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Physical exercise for treating non-motor symptoms assessed by general Parkinson's disease scales: systematic review and meta-analysis of clinical trials

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ABSTRACT

Introduction Parkinson's disease is a movement disorder that also manifests non-motor symptoms (NMS). Physical exercise is a prominent strategy that can have an impact on NMS; however, the evidence is limited. Our aim was to verify the effects of exercise on NMS, as assessed using general NMS scales.

Methods This study is a systematic review and meta-analysis. Two searches were conducted on the PubMed, Cochrane Library, Scopus, Web of Science, Embase, Science Direct and PEDro databases from September to December 2022. The PEDro scale was used to assess the methodological quality of the studies.

Results Twenty-three studies were included. The interventions were classified as multimodal, aerobic, resistance, dance, conventional physical therapy and other types. Five studies had high risk of bias. Eight studies were included in the meta-analyses. According to the criteria, four studies compared exercise with non-exercise (n=159), two compared multimodal exercise with cognitive/leisure approaches (n=128), and two compared aerobic with conventional exercise (n=40). No statistical differences were observed between exercise and non-exercise (−0.26 (−0.58 to 0.05)) and between multimodal and cognitive approaches (0.21 (−0.14 to 0.55)). However, trends were observed in the direction of exercise and cognitive approaches. A significant difference was observed favouring aerobic over conventional exercise (−0.72 (−1.36 to −0.08)).

Conclusions Our findings suggest that exercise may have an effect on general NMS compared with non-exercise, although only a trend was observed. It was also observed for cognitive approaches over multimodal exercises. Aerobic exercise showed near-large effects compared with conventional exercise.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Physical exercise serves as a non-pharmacological approach to diminish the motor symptoms associated with Parkinson's disease (PD) and holds promise in addressing the broader spectrum of non-motor symptoms.

WHAT THIS STUDY ADDS

⇒ This study synthesises the current evidence on the use of physical exercise modalities on non-motor symptoms, as assessed by gross-symptom PD rating scales. In addition, it highlights the limitations of current evidence.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The evidence presented and discussed here offers valuable insights into the impact of exercises, provides understanding and offers recommendations for both clinical applications and future research.

INTRODUCTION

Parkinson's disease (PD) is typically linked to movement deficits that result from dopamine insufficiency in the substantia nigra pars compacta. However, non-motor symptoms (NMS) have recently drawn increasing attention. They result from dopaminergic impairment and other neurotransmitter systems such as the P substance, acetylcholine, serotonin and norepinephrine. They can also be caused by disordered protein aggregation of Lewy bodies in several parts of the nervous system or by the secondary effects of motor compromise.[1] These two facts make these symptoms even more relevant. First, some symptoms, such as hyposmia, REM sleep disorder, constipation and depression, may manifest many years before the motor symptoms.[2] Second, at a later stage of the disease, NMS are the main sources of the functional decline observed in patients.[1 2] Therefore, it is crucial to understand the clinical non-motor picture to develop diagnostic and early intervention strategies. This would lead to better clinical and functional management as well as an increase in the quality of life of patients at the early stages of the disease.[3]

Dysfunctions of the central and peripheral nervous systems and other organic systems vary in the intensity and sequence of manifestation.[1] As a result, the pharmacological approach to these dysfunctions is still limited, leaving an important gap in the global treatment of people with PD, since the dopamine precursors and agonists that are currently used have little or no effect on NMS.[3]

A non-pharmacological strategy broadly known as beneficial to improve the motor function and, to some extent, the NMS in PD is the utilisation of physical exercises and their different modalities.[4 5] Exercise is defined as a type of physical activity that consists of planned, structured and repetitive bodily movement done to improve and/or maintain one or more components of physical fitness, which can be health—or skill-related.[6]

Although the most effective exercise modalities and better prescription strategies are yet to be investigated scientifically, it is accepted that physical exercise plays an important role in the maintenance of functionality and quality of life of patients with PD.[7] In particular, aerobic and resistance exercises are modalities that activate physiological mechanisms, such as the relief of certain hormones, neurotransmitters and cytokines locally and further in the blood chain and thereby in the central nervous system, generating changes at the muscular and central level.[8 9]

Given the systemic effect of physical exercise and its potential use as a symptomatic intervention in PD, it is important to understand the effects of these exercises (and the different modalities) on the NMS of PD. Some reviews have already highlighted this question.[4] However, because of the diversity of NMS and the fact that many of them were not considered as primary outcomes in previous studies, systematic reviews that amplify the search to embody evidence from primary and secondary non-motor outcomes may contribute to a clearer picture of the current evidence surrounding the use of physical exercise as an intervention for those symptoms.

NMS are measured clinically through validated scales, such as Part I of the Unified Parkinson's Disease Rating Scale (UPDRS I) and the Non-Motor Symptoms Scale for Parkinson's Disease (NMSS). These scales measure the presence and severity of a wide range of problems at all stages of PD, although they do not differentiate the nature of these symptoms, that is, whether they are direct results of PD only, but their impact on the disease.[4] They give a common score that can be used to evaluate the progress of NMS as well as their improvement, resulting from therapies. Thus, our aim was to verify the effects of physical exercise on the NMS of PD, as assessed by validated general symptom scales.

METHODS

A systematic review approach and meta-analysis were performed and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Additionally, we assessed the methodological quality of the included studies. This review does not include a registered protocol.

Eligibility criteria

We included all studies that: (1) reported results of randomised controlled studies with no publication date limit, (2) included results of validated general non-motor scales for PD as primary or secondary outcomes, (3) did not associate other neurological diseases and (4) used any modality of physical exercise as an intervention, in comparison to any form of control (mind-body exercises were included only in cases where they were performed through body movement and physical activity). Exclusion criteria were (1) papers that did not clearly report the type of exercise that was performed in the experimental group or the counterpart comparison group; (2) articles that did not show between-group analysis or pre–post data for the outcome of interest; (3) papers not available in full and abstract-only; (4) in languages other than English, Portuguese or Spanish (the languages in which the authors are proficient); (5) other types of publications such as reviews, protocols and animal studies and (6) duplicate studies.

Information sources

Two independent researchers (VC and AOBS) conducted electronic searches on the following databases: PubMed, Cochrane Library, Scopus, Web of Science, Embase, ScienceDirect and Physiotherapy Evidence Database (PEDro) from September to December 2022. Publications were primarily selected based on titles and abstracts through the recommended web application Rayyan[10 11] and referred for further eligibility criteria review and manual data extraction by two other reviewers (TSSB and TFR). Then, two independent researchers, who conducted the searches initially, reviewed all the data for consistency and further checked the data extraction. Disagreements during the screening process were resolved through discussion and consensus between reviewers.

Outcomes

The outcomes were the NMS of PD as measured grossly using the UPDRS I, the NMSS or any other validated general scale.

Search strategy

We performed two searches for general terms. In Search 1, the terms used were 'UPDRS I' *OR* 'Unified Parkinson's Disease Rating Scale' *AND* 'Exercise'. In Search 2, the terms used were 'Non-motor Symptoms' *AND* 'Exercise' *AND* 'Parkinson's Disease'. These strategies were thought of as embracing the main general scales currently used to assess those symptoms, namely, the UPDRS I and its updated version by the Movement Disorder Society (MDS-UPDRS), section 1 of the 4-section scale, and the NMSS.

Methodological quality assessment

The validated PEDro scale was used to assess the methodological quality and risk of bias of the studies.[12] Whenever the scores were not available in the PEDro database, two independent raters (VC and TSSB) conducted the assessment, and a third author (ACG) resolved the discrepancies by consensus. The papers that scored 5 and over were considered good-to-excellent quality and low risk of bias, considering that studies that compared exercises as interventions technically cannot receive scores for the items related to blinding of participants and therapists (items 5 and 6).

Data synthesis

A descriptive analysis was carried out, and data were characterised in the following categories: author/year of publication, study design (type, sample size), population data (age, PD stage), intervention elements (frequency, intensity, time and type) and measurement of outcome (follow-up timeframe and instruments).

Meta-analysis procedures

Inclusion criteria for meta-analysis were as follows: (1) two or more studies revealing similar intervention and control group conditions, (2) mean and SD outcome scores and sample size could be extracted or calculated, (3) comparable study duration (in weeks) and (4) sufficient homogeneity of participants (mean age, PD stage). The exclusion criteria were as follows: (1) studies comparing time and dose only, (2) intervention frequency <2 times per week or less than 4 weeks and treatment duration <30 min per session (to exclude underdose studies).

We performed a main analysis comparing exercise interventions with no exercise/usual routine control. On the other hand, we tried to compare exercise modalities with each other or against conventional rehabilitation exercises, provided that meta-analysis criteria were obeyed.

Meta-analyses were conducted through the Comprehensive Meta-Analysis V.3.0 software. The standardised mean difference between groups was used as an estimate of the effect based on post-treatment mean and SD scores of the comparison groups. The effect size was considered to be small (0.2), moderate (0.5), large (0.8) or very large (1.3). The random effects model was adopted because of the potentially small number of studies and the within-variance and heterogeneity among them, thus allowing for more conservative estimates with a CI of 95%. Study heterogeneity was analysed through indices of dispersion, considering the variance between studies. If at least 10 studies were included in the analysis, visual inspection of funnel plots and Egger's test was used to assess publication bias.

RESULTS

The database searches returned 886 papers. After the application of the eligibility criteria, 23 papers were finally included, and the data were extracted for descriptive analysis. Figure 1 shows the procedures and results of the systematic search in detail, including the number of papers not included, excluded and the respective reasons for that. Table 1 presents the characteristics of the studies included in this systematic review.[13–35]

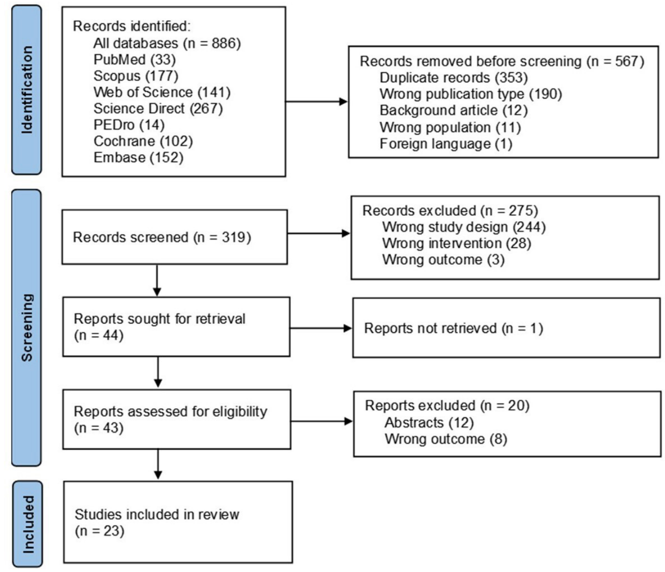

Figure 1 PRISMA flow diagram for papers identification and screening. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Given the heterogeneity of the interventions in the studies and to facilitate our understanding, we classified them into categories according to their main characteristics. The categories were as follows: 'multimodal exercise' (at least three modalities together), 'aerobic training' (continuous activities like biking, cycling or walking), 'resistance exercise' (progressive muscle strengthening exercises), 'dance' (individual, peered, group, multitype), 'conventional physical therapy (PT) exercise' (varied forms of mobility, stretching, positioning, active range of motion, monoarticular or polyarticular, low-moderate intensity, facilitation techniques and other passive techniques conventionally used) and 'other forms of exercise' (those that were not classified in the previous categories).

For multimodal exercises, three out of four studies showed no differences in comparison to control interventions,[13 15 32] whereas one study did not compare groups, only reporting that the intervention group improved, while the control group worsened.[19] For aerobic training (five studies), one study favoured Nordic walking over conventional care,[30] while no differences were found over a conventional walking programme.[14] Two studies reported no differences between aerobic training (treadmill and cycle-ergometer) and either usual routine or conventional motor rehabilitation.[21 29] One study compared regimens of body weight-supported treadmill training and found no differences between them.[22] Only one study reported results on resistance training,[24] but it did not compare between groups for the relevant outcome, reporting that the resistance training group

Table 1 Characterisation of the studies included in the systematic review (general NMS outcome)

Author, year	Design	PD stage and age	Intervention elements	Measurement	Results (statistically significant)
Gryfe *et al*, 2022[13]	RCT (n=40) G1: Exoskeleton multimodal Ex. G2: No exoskeleton Ex. G3: Waitlist	H&Y 1–3 G1: 67.6±5.9 G2: 70.7±7.3 G3: 69.3±8.0	1 hour/session, 2 x/week, 8 weeks.	8 weeks. UPDRS I*	No differences.
Granziera *et al*, 2021[14]	RCT (n=32) G1: Nordic walking G2: Conventional walking	H&Y: 2–3 G1: 68.8±10.2 G2: 68.3±6.20	75 min./session, 2xweek, 8 weeks, in group.	8 weeks. NMSS†	No differences at 8 Weeks.
Gobbi *et al*, 2021[15]	RCT (n=152) G1: Multimodal Ex. G2: Functional mobility Ex. G3: Leisure activities	H&Y: 1–3 G1: 69.6±8.2 G2: 67.8±9.1 G3: 69.5±7.6	60 min./session, 2xweek, 32 weeks.	16 and 32 weeks. UPDRS I*	No differences.
Schaible *et al*, 2021[16]	RCT (n=41) G1: LSVT-BIG G2: Intensive PT Ex. G3: Conventional PT	H&Y: 1–3 G1: 63.29±8.48 G2: 66.20±8.65 G3: 65.50±8.21	1 hour/session, 4xweek, 4 weeks.	8 weeks. NMSS*	Differences between Intensive PT (favoured) and Conventional PT.
Moratelli *et al*, 2021[17]	RCT (n=31) G1: Binary rhythm dance G2: Quaternary rhythm dance	H&Y: 1–4 G1: 68.3±8.60 G2: 64.3±14.8	45 min./session, 2xweek, 12 weeks.	12 weeks. UPDRS I*	No between-group comparison. Both groups improved.
Kuhn *et al*, 2020[18]	RCT (n=20) G1: Kinesiology method+rehabilitation therapies. G2: Rehabilitation therapies	H&Y: - G1: 71.3±7.07 G2: 71.8±7.97	45 min./session, 2xweek, 6 weeks.	6 Weeks. UPDRS I*	No between-group comparison. Only the Kinesiology group improved at 6 weeks.
Johansson *et al*, 2020[19]	RCT (n=13) G1: Balance/agility Ex. G2: Language/voice Ex.	H&Y: 2–3 G1: 72.0 (60-68) G2: 67.5 (63-70)	60 min./session, 2xweek, 10 weeks.	10 weeks. MDS-UPDRS I*	No between-group comparison. Balance group improved while G2 worsened.
Moon *et al*, 2020[20]	RCT (n=17) G1: Qigong exercises G2: Qigong sham	H&Y: 1–3 G1: 66.4±8.1 G2: 65.9±5.4	2 x/day (home)+weekly group sessions (45 min–1 h/session), 12 weeks.	12 weeks. NMSQ, MDS-UPDRS I*	No differences.
Marusiak *et al*, 2019[21]	RCT (n=20) G1: Interval aerobic training G2: Motor rehabilitation, no aerobic training	H&Y: 1.5–3 G1: 72±10 G2: 74±9	1 hour/session, 3xweek, 8 weeks. 60–75% HR_{max}.	8 weeks. UPDRS I (subitems 1–4)†	No differences.
Atan *et al*, 2019[22]	RCT (n=30) G1: 0% BWSTT G2: 10% BWSTT G3: 20% BWSTT	H&Y: 2–4 G1: 69.7±8.0 G2: 72.2±7.9 G3: 68.6±8.2	30 min./session, 5xweek, 6 weeks.	6 weeks. UPDRS I†	No difference between groups. 10% and 20% BWSTT groups improved at 6 weeks.
Michels *et al*, 2018[23]	RCT (n=13) G1: Dance therapy (multi-type) G2: Support group	H&Y: 1–5 G1: 66.44 G2: 75.50	1 hour/session, 1xweek, 10 weeks.	10 weeks. MDS-UPDRS I*	No statistical analysis. G2 improved more.
Ferreira *et al*, 2018[24]	RCT (n=35) G1: Resistance training G2: Usual routine, no Ex.	H&Y: 1–3 G1: 64.1±7.0 G2: 67.6±8.9	30–40 min./session, 2xweek, 24 weeks.	24 weeks. MDS-UPDRS I*	No between-group analysis. Groups improved equally.

Continued

Table 1 Continued

Author, year	Design	PD stage and age	Intervention elements	Measurement	Results (statistically significant)
Lee *et al*, 2017[25]	RCT (n=41) G1: Qi dance (Turo programme) G2: No intervention	H&Y: 1–3 G1: 65.8±7.2 G2: 65.7±6.4	1 hour/session, 2xweek., 8 weeks.	8 weeks. UPDRS I*	No differences.
Yang *et al*, 2017[26]	RCT (n=36) G1: Tai χ group G2: Tai χ individually	H&Y: 1–3 G1: 62.94±5.45 G2: 64.23±5.72	40–45 min./session, 3xweek, 13 weeks.	13 weeks. NMSS*	No differences.
Paolucci *et al*, 2017[27]	RCT (n=34) G1: Mézières method G2: Home posture/ mobility ex.	H&Y: 1–3 G1: 67.0 (11.00) G2: 66.0 (18.50)	1 hour/session, 2xweek, 5 weeks.	5 and 12 weeks. UPDRS I†	No differences.
De la Cruz, 2017[28]	RCT (n=30) G1: Aquatic Ai χ G2: Land therapy	H&Y: 2–3 G1: 66.80±5.26 G2: 67.53±9.89	45 min./session, 2xweek, 10 weeks.	10 weeks, 1 month. UPDRS I*	Differences favouring land therapy.
Altmann *et al*, 2016[29]	RCT (n=30) G1: Aerobic training G2: Stretching-balance training G3: Usual routine	H&Y: 1–3 G1: 62.8+8.6 G2: 63.3+7.3 G3: 67.8+9.8	20–45 min./session, 3xweek, 16 weeks. 50–75% RHR.	16 weeks. UPDRS I*	No differences.
Cugusi *et al*, 2015[30]	RCT (n=20) G1: Nordic walking G2: Conventional care	H&Y: 1–3 G1: 68.1±8.7 G2: 66.6±7.3	1 hour/session, 2 x/ week, 12 weeks, 60–80% RHR.	12 Weeks. NMSS*	Differences favouring Nordic walking.
Sharma *et al*, 2015[31]	RCT (n=13) G1: Hatha Yoga G2: No intervention	H&Y: 1–2 G1: 62.8±13.2 G2: 73.4±6.5	60 min./session, 2xweek, 12 weeks.	12 Weeks. UPDRS I†	No differences.
Gobbi *et al*, 2013[32]	RCT (n=34) G1: Cognitive activities G2: Multimodal Ex. G3: Posture and gait Ex.	H&Y: 1–2 G1: 67.31±9.03 G2: 68.45±10.81 G3: 67.50±8.26	60 min./session, 2xweek, 4 months.	4 months. UPDRS I*	No differences.
Cholewa *et al*, 2013[33]	RCT (n=70) G1: Conventional PT Ex. G2: No intervention	H&Y: 3 G1: 70.20±5.75 G2: 70.17±5.38	1 hour/session, 2xweeks, 12 weeks.	12 weeks. UPDRS I†	Difference favouring conventional PT.
Duncan and Earhart, 2012[34]	RCT (n=52) G1: Tango G2: Usual routine	H&Y: 1–4 G1: 69.3±1.9 G2: 69.0±1.5	1 hour/session, 2xweek, 12 months.	3, 6 and 12 months. MDS-UPDRS I†	No differences in 3, 6 and 12 months.
Modugno *et al*, 2010[35]	RCT (n=20) G1: Theatre workshop G2: Conventional PT	H&Y: 3–4 GE: 62.0±1.58 GC: 63.2±1.13	6 hour/session, 2 days, once or twice/month, 3 years.	3 years. UPDRS I*	Differences favouring theatre workshop.

*Primary outcome.
†Secondary outcome.
BWSTT, body weight-support treadmill training; Ex., exercises; G1, G2, G3, group 1, 2 and 3; HR_{max}, Maximum heart rate; H&Y, Hoehn and Yahr scale (0–5); MDS-UPDRS I, Movement Disorder Society—Unified Parkinson Disease Rating Scale, part 1; UPDRS I, part 1 of the first version of Unified Parkinson Disease Rating Scale; LSVT-BIG, Lee Silverman Voice Treatment; NMSQ, Non-Motor Symptoms Questionnaire; NMSS, Non-Motor Symptoms for Parkinson's Disease Scale; PT, physical therapy; RCT, randomised controlled trial; RHR, reserve heart rate.

improved to the same level as the usual routine group (no exercise).

For dance, three studies compared, respectively, multi-type, Qi dance and Tango with control (no exercise) and found no differences.[23 25 34] However, one of them did not show statistical comparisons, reporting that the scores in the dance group were lower, indicating an improvement in UPDRS I.[23] For conventional PT, one study favoured it over no intervention,[33] while two studies reported that intensive conventional PT and theatre workshop classes were better for reducing NMS scores than conventional PT only. Additionally, conventional PT showed no difference compared with the Lee Silverman Voice Treatment exercises.[16 35]

Table 2 Methodological quality assessment of studies using the PEDro scale

	Criteria											
Included studies	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Total (0–10)**
Gryfe *et al*[13]	■	■		■				■	■	■	■	6
Granziera *et al*[14]	■	■		■			■	■		■	■	6
Gobbi *et al*[15]	■	■		■						■	■	4
Schaible *et al*[16]	■	■	■	■			■	■	■	■	■	8
Moratelli *et al*[17]	■	■		■					■	■	■	5
Kuhn *et al*[18]		■		■			■	■	■		■	6
Johansson *et al*[19]	■	■	■	■				■	■		■	6
Moon *et al*[20]	■	■	■	■			■			■	■	6
Marusiak *et al*[21]	■	■	■					■	■	■	■	6
Atan *et al*[22]	■	■	■	■			■	■		■	■	7
Michels *et al*[23]	■	■					■	■			■	4
Ferreira *et al*[24]	■	■	■	■			■	■	■		■	7
Lee *et al*[25]	■	■		■			■		■	■	■	6
Yang *et al*[26]	■	■	■	■			■	■		■	■	7
Paolucci *et al*[27]	■	■	■	■			■	■	■	■	■	8
De la Cruz[28]	■	■		■			■	■	■	■	■	7
Altmann *et al*[29]	■	■		■			■		■	■	■	6
Cugusi *et al*[30]	■	■		■						■	■	4
Sharma *et al*[31]		■		■						■		3
Gobbi *et al*[32]	■	■		■			■		■	■	■	6
Cholewa *et al*[33]	■	■		■							■	3
Duncan and Earhart[34]	■	■	■	■			■		■	■	■	7
Modugno *et al*[35]	■	■		■				■	■	■	■	6

PEDro criteria: 1. eligibility criteria (not scored); 2. random allocation; 3. concealed allocation; 4. baseline comparability; 5. blind subjects; 6. blind therapists; 7. blind assessors; 8. adequate follow-up; 9. intention-to-treat analysis; 10. between-group comparisons; 11. point estimates and variability.
PEDro, Physiotherapy Evidence Database .

Finally, other forms of exercise have been reported. In general, studies have reported no differences between Qi Gong and Hatha Yoga over sham or no intervention.[20 31] Comparative studies have reported that land-based exercises are better than aquatic Ai Chi,[28] and that there are no differences between individual Tai Chi and in-group practice.[26] One study reported that the Kinesiology method was better than conventional rehabilitation therapy exercises; however, it did not show between-group comparisons, reporting that only the Kinesiology group improved at follow-up.[18] No differences were found between exercises using the Mèziere method and home posture/mobility training.[27]

The majority of those studies used the UPDRS I as the instrument for outcome measurement, whereas only very few studies used the NMSS.[14 16 26 30] The results of the methodological assessments are presented in table 2. Five of the 23 papers were rated as low-quality/high-risk of bias (ie, below 5 out of 10 on the PEDro scale). Two were rated with 3/10,[31 33] and three with 4/10.[15 23 30] The main items not met in these studies were items 5 and 6, as expected for exercise interventions (blinding of subjects and therapists), and items 7–9 (blinded assessors, adequate follow-up and intention-to-treat analysis).

Meta-analyses results

For our main analysis, four studies met the criteria comprising 159 participants with H&Y 1–3.[13 25 29 33] They compared exercise interventions with non-exercise/usual routine controls (for 8–16 weeks). In total, four out of eight were excluded from the analysis due to: (1) data not extractable or available[24 31 34] and (2) low-dose intervention.[23] Difference was not found between exercise and control for NMS general-scale outcome, with a pooled small effect size of −0.26 (95% CI −0.58 to 0.05), $I^2 = 0\%$. A trend favouring the exercise group is shown (figure 2A), with only a small arm of the CI indicating no effects on the outcome. On the other hand, one of the studies was rated as a high risk of bias (see table 2).[33] A sensibility analysis (study exclusion) showed that this study had a

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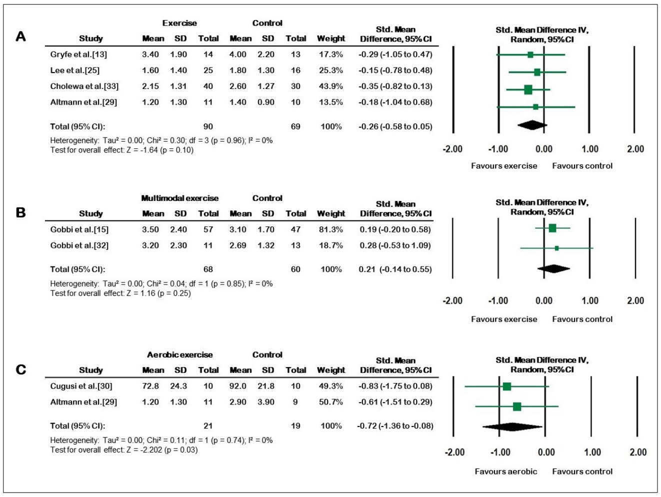

Figure 2 Meta-analyses showing the pooled effects sizes of (A) exercise compared with no exercise/usual routine, (B) multimodal exercise with cognitive/leisure interventions and (C) aerobic exercise with conventional rehabilitation exercises for the NMS outcome assessed by general PD rating scales. NMS, non-motor symptoms; PD, Parkinson's disease.

relevant impact (44%) on the result, although the same pattern observed before was maintained (−0.20, 95% CI −0.62 to 0.22).

Two additional analyses were done, comparing multimodal exercise (for 8–16 weeks) with non-exercise leisure/cognitive interventions (two studies, n=128, H&Y 1–3),[15 32] and aerobic exercise (for 12–16 weeks) with conventional non-aerobic exercises (stretching-balance, motor rehabilitation) (two studies, n=40, H&Y 1–3).[29 30] For the first comparison, no difference was found between conditions with a pooled effect size of 0.21 (95% CI −0.14 to 0.55), I^2=0% (figure 2B). The effect observed varied between an insignificant effect at the exercise arm and a moderate effect at the cognitive/leisure interventions, a pattern that is also observed within studies, sometimes reaching large effects in favour of the last. However, one of these studies was rated as having a high risk of bias (see table 2).[15]

For the second analysis, a significant difference was found between conditions with a near-large pooled effect size of −0.72 (95% CI −1.36 to −0.08), I^2=0% (figure 2C). The data showed a common effect with low heterogeneity, indicating that the effect of aerobic exercise is small for some people but reaches large and very large effects for others, but is always superior to conventional exercise. Notably, one of these studies was rated as having a high risk of bias (see table 2).[30]

DISCUSSION

The assessment of NMS has been part of the PD rating scales, especially the most used UPDRS and NMSS. They give a gross measure of general manifestations of NMS. The UPDRS I is a 13-item subscale measuring a range of several symptoms and their impact on individuals' daily living. Similarly, the NMSS is a 30-item rater-based scale that covers a similar range of symptoms. They are validated instruments that reflect the current frequency and severity of NMS in PD and can be used to measure the effect of different therapies.[36] Since more emphasis has been placed on these symptoms, our aim was to systematically review the literature and synthesise evidence from clinical trials on the use of exercise interventions for treatment. We found a considerable number of papers that used general scales as primary or secondary outcome measures, mostly within the last 10 years. However, given the heterogeneity of interventions, exercise modalities, variations in intervention duration, frequency and timeframe, few studies could be grouped for meta-analysis. We identified six main modalities of physical exercise, classified as multimodal, aerobic, conventional PT, dance and other types (that varied from mind-body exercises to very specific techniques). These interventions frequently presented ambiguous results throughout the studies, warranting increased attention from exercise scientists.

Our main meta-analysis showed no differences between exercise and non-exercise/usual routines. Caution should be taken when interpreting this finding as an undoubtable trend was observed in the data, which was maintained after sensibility analysis. The effect observed was small, yet it showed a CI that indicates that the true effect could vary from null to moderate. Further studies are strongly recommended to investigate the effect of exercise on this outcome. Accumulated evidence has demonstrated the effect of physical activity on motor function and NMS in PD, although the most effective modalities are yet to be demonstrated.[37] Large-sample and good-quality studies may confer sufficient statistical power to reveal the true effect. The general scales for NMS usually assess a diverse array of symptoms that can vary substantially between individuals.

Our secondary meta-analysis showed no difference between multimodal exercises and approaches based on cognitive and leisure activities. Again, a trend was observed in the data showing that these interventions may have a greater effect on general NMS than multimodal exercises. Accordingly, previous studies have suggested that cognitive-stimulating interventions have the potential to reduce many NMS, such as cognitive impairment, apathy, depression, anxiety, among others.[38]

On the other hand, a near-large effect size was found favouring aerobic training against more conventional forms of exercise. One frequent physiological effect of this modality is the systemic effect of neurotransmitter release and neuroendocrine system regulation,[8 9] which may account for the positive impact on some NMS, like reduction of sleep disturbance, cognitive loss, anxiety and depression, cardiovascular and gastrointestinal dysfunction, among others, that is likely less emphasised by general or conventional exercise approaches.[39] Our findings must be interpreted with some caution due to the methodological limitations of the studies (small size, low quality). Therefore, the superiority of aerobic training over other modalities must be further investigated for overall NMS and targeting-specific symptoms.

No studies investigating resistance training, conventional PT or dance met the criteria for the meta-analysis. However, from this systematic review, we can see that the results are inconclusive for the overall NMS score; hence, further investigation is required.

This systematic review and meta-analysis have some limitations. First, only randomised controlled trials were included, which means that non-randomised trials with likely favourable results to exercise interventions were not considered, and consequently, an evidence hierarchy could not be built, and some modalities of exercise may have been left out. However, by not including those studies, we ensured higher quality evidence. Second, some studies may have not been reached for being indexed in other databases, which was actually minimised because we adopted the main databases for indexation of health sciences studies. Third, health-related quality of life was not considered. This is because, from our understanding, it is not a function (or dysfunction), but a generic construct that reflects more than just the consequence of disease, being better gathered and discussed if addressed under specific considerations. Therefore, we did not include the results of studies that used quality of life questionnaires as outcome measures, which may have assessed in their subdomain aspects such as anxiety, emotion, pain ancognition, among other NMS.

Due to the small number of studies included in the meta-analyses, we opted not to show dispersion intervals and funnel plots for publication bias and did not perform further assessment of confidence on cumulative evidence and strength of recommendations. Future research targeting general scales for NMS as primary or secondary outcomes should focus on appropriate study design (especially power), methodological quality to avoid bias and standardisation of reporting interventions *and* controls (so they can be compared in the future). Finally, researchers must make more available and transparent raw data sets to enable the development of more accurate and concise syntheses of evidence.

CONCLUSION

Our findings indicate that exercise interventions may have an effect compared with non-exercise interventions in treating NMS of PD, as assessed by gross-symptom scales. However, further investigation is necessary for this outcome, as it seems that the power of the studies was insufficient to detect differences. Multimodal exercise was not better than cognitive approaches. A trend was observed in favour of the control intervention. Aerobic modalities show promise as effective strategies for managing general NMS with a moderate-to-large effect size in comparison to more conventional approaches. Further investigation through primary and synthetic studies is warranted to ascertain the optimal interventions for specific symptoms, thereby providing clearer guidance on the most effective modalities.

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