Influence of Aerobic Exercise on Functional Capacity and Maximal Oxygen Uptake in Patients With Parkinson Disease: A Systematic Review and Meta-analysis

Running Head: Aerobic exercise and Parkinson's disease

Influence of aerobic exercise on functional capacity and maximal oxygen uptake in patients with Parkinson's disease: a systematic review and meta-analysis

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None.

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Abstract

Objective: to determine the effects of aerobic training in randomized controlled clinical trials on functional capacity, motor symptoms, and oxygen consumption in individuals with PD through a systematic literature review and meta-analysis.

Data Sources: PUBMED, Web of Science, CINAHL, SciELO, and Medline databases were searched to identify published studies until September 2023.

Study Selection: Randomized controlled clinical trials that evaluated the long-term effect of aerobic exercise in individuals with PD were included.

Data Extraction: Two independent reviewers extracted the data, assessed the risk of bias and the Grading of Recommendation Assessment, Development, and Evaluation (GRADE). In case of disagreement, a third reviewer was consulted.

Data Synthesis: 13 studies were included in the systematic review and the number of participants was 588 with an average age of 66.2 years (57 to 73 years). The study's exercise intervention lasted between 6 to 70 weeks, with most studies lasting 10-12 weeks, with three sessions/week and an average duration of 47 minutes/session. The meta-analysis revealed that aerobic exercise is effective in enhancing maximal oxygen uptake (SMD 0.42 [CI95% = 0.18, 0.66; p = 0.0007]) and functional capacity (SMD 0.48 [CI95% = 0.24–0.71; p < 0.0001]). In addition, aerobic exercise can reduce the UPDRS III (mean difference -2.48 [CI95% = -3.16, -1.81; p < 0.00001]) score in individuals with PD.

Conclusion: Aerobic exercise training conducted 2 to 3 times a week, with different intensities (low to high) can be an effective intervention for enhancing functional capacity, maximizing oxygen uptake, and reducing the UPDRS scores in individuals with Parkinson's disease (PD).

Keywords: Parkinson's disease; Aerobic exercise; maximal oxygen uptake; functional capacity; meta-analysis

Abbreviations

PD: Parkinson's disease

TUG: Timed up and go test

6MWT: 6-minute walk test

UPDRS III: Motor Unified Parkinson's disease rating scale

MD: Mean difference

SDM: Standardized difference of measurement

I^2: inverse variance

VO_2max - maximal oxygen uptake

HR: heart rate

1. Introduction

Parkinson's disease (PD) is among the most prevalent neurological disorders worldwide, primarily affecting individuals over the age of 60 [1]. It is characterized by the loss of dopaminergic neurons in the substantia nigra, leading to reduced dopamine levels in the nigrostriatal pathway. This reduction in dopamine results in symptoms such as bradykinesia (slowness of movement), resting tremor, and stiffness [1, 2]. In addition, individuals with PD may experience non-motor symptoms, including respiratory dysfunction [3] and speech deficits [4], as well as sleep and cognitive disorders, and autonomic dysfunction [5-7]. These motor and non-motor symptoms often lead to a sedentary lifestyle in most individuals with PD, negatively affecting their maximal oxygen uptake (VO_2max) and functional capacity [8]. Furthermore, recent studies have suggested that autonomic dysfunction, which can be altered by various factors including a response to exercise training, may be associated with both motor and non-motor symptoms and may also compromise the quality of life for individuals with PD [9, 10].

To deal with these motor and non-motor symptoms and enhance the level of physical capacity of individuals with PD, several pharmacological and non-pharmacological therapeutic approaches have been proposed. Exercise has emerged as one of the most recommended strategies. Exercise has the potential to improve motor and non-motor functions by enhancing muscle mass, cardiovascular health and flexibility [2], and promoting neuroplasticity [11]. Among various exercise modalities, aerobic exercise has been well-established as an effective intervention for this population. Aerobic exercise is favored due to its safety, ease of application, affordability, and high acceptability among individuals with PD. Moreover, aerobic exercise has been shown to improve functional

capacity (e.g., Timed up and go test – TUG, and 6-minute walk test – 6MWT) [12], VO_2max [13], and reduce motor symptoms (e.g., motor Unified Parkinson's disease rating scale - UPDRS III) [14]. Despite the considerable evidence supporting the positive effects of exercise in enhancing functional capacity among individuals with PD [15, 16], limited information is available regarding its impact on peak or VO_2max, which is an important factor affecting the quality of life in people with PD. In addition, VO_2max is associated with mortality, functional capacity, and cardiovascular health in this population [19-22].

Previous systematic reviews have addressed the effects of aerobic exercise on PD [12, 17, 18]. De Sena et al. [17] focused specifically on the effect of high-intensity interval training, while Zhou et al. [18] did not consider the oxygen uptake as an outcome. Finally, Gamborg [12] combined studies prescribing supervised and non-supervised exercise programs in their systematic review, as well as included subjects with de novo PD (i.e. patients with PD not yet taking prescribed specific medications for PD), both of which could be a potential source of heterogeneity. However, the knowledge gap about the impact of aerobic exercise on peak or VO_2max persists. In addition, although aerobic exercise is one of the most widely used forms of training programs for individuals with PD, the prescription and control of the intensity are currently limited (Panassollo, et al 2024). Existing methods for prescription and control of the intensity of aerobic exercise in people with PD rely on guidelines based on maximum heart rate percentage, prediction equations, or self-reported perceived exertion levels. However, these methods have serious limitations as individuals with PD may have autonomic disorders that affect their ability to raise their heart rate (HR) (Panassollo, et al 2024) or accurately report perceived exertion (Mavrommati, et al., 2017). This can lead to an underestimation of the appropriate training intensity for people with PD.

Therefore, it is necessary to use individualized measures to determine exercise intensity, and cardiopulmonary exercise testing data can be a valuable alternative method (Panassollo, et al 2024). Understanding the effects of aerobic training on VO_2max is crucial in order to incorporate this variable into the prescription and control of aerobic training for individuals with PD. Additionally, VO_2max is associated with mortality, functional capacity, and cardiovascular health, all of which are important factors in determining the quality of life for this population[19-22]." Therefore, it is necessary to use individualized measures to determine exercise intensity, and cardiopulmonary exercise testing data can be a valuable alternative method (Panassollo, et al 2024). Understanding the effects of aerobic training on VO2max is crucial in order to incorporate this variable into the prescription and control of aerobic training for individuals with PD.

This absence of comprehensive research is significant in practical settings as it can guide healthcare professionals in prescribing evidence-based exercise programs and underscore the importance of monitoring physical capacity and oxygen uptake adaptations in PD individuals. Therefore, the purpose of this study was to investigate, by a systematic literature review and meta-analysis, the effects of aerobic training in randomized controlled clinical trials on functional capacity, motor symptoms, and oxygen consumption in individuals with PD. This research can offer valuable insights for clinical practice by elucidating the impact of aerobic exercise training as a supplementary intervention on functional capacity and oxygen uptake for PD individuals.

2. Method

2.1. Search plan and literature selection

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and the Meta–Analyses (PRISMA) [23, 24]. Moreover, the study selection was based on the “PICOS” tool [25]: participant profiles (Population), intervention features (Intervention), outcome targets (Comparison and Outcomes), and study design. The articles were identified by manual searches of the reference system databases PUBMED, Web of Science, CINAHL, SciELO, and Medline in May 2023 with an update in September 2023. No systematic review that included only randomized controlled clinical trials on the topic was found, and all studies that met the inclusion criteria were considered, regardless of the date of publication. The descriptors "physical exercise," "Parkinson's disease," "oxygen uptake," "functional capacity," "aerobic capacity," and "heart rate variability" were used in English, Spanish, and Portuguese. Combinations of these descriptors for searches were made using the Boolean operators "AND" and/or "OR". In addition, the references of all the included studies were hand-searched to check for possible additional references not identified by the electronic searches. When the full text of a study was not available, one of the investigators contacted the corresponding author to request the full version of the manuscript. Authors who did not respond to the mail or did not send the full version were excluded from the analysis.

2.2. Type of study and participants

We only included randomized controlled clinical trials that evaluated the long-term effect (≥ 4 weeks) of aerobic exercise in individuals diagnosed with idiopathic PD, regardless of sex, degree of impairment, or time of disease. In addition, only studies assessing the outcomes “on medication” condition were included.

2.3. Type of intervention and outcome measures

Studies proposing any aerobic endurance physical exercise intervention, regardless of type or intensity, lasting at least 4 weeks that evaluated one or more of the following outcomes: 1) functional capacity (e.g., TUG and 6MWT); 2) motor symptoms (e.g., UPDRS III); and 3) maximal oxygen uptake or anaerobic threshold, obtained directly or indirectly.

2.4. Study selection

Two reviewers (NZ, VM) independently screened the studies identified by the search strategy, using the software StArt (State of the Art through Systematic Review, developed by the Federal University of São Carlos). Two researchers (NZ, VM) independently analyzed the selected studies. They were first identified by titles and abstracts. To be selected, abstracts had to clearly identify the study design, population, and relevant intervention components, as described above. Next, full reports of all potentially relevant trials were obtained and independently reviewed for eligibility based on the already defined inclusion criteria. In case of disagreement, a third investigator (CK) was consulted. Studies involving robotic walking aids, animal studies, and non-accessible full-text studies were excluded. In addition, study designs such as non-randomized clinical trials, quasi-experimental studies, and cross-sectional studies were not considered in this review.

2.5. Data extraction

Following study selection, three reviewers (NZ, VM, CK) independently extracted information from each study regarding methodology (objectives, study design, and

control/intervention group), participant data (number of participants, number of men and women in each group, ages and time of disease diagnosis), information regarding the type of intervention (duration, type of exercise, weekly frequency, exercise intensity, and monitoring) and the outcomes related to aerobic assessments (maximal oxygen uptake), functionality (TUG, 6MWT, 10-meter walk test and 20-meter walk test) and motor symptoms (UPDRS III). Data presented in the figures were extracted through MATLAB® (The MathWorks Inc., Natick, USA; using the "ginput.m").

2.6. Risk of bias and quality of the scientific evidence

The risk of bias in the studies was assessed using the Cochrane risk of bias tool, in which there are six domains of bias: selection, conduct, detection, attrition, reporting, and others. Each domain is rated as high, low, or unclear risk of bias [26]. Two independent reviewers (NZ, VM) assessed the risk of bias. In case of disagreement, a third investigator (CK) was consulted.

The quality of evidence of the studies was assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) criteria, including study limitations, consistency of effect, imprecision, evidence, and publication bias. Two reviewers (NZ, VM) independently examined the methodological quality of the studies.

2.7. Statistical analysis

Meta-analyses were performed using Review Manager software (RevMan; version 5.3) to compare the responses of the intervention (i.e., aerobic training) versus the control group.

We reported the weighted mean difference (MD) with 95% confidence intervals (95% CI) when the combined studies presented the variables using the same measurement unit. When the combined studies presented different measurement units for certain variables analyzed, the standardized difference of measurement (SDM) with the respective 95% CI was reported. Effects sizes were estimated as the SMD between intervention and control groups using the values obtained after the intervention. Considering some differences in the aerobic prescription, calculations were performed using a random-effects model. The significance level was set at 5% for all analyses. Heterogeneity was assessed through the Q statistics and inverse variance (I^2), classified as: low: $I^2 < 25\%$; moderate: $I^2 = 25.1\text{-}50\%$; high: $I^2 > 50.1\%$ [27].

3. Results

3.1. Search results

Figure 1 demonstrates the flowchart of the literature search and selection. After selection, 13 articles were included in the data extraction phase.

>>> **Figure 1** <<<

3.2. Study and patient characteristics

The number of subjects in the experimental group was 311 participants (179 men and 97 women), however, one study did not specify the participants' sex [28]. The ages of these participants ranged from 57 to 73 years, with an average age of 66.2 years. The participants were on stable medication, although medication status was not mentioned in two studies [29, 30] that were not included in the meta-analysis statistics. On average, the duration of

disease diagnosis was 11.2 years, and the average stage according to the Hoehn and Yahr scale was 2.3 (ranging from 1 to 3). Two studies did not specify the range of inclusion in terms of disease stage [30, 31]. The average score on the UPDRS III was 28.7, although this value was not mentioned in five studies [29, 30, 32-34]. Finally, it is important to note that eight out of the 13 selected articles reported losses of participants in the course of the studies [2, 30-33, 35-38] and five maintained the number of patients unchanged.

3.3. Intervention characteristics

Table 1 summarizes exercise protocols applied in the studies included in the systematic review and meta-analysis. The exercise intervention duration varied among the studies. Four studies had a maximal duration of 6 weeks [28, 29, 32, 34], six studies lasted between 10-12 weeks [2, 30, 33, 35, 38, 39] and the study by Collett et al. [31] and Schenkman et al. [36] had longer exercise intervention with 24 and 70 weeks, respectively. The studies usually prescribed three sessions/week with an average session duration of 47 minutes. Six studies performed only aerobic exercise [28, 30, 34, 37-39], while six studies have combined aerobic exercise with other training (strength, calisthenics, functional training and/or body weight supported training). The most common aerobic exercise applied (in nine studies) was walking/running on a treadmill or in the field. Furthermore, seven studies performed progressions in the training load throughout the training period [2, 28-30, 33-35]. Also, only Fernandes et al. [33] applied a high-intensity interval training model to patients with PD.

>>> Table 1<<<

3.4. Evidence Synthesis

The GRADE system establishes a series of items that should be considered to assess the level of quality of evidence, which are limitations in study design, inconsistency of results, uncertainty about whether the evidence is straightforward, imprecision, and publication bias.

Table 2 shows the synthesis of evidence regarding aerobic and combined physical exercise to improve functional capacity and aerobic capacity in people with PD. The quality of the evidence was categorized as moderate for the functional variables measured by the 6MWT and the 2MWT, and for aerobic capacity considering maximal and peak oxygen uptake. This means that there is a possibility that the actual effect is far from the estimated effect. However, a high certainty of evidence was found for the UPDRS III, indicating a high agreement between the actual and estimated effect.

>>> **Table 2**<<<

3.5. The risk of bias

Figure 2 depicts the risk of bias assessed using the Cochrane risk of bias tool. The studies evaluated obtained a low risk of "incomplete outcome data" and "selective reporting", which deal with the provision of information on the results and their availability. On the contrary, a moderate to high risk of bias was obtained in "allocation concealment", "blinding of participants" and "blinding of outcome assessment".

>>> **Figure 2** <<<

3.6. Functional capacity

Functional capacity was assessed by combining various functional tests from the studies analyzed. To summarize the results of functional tests conducted across multiple studies, we grouped them based on the method used (i.e., 6MWT, 2MWT). The study of Pelosin et al. (28) was not included in the meta-analysis statistics because it used the 10-meter walking test. There was a low heterogeneity ($I^2 = 0\%$). The overall standardized mean

difference between the exercise group and the control group was 0.48 [$CI_{95\%}$ = 0.24–0.71; p < 0.0001], indicating that the exercise group presented better results in the functional tests (Figure 3A). The quality of evidence was moderate.

3.7. UPDRS III

For the UPDRS III outcome, we found a high quality of evidence and a moderate heterogeneity among the included studies (I^2 = 28%). The results demonstrated an improvement for the experimental group post-intervention with an overall mean difference of -2.48 [$CI_{95\%}$ = -3.16, -1.81; p < 0.00001] (Figure 3B).

3.8. Maximal oxygen uptake

Regarding the oxygen uptake assessed by the VO_2max, only five studies met the criteria to be included in the meta-analysis. The included studies presented low heterogeneity (I^2 = 0%), high quality of evidence and an overall standardized mean difference of 0.42 [$CI_{95\%}$ = 0.18, 0.66; p = 0.0007] in favor of the exercise group (Figure 3C).

>>> Figure 3A, B and C <<<

4. Discussion

This systematic review examined the results of randomized controlled clinical trials involving aerobic training in individuals with PD. In summary, the analysis of the 13 included studies revealed that aerobic exercise is effective in enhancing the VO_2max and functional capacity and reducing the UPDRS III score in individuals with PD. Therefore, this systematic review highlights the relevance of incorporating aerobic exercise into the training programs for individuals with PD as a strategy to improve their functional capacity, alleviate motor symptoms, and enhance VO_2max.

The current meta-analysis findings corroborate to positive effects of aerobic exercise on functional capacity (i.e., 6MWT, 2MWT) (Gamborg et al., 2022), as well as on the UPDRS-III (Gamborg et al., 2022; Zhou et al., 2022) as reported in previous systematic reviews. However, different from our study, previous systematic reviews showed a high degree of heterogeneity likely due to including patients in the different medication states (on- or off-medication) and/or de novo Parkinson in the meta-analysis, generating low evidence certainty.

Regarding VO_2max, our findings support previous systematic reviews (Gamborg et al., 2022; Sena et al., 2023). However, Sena et al., 2023 suggested that high-intensity exercise intervention could increase maximal oxygen consumption, but the meta-analysis displayed a high heterogeneity (82%) and very low evidence certainty. Additionally, Gamborg et al., 2022 only included aerobic interventions with a minimal intensity of 60% of the maximal heart rate (ranging from moderate to high-intensity exercise), a type of exercise that can be challenging for all individuals with PD. Our study revealed a positive impact of aerobic exercise on functional capacity, VO_2max, and UPDRS-III from aerobic interventions with

moderate intensities, as we only included one study with high-intensity exercise (Fernandes et al., 2020). This confirms the significance of aerobic exercise with various intensities in enhancing functional capacity, maximal oxygen uptake, and UPDRS-III for this population.

4.1. Study Participants

The average age of the intervention subjects found in the present review ranged from 57 to 78 years of age, predominantly male. Regarding the disease stage, the studies included participants with Hoen & Yahr ranging from 1 to 3. This study contributes to our understanding of the effects of aerobic exercise on oxygen consumption and functional capacity in the older population with PD with mild to moderate levels of disease. Although PD is considered a disease associated with older adults [40], there are cases of subjects diagnosed as early as 40 years of age [41]. Therefore, there remains a need for further research to clarify how aerobic exercise impacts the younger population with PD. Also, investigating the effects on individuals with more advanced levels of disease is relevant for understanding PD progression. Such studies could help broaden our knowledge and develop tailored exercise interventions for individuals diagnosed with PD at a younger age.

4.2. Aerobic exercise protocols

The studies included in this review exhibited similarities regarding the type and weekly frequency of the exercise protocol. Most studies (8 out of 13) used overground or treadmill walking/running with moderate intensity. However, there were notable variations in the intensity, duration, monitoring, and progression of exercise sessions across these studies.

Overall, most of the studies had a frequency of two to three times per week and exercise intensity between 60-80% of heart rate reserve or maximal HR. Treadmill/walking training was the most preferred aerobic exercise modality. This could be explained by the fact that there is evidence that this modality is effective in improving some gait parameters such as the gait speed and the stride length [42]. Moreover, the treadmill can be a valuable tool for controlling intensity during exercise for individuals with PD, functioning as a sort of "pacemaker" [43]. Nevertheless, it is worth noting that the use of a treadmill by individuals with PD can potentially lead to a greater reliance on external cues to regulate gait rhythm, which may result in a more cautious gait pattern, characterized by reduced gait speed concomitant to a decreased step length [43]. Therefore, its use by individuals with PD should be considered with caution.

Concerning the modality of aerobic exercise, only the study by Fernandes et al. [33] implemented a high-intensity interval training. The authors showed that high-intensity interval training elicited better results in gait parameters than moderate-intensity continuous training. Their protocol consisted of three sessions per week, with intensity prescribed based on the perceived exertion. These findings contrast in parts with those obtained by Shulman et al.,[2] who compared a higher and a lower-intensity continuous treadmill exercise. Despite both intensities improving cardiovascular fitness, the lower-intensity program was more effective in improving the gait speed. It is important to note that with the high-intensity interval training program, it is possible to implement exercises at much higher intensities than a high-intensity but continuous workout. Therefore, more studies utilizing high-intensity interval training protocols are required to gain a deeper

understanding of the effects of exercise intensity on physical capacity and oxygen uptake in persons with PD.

It is essential to highlight that almost half of the studies included in the meta-analysis (6 out of 13) incorporated other exercise modalities (i.e. strength, calisthenics, functional training, and/or body weight-supported training) in combination with aerobic exercise. It is known that strength training can provide neurological benefits, reducing bradykinesia [44] and freezing of gait [45] while enhancing functional capacity and the quality of life for individuals with PD. Consequently, the combination of strength training with aerobic training may lead to increased gains in physical capacity and oxygen consumption. However, more randomized controlled clinical trials focusing solely on aerobic exercise are necessary to gain a better understanding of its effects on physical capacity and oxygen uptake.

4.3. Effects of aerobic exercise on functional capacity, motor symptoms, and oxygen consumption

The systematic review and meta-analysis revealed that aerobic exercise leads to significant improvement in functional capacity, motor symptoms, and VO_2max. These findings are particularly notable because of the moderate to high quality of evidence supporting them (moderate for functional capacity, and high for VO_2max and UPDRS III score) as well as the low to moderate heterogeneity (low for functional capacity and VO2max, and moderate for UPDRS III score). The moderate heterogeneity observed in UPDRS III results may be

attributed to variations in the aerobic interventions used across studies, including cycling [31], treadmill [32, 36] and walking [39].

The results demonstrated that aerobic physical exercise leads to clinically significant improvement in motor symptoms (UPDRS III) in people with PD when performed 2 to 3 times per week with intensities of 55 to 80% of the maximum or reserve heart rate, regardless of the specific type of aerobic activity. Despite the studies that promoted larger effect sizes on UPDRS III were those prescribing walking/treadmill [32, 36], Cugusi et al. [39] with cycling exercise reported 8-point decrease on the UPDRS-III after exercise and the combination of aerobic exercise and body weight support exercises also showed benefits [32]. Improvement in motor symptoms after treadmill exercise can be explained by several mechanisms [48, 49]. Exercising on a treadmill reduces distractions that may occur outdoors/overground due to less visual stimuli [48], thus increasing the focus on walking. Another potential mechanism is the constant speed imposed by the treadmill, helps minimize stride variability [49]. Bello et al. [48] also suggest that the movement of the treadmill belt provides crucial proprioceptive feedback during exercise, possibly facilitating the use of the cerebellum-premotor pathway instead of the basal ganglia-supplementary motor area pathway.

Likewise, aerobic exercise improves functional capacity, which could be explain by the improvement in motor symptoms after aerobic exercise. However, little information is available on the minimal clinically important difference for functional tests in PD. Regarding the 6MWT, Perera et al [50] propose that increasing 50 meters reflects a substantial improvement in older adults. Therefore, we could infer that, except for Shulman et al. [51], all included studies using the 6MWT reported clinical improvement (> 50 m)

compared to the control group. As most of the tests used by the studies of this review were related to mobility (e.g., 6MWT, 20-meter walk test, TUG) and the main aerobic exercise applied was walking, it is expected that functional capacity would be better after training. On the other hand, the exercise intensity and prescription varied among those studies. Pelosin et al. [28] prescribed the exercise intensity at 90% of the walking speed. Atan et al. [32] considered the HR obtained at the sixth minute of a 6MWT as the prescribed intensity. Finally, Collett et al. [31] prescribe the exercise at 55-85% of the HRmax. Therefore, healthcare professionals can consider several possibilities for prescribing exercise depending on their available resources and equipment. Further studies should compare different intensity prescriptions as well.

Regarding the aerobic capacity, as measured by the VO_2max, three studies met the criteria to be included in the meta-analysis. Our results showed that aerobic exercise significantly improves the aerobic capacity in persons with PD. Collett et al. [31] and Demonceau et al. [35] reported significant improvements in the VO_2max of individuals with PD after an exercise protocol, with a higher effect size reported by Demonceau [35]. The exercise protocols comprised a frequency of 2 to 3 times per week, with a duration of 40 to 90 minutes and intensities ranging from 55% to 85% of maximum HR [31] or 50% to 80% of power output load [35]. Only Collett et al. [31] found no improvement in the VO_2max compared to the control group. However, these results should be interpreted with caution since the study by Collett et al. [31] was not designed to determine the efficacy of the aerobic training, the number of patients was not large, and both groups (control and exercise) increased physical activity levels from baseline. Moreover, no studies have established the minimal clinically important difference for VO2peak in PD. However,

further studies are needed to establish the long-term clinical effects of aerobic exercise on VO_2max, especially in training programs exclusively involving aerobic exercise for patients with PD.

4.4. Considerations and limitations

Nine of the 13 studies included in the meta-analysis used heart rate to prescribe and control the intensity of aerobic training. This is a simple and widely applied strategy in training. Due to the great use of heart rate in training control, this systematic review included the descriptor "heart rate variability" in the literature. However, no randomized controlled clinical trials studied the effects of exercise on the cardiac autonomic control of patients with PD. Recently, some authors [52, 53] studied the association between cardiac autonomic control with postural control and with the freezing of gait during gait trials, respectively. The results suggested an involvement of the autonomic nervous system in motor symptoms in individuals with PD. As aerobic exercise can improve the autonomic nervous system functioning, future randomized controlled clinical trials are needed to verify its effects on heart rate variability and how it could be related to the improvement of motor symptoms.

A limitation of the present study was the inclusion of studies that combined other types of exercises (non-aerobic) in the training session. Despite this, we believe that the results of the present meta-analysis are highly relevant, as they only include randomized controlled clinical trials studies, since the recommendations for aerobic exercise sessions for individuals with PD work with different stimuli so that they have better results on motor and non-motor symptoms[54]. Although it does not diminish the significance of our findings, it is worth noting that the number of randomized controlled clinical trials

investigating the effects of aerobic training on functional capacity, motor symptoms, and oxygen consumption in individuals with Parkinson's disease is still relatively limited.

4.5. Implication for practice

These findings emphasize the significance of incorporating aerobic exercises as a non-pharmacological intervention and call upon healthcare professionals to consider it as a crucial component, alongside neuromotor training, in rehabilitation programs for individuals with PD. Currently, pharmacological treatment remains the primary approach to managing PD [55-57]. However, existing literature suggests that aerobic exercise can provide a cost-effective solution for addressing both motor and non-motor symptoms [16, 58].

This systematic review assessed the impact of aerobic exercise on functional capacity, motor symptoms, and aerobic capacity in individuals with PD. The results indicate that effective aerobic exercise protocols for enhancing functionality and cardiovascular capacity in people with PD typically involve sessions conducted 2 to 3 times per week [28, 32] with low [2] to moderate intensities [33, 38, 39] and sessions lasting around 30 minutes. These exercises are predominantly performed on a treadmill [34] or a stationary bike [35]. This information can guide healthcare professionals in designing exercise programs tailored to individuals with PD to achieve the best outcomes in terms of functional capacity, motor symptoms, and aerobic capacity.

5. Conclusion

In conclusion, aerobic exercise training conducted 2 to 3 times a week, with a range of intensities from low to high, proves to be an effective intervention for enhancing functional capacity, maximizing oxygen uptake, and reducing the UPDRS scores in individuals with idiopathic Parkinson's disease (PD) at Hoehn and Yahr stages 1 to 3. However, further studies are warranted to comprehensively understand the impact of exercise on cardiovascular autonomic control, and this should be a key focus in future research endeavors.

6. Contributors

FAB, VCM, CKF, NZA, and ARZ designed the study. NZA, VCM, and CKF selected, screened, and analyzed the studies. RAB, NZA, and ARZ drafted the manuscript. RAB, FAB, NZA, VCM, and CKF critically reviewed the manuscript. All the authors read and approved the final version of the manuscript.

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Figure legends

Figure 1. Flowchart detailing the selection of included articles.

Figure 2. Cochrane risk of bias tool.

Figure 3. Statistical results of the meta-analysis of the functional capacity (A), UPDRS III (B), and oxygen uptake (C). *Assessed using the six-minute walk test; #Assessed using the two-minute walk test

Figure 1

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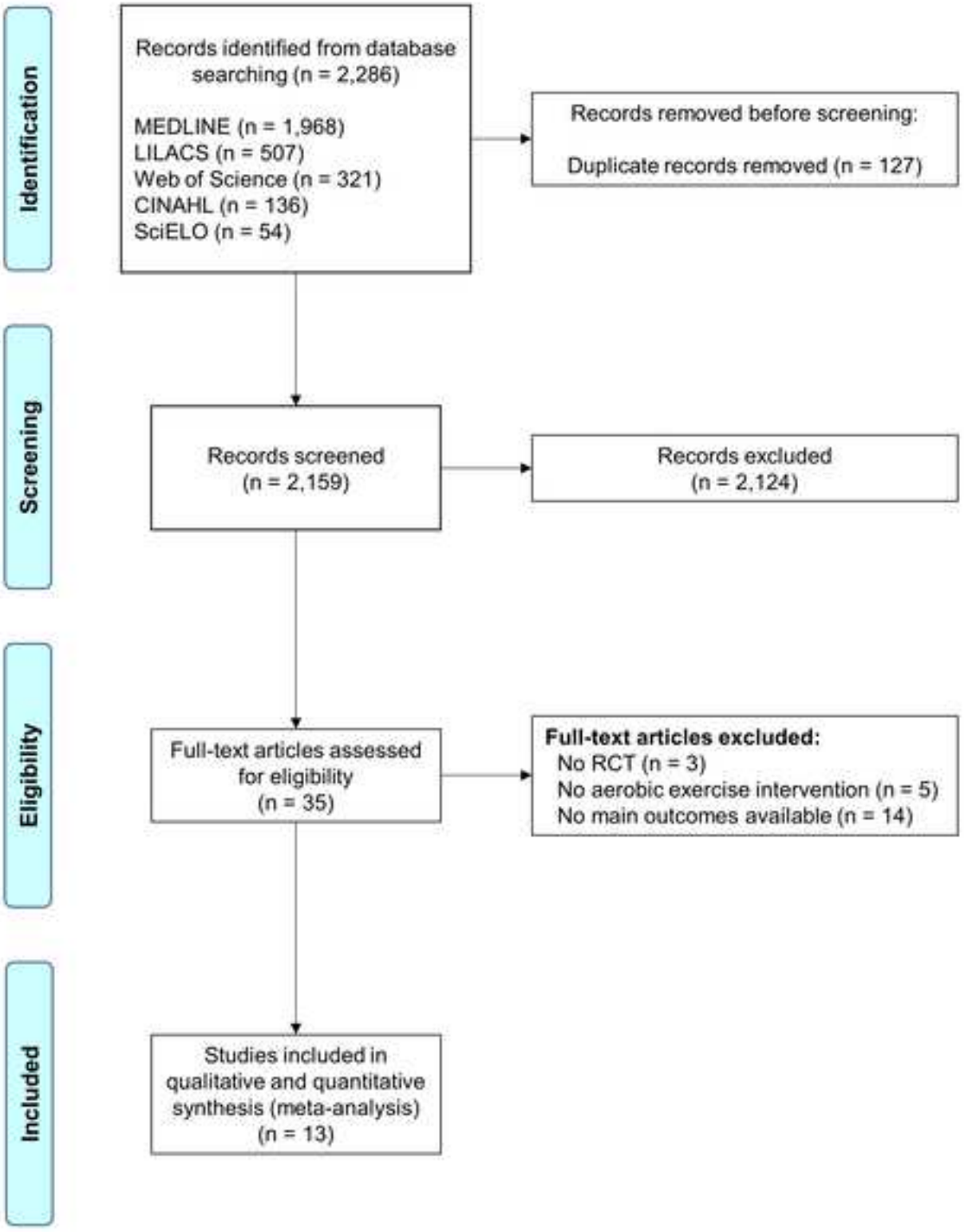

Figure 2

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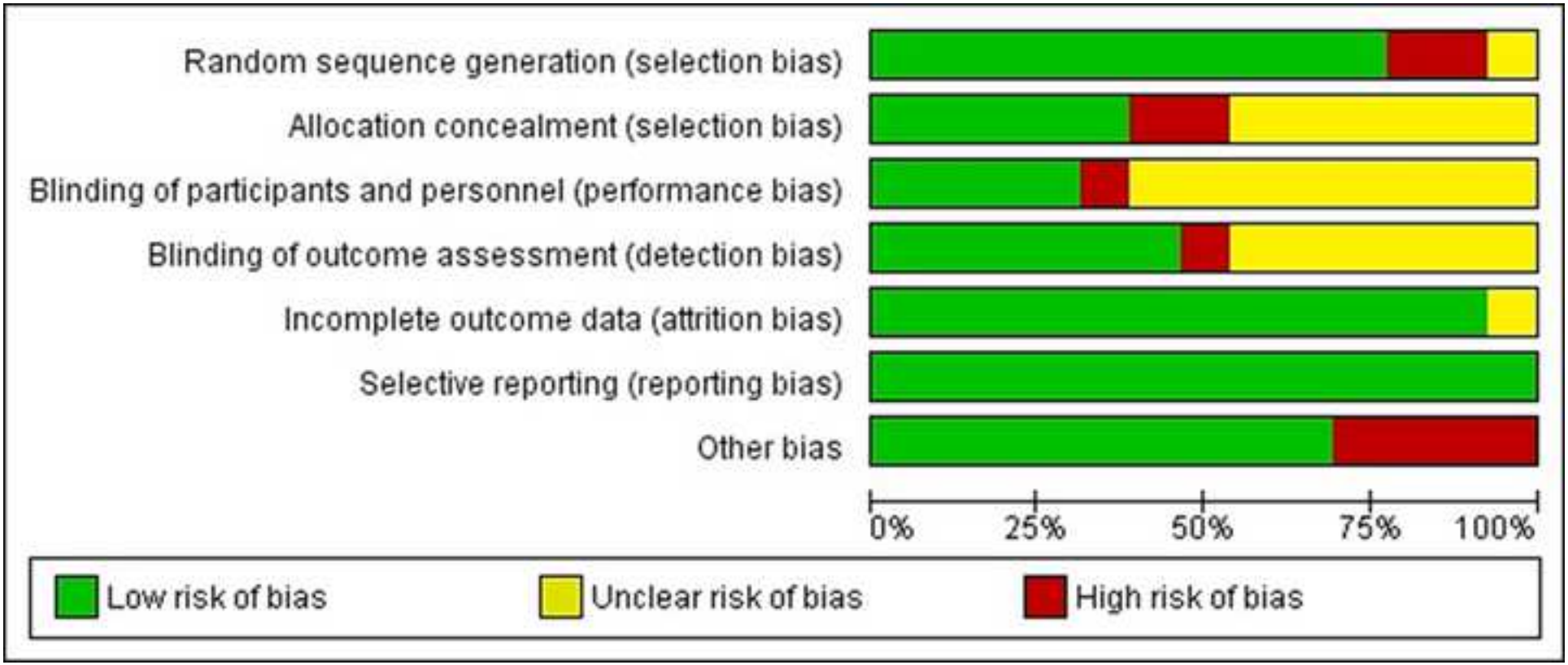

Figure 3

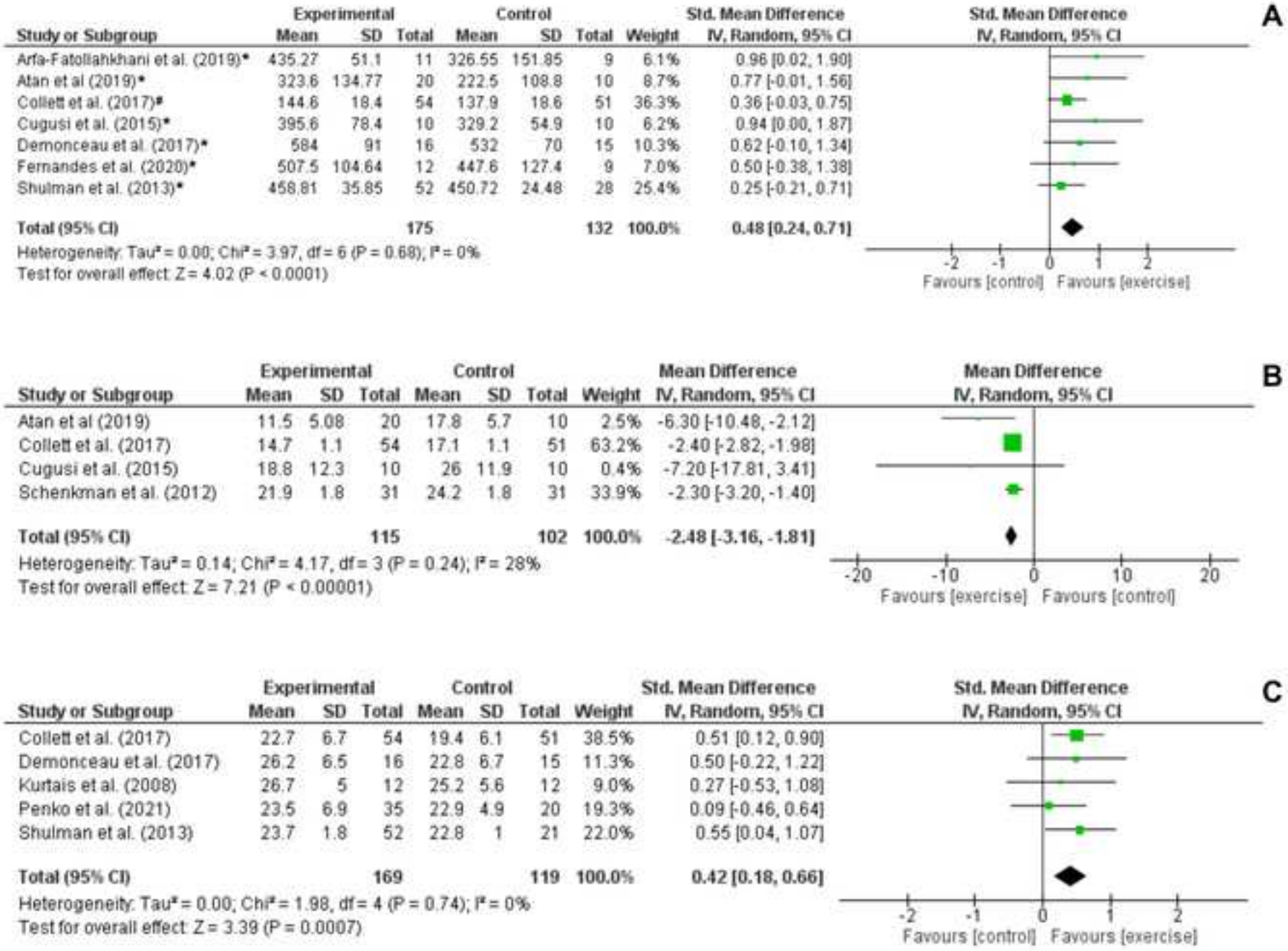

Table 1. Summary of the training variables applied in the studies included in the systematic review and meta-analysis.

Author	Type Exercise	Duration Frequency (weeks)	Frequency (days)	Session duration (minutes)	Intensity	Internal Monitoring	Progression
Kurtais et al. (2008)	Walking training	6	3	40	70-80% HR max.	HR	Gradually increased over time.
Schenkman et al. (2012)	Aerobic exercise (treadmill, cycling, elliptical) and functional exercise	70	3	40-50	65-80% HR max	-	-
DiFrancisco et al. (2012)	Treadmill training and strength resistance (machines)	6	2	20-40	60-70 VO_2max 8-15 rep. 50-80% 1RM	-	5-lb in strength training when achieved 15 repetitions in one set
Shulman et al. (2013)	Treadmill training and strength resistance	12	3	15-50	70-80% HRR 40-50% HRR 2x10 strength legs	HR	Every 2 weeks 5 min 0,2 km/h; every 2 weeks 5 minutes
Cugusi et al. (2015)	Nordic walking	12	2	60	60-80% HRR	HR	-
Duchesne et al. (2015)	Cycling	12	3	20-40	60-80% VO_2peak	HR	5 min and 5% of intensity every week
Collett et al. (2017)	Cycling and strength resistance	24	2	60	55%-85% HR max.	HR	-
Demonceau et al. (2017)	Cycling and strength resistance	12	2-3	60-90	50-80 PWL 50-90 RM	HR; BP	Linear
Pelosin et al. (2017)	Walking training	2-5	5-3-2	45	90% walking speed	-	Increase 5% speed every 2 sessions
Atan et. Al. (2019)	Body weight supported (BWS) treadmill training	6	5	60	HR 6MWT (submaximal)	BP; HR	-
Arfa-Fatollahkhani et al. (2019)	Treadmill training	10	2	30	60% HRR RPE 11-13	HR; SpO2	-
Fernandes et al. (2020)	HIIT and Moderate continuous exercise calisthenics/balance exercises	12	3	45-55	11-14 RPE 15-17 RPE	RPE	Linear
Penko et al. (2021)	Forced and voluntary high-intensity aerobic cycling	8	3	50-60	60-80% of HRR	RPE, HR	-

HRR: heart rate reserve; HR: heart rate; RPE: rating of perceived exertion; SpO2: oxygen saturation; 6MWT: 6-min walk test; PWL: power output load; 1RM: one-repetition maximum; BP: blood pressure; VO_2max: maximal oxygen uptake; VO_2peak: peak oxygen uptake; Linear: Progressive increase over the weeks until maximum training time is reached

Table 2. Summary of results of the control versus exercise group according to GRADE.

Certainty assessment						Number of patients		Effect		Certainty
Number of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Exercise**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**	
Functional Capacity (follow-up: mean 12 weeks; assessed with: 6MWT, 2MWT)										
281 (7 RCTs)	not serious	not serious	not serious	serious	none	175	132	-	SMD **0.48** (0.24 to 0.71)	⊕⊕⊕◯ Moderate
Motor Symptoms (follow-up: mean 14 weeks; assessed with: UPDRS III)										
217 participants (4 RCTs)	not serious	not serious	not serious	not serious	none	115	102	-	SMD **-1.35** (-2.03 to -0.67)	⊕⊕⊕⊕ High
Aerobic Functional Capacity (follow-up: mean 18 weeks; assessed with: VO2max or VO2peak)										
288 participants (5 RCTs)	not serious	not serious	not serious	serious	none	169	119	-	SMD **0.42** (0.18 to 0.66)	⊕⊕⊕◯ Moderate

CI: confidence interval; **MWT:** minute walk test; **SMD:** standardized mean difference.