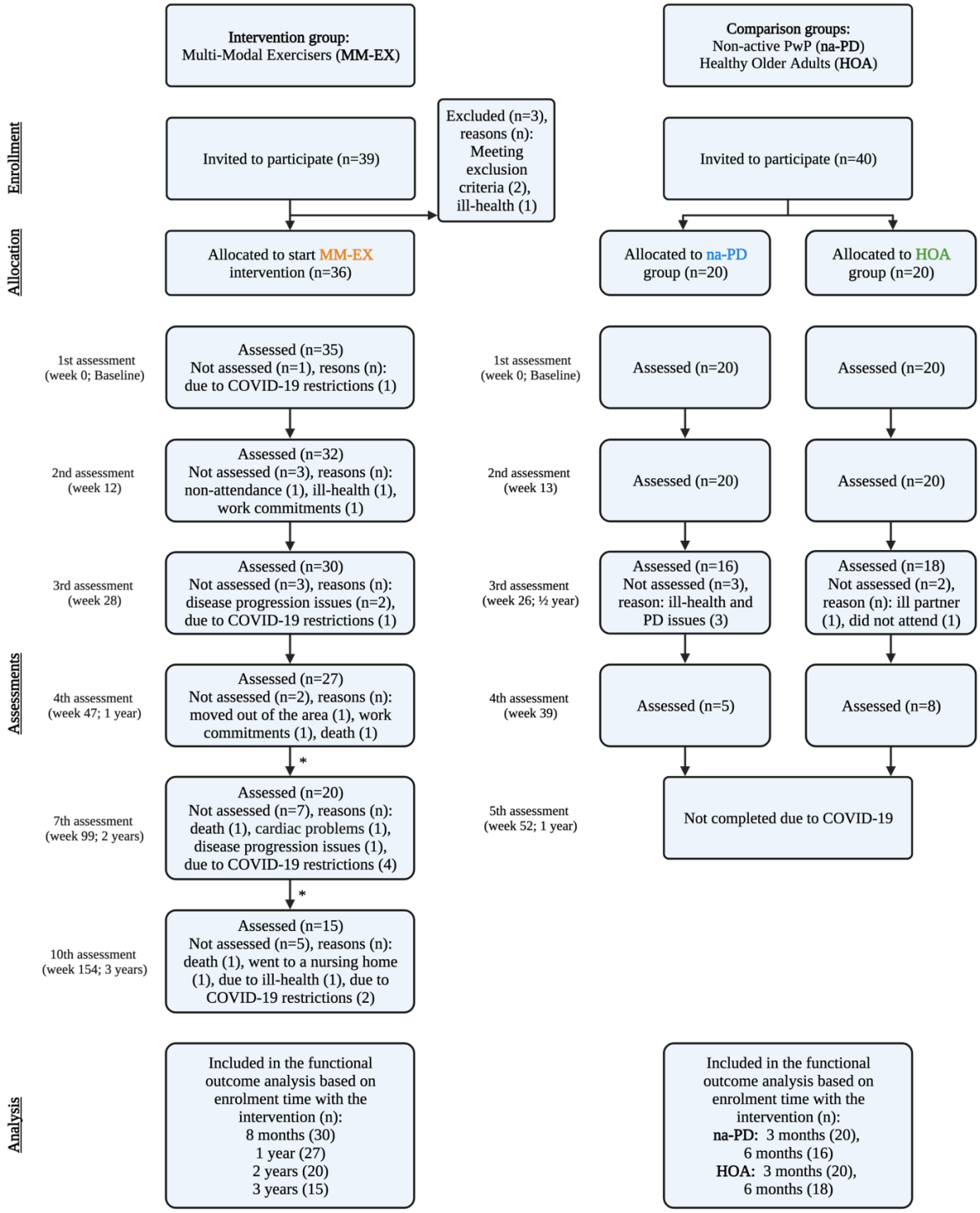
Table 3 Estimated marginal means for each group's physical and cognitive function measurement throughout the assessments and its respective 95% confidence intervals (CI). Numbers in bold represent significant improvements compared to: [a]1st assessment, [b]HOA group, [c]MM-EX group or [d]na-PD group (P<.05). *Significant differences compared to previous assessment.

	Group	***n***	***1st Assessment (Baseline)***	***2nd Assessment***	***3rd Assessment***
Physical Outcome Measures					
6MWT (m)	**HOA**	18	**560 (516-604)[c,d]**	**569 (525-613)[c,d]**	**589 (545-633)[a,c,d]**
	MM-EX	29	430 (396-465)	428 (393-463)	443 (408-478)
	na-PD	16	427 (380-474)	437 (390-483)	438 (392-485)
TUG (sec)	**HOA**	18	**6.6 (5.8-7.4) [c,d]**	**6.8 (6.0-7.7) [c,d]**	**6.4 (5.6-7.2) [c,d]**
	MM-EX	30	9.1 (8.2-10.0)	**8.3 (7.5-9.1)[a]**	**8.3 (7.6-9.2)[a]**
	na-PD	16	9.5 (8.3-10.8)	9.3 (8.1-10.6)	8.9 (7.8-10.1)
1-STS (rep)	**HOA**	18	**27.3 (24.2-30.5)[c,d]**	**27.3 (24.2-30.5)[d]**	**29.8 (26.7-33.0)[c,d]**
	MM-EX	30	20.1 (17.6-22.5)	**23.0 (20.5-25.4)[a]**	**22.8 (20.3-25.2)[a]**
	na-PD	16	19.5 (16.1-22.9)	19.8 (16.4-23.1)	20.1 (16.7-23.5)
L-GS (kg)	**HOA**	18	31.2 (26.9-35.5)	30.9 (26.6-35.2)	32.0 (27.7-36.3)
	MM-EX	30	31.2 (28.4-35.1)	30.8 (27.4-34.2)	30.8 (27.4-34.2)
	na-PD	16	28.2 (23.6-32.8)	29.0 (24.4-33.6)	28.5 (23.9-33.1)
R-GS (kg)	**HOA**	18	34.6 (29.8-39.3)	36.0 (31.3-40.8)	35.6 (30.9-40.3)
	MM-EX	30	32.8 (29.2-36.5)	33.4 (29.7-37.0)	32.9 (29.2-36.6)
	na-PD	16	31.3 (26.2-36.3)	31.4 (26.4-36.4)	30.9 (25.9-36.0)
Cognitive Function Measures					
MMP (score)	**HOA**	18	30.0 (28.7-31.3)	29.9 (28.6-31.2)	30.2 (28.9-31.5)
	MM-EX	9	28.2 (26.4-30.1)	27.9 (26.0-29.7)	**29.8 (27.9-31.6)***
	na-PD	16	28.5 (27.1-29.9)	28.5 (27.1-29.9)	28.6 (27.2-30.0)
TMT-A (sec)	**HOA**	18	24.3 (18.1-30.5)	23.2 (16.9-29.4)	23.1 (16.9-29.3)
	MM-EX	8	**39.7 (30.3-49.2)[b]**	33.8 (24.5-43.2)	34.9 (25.6-44.2)
	na-PD	16	33.1 (26.5-39.7)	**34.5 (27.9-41.1)[a]**	31.8 (25.2-38.4)
TMT-B (sec)	**HOA**	18	46.3 (23.2-69.4)	43.5 (20.4-66.5)	42.8 (19.7-65.8)
	MM-EX	8	79.4 (43.8-114.9)	71.7 (37.1-106.3)	**96.3 (61.7-130.9)[b]**
	na-PD	16	70.6 (46.0-95.2)	69.5 (45.0-93.9)	75.3 (50.8-99.7)

Table 4 BDNF rs6265 genotype distributions and allele frequency. The combination of Val and Met alleles results in three different Val66Met genotypes: GG (Val/Val), GA (Val/Met) and AA (Met/Met). Chi-square and Fisher's exact tests were calculated. Values are absolute (relative frequencies in parenthesis). *Significant result (P<.05).

Group	***n***	***Genotype***			***P***	**Allele frequency**		***P***
		GG (%)	**GA (%)**	**AA (%)**		**Val (%)**	**Met (%)**	
HOA	16	7 (44)	4 (25)	5 (31)	.394	14 (44)	18 (56)	.003*
MM-EX	23	16 (69)	5 (22)	2 (9)		37 (80)	9 (20)	
na-PD	13	8 (62)	2 (15)	3 (23)		18 (69)	8 (31)	

Supplementary Material



Supplementary Figure 1 Participant's flow chart. MM-EX participants were consolidated in testing sessions over one or two consecutive days every approximately 4 months. HOA and na-PD participants completed the study assessments in different occasions, each, approximately, 3 months apart. Flow chart created with BioRender.com.

List of techniques used:

Finger-tip capillary blood collection. At the appropriate assessments, finger-tip capillary blood was collected in K_2EDTA microvettes® (Microvette® CB 300 K2EDTA, Germany) and then centrifuged with a portable centrifuge (Mini-centrifuge, CAT No. 12-006-901, Fisher Scientific UK Ltd., Loughborough, UK) for 10 minutes at 2700 *g* at room temperature. The supernatant was transferred into microcentrifuge tubes and stored at -80ºC for later analysis.

Saliva collection. Unstimulated saliva samples were collected in pre-weighted universal tubes for 4 minutes using the passive drool technique (an extra 2 minutes were allowed if participants did not reach the minimum amount of sample that was required within the initial 4 minutes, i.e., up to the bottom line separating the conical part of the tube). Consumption of alcohol, food, fizzy drinks and water were documented prior to the saliva sample collection. Immediately after collecting the sample, the universal tubes were weighed to the nearest centigram and centrifuged at 17000 *g* for 5 minutes (AccuSpin Micro 17R, Fisher Scientific UK Ltd., Loughborough, UK). The supernatant was then collected and aliquoted in microcentrifuge tubes that were immediately stored at -80 °C for later analysis.

Enzyme-linked immunosorbent assay (ELISA). After thawing the samples of interest, BDNF concentrations were determined using the DuoSet ELISA Development System (cat #DY248, R&D Systems Europe Ltd., Abingdon Science Park, UK). All assays were performed using the manufacturer's recommended buffers and substrates, and in-house optimised diluents.

DNA purification. Genomic DNA was isolated from saliva samples using a commercially available genomic DNA extraction kit named (DNA Mini Kit, QIAgen GmbH, Hilden, Germany) according to the manufacturer's instructions. In brief, 200 µl of sample was added to a microcentrifuge tube with 20 µl of QIAGEN Protease. After adding 200 µl of buffer AL, the mix was vortexed and incubated for 10 min at 56°C. Subsequently, 200 µl of ethanol was added to the sample. The mixture was then pipetted into a QIAmp Mini spin column and centrifuged at 6000 *g*. Two more elution steps removed any residual contaminants from the mix. Once all the extractions where completed, the purified DNA samples were immediately frozen at -80°C until analysis.

rs6265 single nucleotide polymorphism (SNP) genotyping. Genotyping of the rs6265 SNP in the BDNF gene from saliva was completed using a RNase H2 enzyme-based amplification (rhAmp) assay, a PCR-based genotyping technique (Assay ID: CD.GT.WSKT3824.1; Integrated DNA Technologies, Coralville, Iowa, USA). A LightCycler 96 (Roche, Basel, Switzerland) instrument was used for amplification and detection under thermal cycling conditions of: 1 pre-incubation cycle of 10 minutes at 95 ºC (for enzyme activation); 40 amplification cycles of 10 sec at 95ºC (for denaturation), 30 sec at 60ºC (for annealing), and 20 sec at 68ºC (for extension). Fluorescence from the probe was measured at the end of each amplification cycle (during extension). Controls were added to the assay.

Supplementary Table 5 Structure of the multimodal exercise class and details of the different modules of the session. Each station of the circuit was completed during 1 min under the instruction to work "as hard as you can" followed by 30 sec of active rest (i.e., stay gently marching) allowing enough time to transition to the next station. Progressions and regressions were provided according to each individuals' capacity and constant encouragement was given to all participants throughout the class by instructors and student volunteers. The exercises listed as example are not exclusive for the training component and usually impact more than one element.

Warm-up (15 min) – *instructor led*					
Components	General stretching Muscle activation from head to toes, whole body mobility (covering all main body parts and components included in the circuit) Walking in different directions, increasing step and stride length, engaging with arm movements, coordination between upper body and lower body, etc.				
Multimodal Circuit (35 min) – *participants working individually with supervision from instructors and volunteers*					
Training Components	***Muscular Strength*** *(core stability, strengthening, posture, reduce rigidity)*	***Aerobic fitness*** *(cardiovascular conditioning, exercise capacity)*	***Coordination and Balance*** *(multi-directional exercises, working on range of motion, dual tasks)*	***Gait impairments*** *(step and stride length, postural control whilst moving, bradykinesia, freezing)*	***Cognitive Tasks whilst doing physical exercises*** *(processing speed, cognitive flexibility, memory)*
Example of exercises	Overhead ball throw Squats with arm row One step forward with wide arms using a thera-band (or other light-weight materials) Wall press-ups Arm rows (using a band) Bell ringing (arm swing and squat)	Step-ups/astride jumps High knee marching Jogging on the spot Half star jump/jumping jacks Climb the ladder (knee lift with opposite arm raise)	Heel to toe walking Reach and Twist Punching and marching Step back and lift opposite arm forwards High knee lift with finger clicks or clap Throw and catch a scarf Arm rolling with steps	Step across the river Fast shuttle walk with big arm swing, turnings and stops Box step to coloured cones 2 side steps and clap Sideways walking crossing feet over each other	Saying the months of the year in alphabetical order/reverse alphabetical order Stroop colour-word test Voice projection Looking around the class, try to find 5 red things
Cool-Down (10 min) – *instructor led*					
Components	Gentle walking Static balance exercises and proprioception Posture control General stretching (aimed at improving mobility and range of motion)				

Statistical analysis

In part one, the covariate LEDD significantly predicted 6MWT measures over time in the analyses of 1 year data (*b*=-0.056, F(1,25.064)=4.982, P=.035, η^2_p=0.170). Since it significantly improved the model (χ^2(1)=4.906, P=.027), it was added in the 6MWT analyses. Regarding TUG or 1-STS, none of the assessed covariates significantly predicted the response variable or improved the model fit and, thus, were not added in the analyses.

For the 3 year group, the covariate LEDD only significantly predicted 1-STS measures over time (F(1,13.006)=5.453, P=.036) and significantly improved the model (χ^2(1)=5.254, P=.022). Hence, participants with higher LEDD presented lower 1-STS measures over time compared to those participants taking less medication (*b*=-0.005, *t*(13.006)=-2.335, P=.036).

In part two, none of the assessed covariates significantly predicted the response variable or improved the model fit and, therefore, were not included in the analyses.

Results

Supplementary Table 6 The IPAQ Short form was used as a measure of total physical activity in MET-hours/week. Data are presented as estimated marginal means and its respective 95% confidence intervals.

	Group	***1st assessment (Baseline)***	***2nd assessment***	**3rd assessment**
IPAQ Short form (MET-hours/week)	HOA	71 (52-90)	46 (27-65)	39 (20-57)
	MM-EX	54 (26-82)	45 (17-73)	46 (18-74)
	na-PD	28 (8-48)	29 (9-49)	33 (13-53)

BDNF Genotyping

A total of 64 participants were included in the analyses (24 participants in the MM-EX group, 18 participants in the na-PD group and 14 participants in the HOA group). After the analyses, a total of 4 samples were deemed unknown (1, 1 and 2, from the MM-EX, na-PD and HOA groups, respectively) and, therefore, 23 participants in the MM-EX group, 13 participants in the na-PD group and 16 participants in the HOA group were finally included.

Although BDNF levels of Met carriers ($BDNF_{MET}$) did not significantly change compared to individuals with the $BDNF_{VAL}$ genotype, it is worth noting that $BDNF_{VAL}$ carriers in the na-PD group presented worse results over time than na-PD participants with the $BDNF_{MET}$ genotype. Interestingly, the opposite was observed in the MM-EX group. After engaging with the MM intervention, participants with the $BDNF_{VAL}$ genotype, obtained better scores in the evaluated tests than $BDNF_{MET}$ carriers. Regarding cognitive function, the change in scores in the MMP test was evaluated. The main effects of group and genotype were not significant; however, the results followed a similar distribution to the above-mentioned outcomes. That is, MM-EX participants with the $BDNF_{VAL}$ genotype improved their MMP scores after the MM intervention, whilst $BDNF_{MET}$ carriers did not present any change in MMP scores. On the contrary, participants in the na-PD group presented the opposite results distribution – participants with the $BDNF_{MET}$ polymorphism presented better MMP scores.

Finger Prick BDNF

Finger prick BDNF values were evaluated whilst taking into account participants BDNF genotype. A total of 33 participants were included in the analyses (7 participants in the MM-EX group, 11 participants in the na-PD group and 15 participants in the HOA group). Not all participants' genotype could be analysed due to limitations in sample volume.

Non-parametric Wilcoxon Signed-Rank Tests indicated that none of the BDNF genotype subgroups ($BDNF_{MET}$ and $BDNF_{VAL}$) within each of the comparison groups (MM-EX, na-PD and HOA) presented significantly different levels of BDNF between the 1st and 3rd assessment (see **Supplementary Table 7**). However, a trend was observed, that is, na-PD and HOA participants with the $BDNF_{VAL}$ genotype presented a decline trend in their BDNF levels (Z=-1.690, P=.091, and Z=-1.782, P=.075, respectively). As presented in **Supplementary Table 7**, BDNF levels of na-PD and HOA participants with the $BDNF_{MET}$ genotype also presented a decline over time, however, results were not significant (Z=-.730, P=.465, and Z=-1.599, P=.110, respectively).

Supplementary Table 7 Geometric mean (Geometric Standard Deviation) for each group's BDNF measurement (in pg/mL) at the 1st and 3rd assessments separated by BDNF genotype.

Group	***BDNF genotype***	***n***	***Baseline (1st assessment)***	***3rd assessment***
HOA	$BDNF_{MET}$	9	4601 (4)	1714 (2)
	$BDNF_{VAL}$	6	3642 (2)	1326 (2)
MM-EX	$BDNF_{MET}$	2	926 (9)	2688 (9)
	$BDNF_{VAL}$	5	2361 (3)	4574 (2)
na-PD	$BDNF_{MET}$	4	4600 (4)	1659 (3)
	$BDNF_{VAL}$	7	4489 (2)	1852 (2)