Universidade de Lisboa

Faculdade de Medicina de Lisboa

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Orientador: Prof. Doutor Joaquim Ferreira

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Dissertação especialmente elaborada para a obtenção do grau de Mestre em Neurociências

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Abstract

Background

Parkinson Disease (PD) is the second most common neurodegenerative disorder characterized by motor and non-motor symptoms that frequently affect patients' physical activity.

Recent studies showed that PD patients spend 75% of all awake time in sedentary behaviors and are 30% less physically active than age-matched comparison subjects.

Exercise may improve PD symptomatic control, and perhaps even modify diseases progression. Even though several studies have been published, in the last years, a robust evidence of exercise efficacy in PD is still missing. This study intends to investigate the efficacy of exercise, described as a structured and planned physical activity, associated with an energy expenditure, with the aim of improving physiological and motor function, as a therapeutic intervention in PD. Based on this, assumptions for PD clinical practice and research are made.

Methods

It was performed a systematic review of published randomized clinical trials assessing exercise interventions in Parkinson Disease. Studies were identified using MEDLINE, PubMed, PEDro and Cochrane Library (from its inception to February 2017). A mixed methods approach was undertaken using narrative and random effects meta-analysis methods. The methodological characteristics and quality of reporting were assessed using Cochrane Risk of Bias tool.

Results

Fifty-two studies were included. The most frequently used type of exercise was aerobic exercise (32.6% of the included studies). It is also important to highlight that 34.6% of the included studies assessed the effect of the exercise on motor impairment/disability.

Exercise appears to be efficacious improving UPDRS III score, falls frequency and gait measured through the 6-minutes walking test. However, due to the reduced number of studies, conclusions cannot be drawn about the relevance of the improvement.

Exercise has not shown to contribute to a significant improvement in the quality of life and balance of Parkinson's disease patients. Conclusions

Data, from the included studies, suggests that exercise has a potential positive effect in falls frequency, PD patients' motor impairment and gait parameters. However, the number of studies was small and to better conclude about exercise efficacy on PD additional studies with larger samples, using the recommended outcomes tools for PD and a placebo or sham-intervention comparator should be performed. The role of exercise as disease modifying intervention, the best type of exercise, intensity and frequency of exercise for each disease stage and therapeutic purpose are still unanswered questions.

Key words

Parkinson Disease, exercise, systematic review, clinical trials

Resumo

Contextualização

A doença de Parkinson é a segunda doença neurodegenerativa mais comum. Um conjunto de sintomas motores e não motores conduzem a uma progressiva dependência nas atividades da vida diária e consequente perda de qualidade de vida para estes doentes. Os primeiros sintomas e a sua progressão não são lineares, existindo uma grande variabilidade no decurso da doença. Habitualmente, no início, a doença de Parkinson é unilateral e o tratamento farmacológico permite o controlo sintomático. Contudo após dois a cinco anos, a maioria dos pacientes desenvolve complicações motoras associadas à Levodopa.

Estudos recentes mostraram que os doentes com Parkinson gastam 75% do seu tempo em atividades sedentárias e que, em comparação com adultos da mesma idade, são 30% menos ativos, diferença que se acentua com a progressão da doença.

O exercício tem sido cada vez mais recomendado como intervenção coadjuvante às intervenções farmacológica e cirúrgica. Por isso, torna-se cada vez mais relevante investigar que efeitos tem o exercício e como atua nos sintomas e nos mecanismos neurofisiológicos da doença de Parkinson. Estudos prévios em animais realçaram o seu potencial benefício na neuroplasticidade, uma vez que, com o exercício ocorre um aumento da síntese e libertação de dopamina e um aumento dos seus níveis no estriado.

Esta revisão sistemática da literatura é especialmente relevante para investigar a eficácia do exercício na DP e para definir diretrizes para novos ensaios clínicos e para o seu uso enquanto potencial ferramenta terapêutica, quer como coadjuvante, quer como potencial modificador da progressão da doença.

Objetivos

Este estudo visa investigar a eficácia do exercício cujo objetivo é a melhoria da função fisiológica e motora como intervenção terapêutica na DP, descrito como uma atividade física estruturada e planeada, associada a um gasto energético, e cujo objetivo é a melhoria da função fisiológica e motora. Com base nos resultados, procuraremos delinear recomendações para a prática clínica e investigação na área da DP.

Métodos

Foi realizada uma pesquisa eletrónica de ensaios clínicos que investigassem o efeito do exercício na doença de Parkinson nas seguintes bases de dados: MEDLINE, PubMed, PEDro and Cochrane Library, desde o início do estudo até Fevereiro de 2017.

Na seleção de artigos foram considerados os seguintes critérios de inclusão: 1) estudos clínicos randomizados e controlados 2) a população incluída nos estudos ser composta por doentes de Parkinson em qualquer estádio da doença 3) estudos que avaliem eficácia terapêutica do exercício, entendido como uma atividade física planeada e estruturada, à qual está associado um gasto de energia e cujo objetivo é a melhoria da função fisiológica e motora 4) estudos com uma das seguintes intervenções como grupo de controlo: não intervenção, cuidados habituais, placebo, *sham-intervention* ou outro tipo de exercício 5) incluir pelo menos um dos seguintes *outcomes*: marcha, qualidade de vida, incapacidade, capacidade aeróbia, amplitudes articulares, força muscular ou cognitivo.

Foi construída uma grelha de recolha de dados dos artigos selecionados, na qual cinco domínios foram tidos em conta: informação geral (título, nome e país do autor de correspondência, língua de publicação, ano e jornal de publicação, tipo de intervenção, aprovação ética e consentimento informado), métodos (critérios de elegibilidade, tipo de desenho do estudo, método de randomização, presença de ocultação da aleatorização, tipo de ocultação e duração do follow-up, número total de doentes e de doentes por grupo), intervenção (tipo, duração e *timming* da intervenção), análise dos dados (tipo de análise, métodos estatísticos utilizados, objetivos, desistências, cálculo do tamanho da amostra, *outcomes* pré-definidos, instrumentos de avaliação e comparabilidade dos grupos) e resultados.

A qualidade metodológica dos estudos foi avaliada com recurso à ferramenta da Cochrane para avaliar o risco de viés – *Cochrane tool Cochrane Risk of bias.* Todos os estudos foram classificados de acordo com o risco de viés.

Foi realizada uma análise estatística descritiva dos resultados. A meta-análise foi conduzida recorrendo ao *RevMan 5.3.5 software.* Para que se pudesse avaliar a eficácia, apenas os estudos que tinham como intervenção no grupo de controlo o não exercício, foram incluídos na meta-análise. Os estudos foram analisados de acordo com os *outcomes* e incluídos na meta-análise se o *outcome* e a respetiva ferramenta de avaliação fossem usados em pelo menos outros dois estudos. Foi conduzida uma análise por subgrupos tendo por base o tipo de exercício (exercício aeróbio vs multimodal), para o único *outcome* que tinham dados suficientes para comparar dois tipos de exercícios diferentes e outra com base na progressão da intensidade ao longo do estudo (intensidade mantida versus aumento progressivo da intensidade ao longo do estudo).

<u>Resultados</u>

A pesquisa eletrónica identificou 368 citações, das quais 159 potencialmente elegíveis. A aplicação dos critérios de inclusão resultou na exclusão de 107 estudos. As principais razões de exclusão foram: não serem ensaios clínicos randomizados (n=32), não avaliarem a eficácia do exercício (n=48), o grupo de controlo ser constituído por participantes sem doença de Parkinson (n=18), tipo de *outcomes* (n=2), estudos duplicados (n=6) e a língua de publicação (n=1). A intervenção mais frequentemente utilizada nos estudos incluídos foi o exercício aeróbio (32.6% dos estudos) e os doentes foram, na sua grande maioria avaliados sob o efeito da medicação. O *outcome* primário mais utilizado foi o comprometimento motor/incapacidade e os *outcomes* secundários mais avaliados foram a marcha e a qualidade de vida. Na meta-analise avaliámos o efeito do exercício nos seguintes *outcomes:* comprometimento motor/incapacidade, equilíbrio, parâmetros de marcha, frequência de quedas e qualidade de vida.

O exercício poderá ter benefícios no comprometimento motor (UPDRS, parte III), na diminuição da frequência de quedas e na marcha avaliada através do teste dos 6 minutos de marcha, no entanto, em nenhuma das análises a melhoria foi significativa. Na análise de subgrupos, foram comparados o exercício multimodal com o aeróbio, sendo mais benéfico o exercício multimodal para a melhoria na UPDRS parte III, no entanto, mais uma vez os resultados não foram estatisticamente significativos. Na análise de subgrupos, na qual comparámos estudos com intensidade mantida com estudos com aumento progressivo da intensidade, não se registaram diferenças significativas, embora o aumento progressivo da intensidade tenha melhorias superiores na UPDRS parte III. A maioria dos estudos não reporta efeitos adversos da intervenção, apresenta baixo risco de víeis e só têm ocultação do avaliador.

<u>Conclusões</u>

A revisão sistemática sugere que o exercício poderá ter um impacto positivo nos sintomas motores da doença de Parkinson, com especial impacto no comprometimento motor/incapacidade, avaliado pelo UPDRS parte III, na frequência de quedas e nalguns parâmetros da marcha. No entanto, as melhorias encontradas não são estatisticamente significativas. Nos estudos incluídos, nesta revisão sistemática da literatura, não foram encontrados benefícios significativos do exercício para a qualidade de vida ou para a melhoria do equilíbrio na DP.

Este estudo observou que, na maioria dos estudos incluídos, a intensidade e frequência do exercício seguem as indicações definidas pelas ACSM relativas à prescrição do exercício para o adulto idoso.

O número reduzido de estudos, o tamanho reduzido da amostra, a diversidade de *outcomes* entre os estudos limitam as conclusões sobre os benefícios do exercício em doentes de Parkinson, que podem ser retiradas com esta revisão sistemática. Estudos futuros são necessários para perceber os efeitos do exercício noutros parâmetros de saúde e para avaliar a correlação entre o exercício e os benefícios alcançados porque só assim será possível que os profissionais de saúde escolham o programa mais eficaz para os doentes de Parkinson. Outro aspeto importante passa pela avaliação da eficácia em estádios mais avançados da patologia, assim como o estudo do impacto do recurso ao exercício em fases precoces da doente e do seu potencial papel como modificador da progressão da doença.

Palavras-chave

Doença de Parkinson, exercício, revisão sistemática, ensaios clínicos

Contents

Abbreviations

- 6MWT – 6-Minute Walk Test
- ACSM – American College of Sports Medicine
- BBS – Berg Balance Scale
- CI – Confidence Intervals
- EBM – Evidence-Based Medicine
- EMA – European Medical Agency
- FES – Falls Efficacy Scale
- ICHO – The International Consortium for Health Outcomes
- MD – Mean difference
- PA – Physical activity
- PD – Parkinson Disease
- PDQ-39 – Parkinson Disease Questionnaire–39
- Rob – Risk of bias
- SOT – Sensory Organization Test
- UPDRS – Unified Parkinson's Disease Rating Scale

Introduction

This work was prepared as part of the 2nd cycle of Masters in Neuroscience at the Faculty of Medicine, University of Lisbon.

The original idea was born from the awareness that research is necessary to understand the benefits of exercise in Parkinson Disease and to guide health professionals' interventions.

Hoping to provide the best evidence to guide health professionals in clinical practice, a systematic review of clinical trials in exercise was made with the goal of evaluating the potential benefits of exercise in PD.

This paper has four main sections. In the first one, we present a brief theoretical background on the addressed issues. The second section describes the methodology used in the systematic review, followed, in the third section, by the presentation of the results. The final section comprises the discussion of the results, shortcomings of the study and some final conclusions.

I. Background

Parkinson's disease

Parkinson Disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. (1,2) Due to the increasing life expectancy and as PD incidence is associated with aging, the number of individuals affected is expected to increase considerably over the next decades. (3)

Parkinson's disease neurodegenerative process is associated with the death of dopaminergic neurons from the substantia nigra pars compacta, being estimated that about 70-80% of dopaminergic neurons are lost at the onset of motor signs. (4–6)

Although clinical diagnosis is focused on the presence of bradykinesia, plus rest tremor, rigidity, or both, PD is usually a heterogeneous disease, with a high variety of disabling motor and non-motor symptoms. (6–11) Postural instability and gait disturbances, not being part of the cardinal signs of the disease, are two important and very common features with a high impact in patients' quality of life. They are frequently associated with increased risk of falls (12–14), poor physical function (15,16) and reduced quality of life. Its early onset in the disease course may suggest the presence of an atypical parkinsonism, since in PD it usually takes a few year to develop. (15,17,18)

Typically, PD symptoms start insidiously, are unilateral and mild, with an excellent response to pharmacological treatment. After 2–5 years of disease onset, most patients develop levodopa-induced motor complications, wearing-off symptoms and dyskinesias and after 10 years, a clearly bilateral disease, with bradykinesia have a profound impact on patients' disability. (17,19) Even with an optimal medical management, due to the high disability associated with disease progression, patients usually adopt a sedentary lifestyle, which is associated with increased comorbidities and mortality.

Exercise as a therapeutic intervention

Exercise is defined as a structured and planned physical activity, associated with energy expenditure, that aims to improve subjects' physiological and motor function (20–22). According to the American College of Sports Medicine (ACSM), exercise can be divided in aerobic (or endurance), strength, flexibility, balance and neuromotor training. The type of training, frequency, intensity and duration influence the benefits that can be achieved. Besides helping maintaining and improving physical fitness (22), exercise is also associated with other general health benefits, including: the improvement of cardiovascular and cerebrovascular health; reduction of osteoporosis and age-related sarcopenia; improvement in psychological and autonomic disorders; and a general anti-inflammatory effect (23). Previous studies in aging and neurodegenerative diseases field, showed positive effects of exercise in patients quality of life, brain plasticity, cognitive functions and in neuroimmune system functioning. (24–27).

Exercise and Parkinson’s disease

PD is associated with a physical activity (PA) decline, in volume and intensity, and reduction of patients’ functional capacity and quality of life. (28)

Recent studies showed that PD patients spend 75% of all awake time in sedentary behaviors, 18% in low levels of PA and 6% in a combination of moderate and vigorous levels of PA. Comparing with healthy-controlled matched patients for age, PD patients were approximately 30% less physically active, with a bigger difference as the disease progresses. (28,29)

Previous animal studies have also demonstrated the benefits of exercise in brain functioning. Specifically, an increase in synthesis and release dopamine and its level of concentration in the striatum was registered following acute bouts of exercise. Endurance exercise was additionally shown to improve gait parameters, quality of life, and levodopa efficacy in PD patients. (30–34)

Based on small studies and empiric evidence, exercise has been recommended as an adjuvant to pharmacological interventions for the management of PD symptoms unresponsive to pharmacological treatment (30–32). However, a systematic review synthesizing and critically evaluating the research findings is still missing. Therefore, this project uses a systematic review methodology to evaluate the efficacy of exercise, described as a structured and planned physical activity, associated with an energy expenditure, with the aim of improving physiological and motor function, as a therapeutic intervention in PD. Based on this, assumptions for PD clinical practice and research are made.

II. Methods

Search Strategy

A comprehensive literature search was performed across PEDro, MEDLINE and CENTRAL from inception to February 2017. The keywords used were Parkinson’s disease, exercise, therapeutic exercise and physical activity. Titles and abstracts of citations were screened according to the review study selection criteria further explained. The inclusion or exclusion criteria were applied, and studies were selected for consideration based on the full paper review.

Study Selection

Titles and abstracts were screened from the database search. The full-text of potentially relevant articles was retrieved for further assessments. Studies were included based on the following eligibility criteria:

Inclusion criteria:

(1) Type of studies: Randomized controlled trials
(2) Participants: Parkinson’s disease patients a) any disease stage b) any duration of PD c) all ages d) any drug therapy
(3) Type of interventions: studies evaluating the efficacy of exercise as a therapeutic intervention in PD. Exercise should be described as a structured and planned physical activity, associated with an energy expenditure, with the aim of improving physiological and motor function.
(4) Type of comparators: Non-intervention group, usual care, placebo, sham-intervention or another type of exercise. For meta-analysis, only studies where the comparator was a non-exercise intervention were included. Non-exercise control group interventions included: sham intervention, no intervention, usual care and Qi-gong (when only restricted to meditation and relaxation)
(5) Types of outcomes measures:

a) Gait outcomes	- Two- or six-minute walk test (m) (6MWT) provide a measurement of walking endurance by measuring the number of meters a person can walk in two or six minutes (35) - Walking speed - 10- or 20-metre walk test (s) provide a measurement of gait speed by measuring the time in seconds that a person takes to walk 10 or 20 meters (35) and Speed (m/s) which measures the rate of change of position, recorded in meters per second (36) - Cadence: number of steps per minute (36) - Stride length (m): distance (in meters) between two successive placements of the same foot (37) - Step length (m) measures the average distance (in meters) between successive foot-to-floor contacts with opposite feet (36) - Freezing of gait: 6 self-reported questions about gait quality and freezing episodes (38)
b) Functional mobility and balance outcomes	- Timed Up and Go (TUG): time necessary to get up from a chair, walk 3 m, return and sit in the chair - Improving sit to stand - Functional Reach Test: the maximal distance one can reach, maintaining a fixed base of support in the standing position (39) - Berg Balance Scale: 14-item test which measure functional standing balance of the older adult. Total score 0-56 (0- unable) (40) Activity Specific Balance Confidence: 16-item self-report questionnaire about the confidence patients have that they will maintain their balance during daily activities. Each item is rated from 0% (no confidence) to 100% (complete confidence) (41) - MiniBESTest: 14-item test. Total score 0-28 (higher scores=better balance)
c) Falls	- Number of falls: failing diary - Falls Efficacy Scale (FES): 10-item self-report questionnaire that measure the confidence patients feel in carrying out activities of daily living (ADL) (42)
d) Impairment and disability measures	- Hoehn and Yar – describe the progression of PD symptoms (43) - Unified Parkinson Disease Rating Scale (UPDRS): assess motor impairment and disability (44) - UPDRS-MDS: Unified Parkinson Disease Rating Scale movement disorder society
e) Quality of life	- Parkinson Disease Questionnaire (PDQ-39): self-reported questionnaire (39 questions on 8 domains – mobility, activities of daily living ADL, emotional well-being, stigma, social support, cognition, communication and bodily discomfort). (45) - Parkinson Disease Questionnaire (PDQ-8): short form of PDQ-39. - PDQL: PD-specific health-related quality of life questionnaire with 37 items grouped into four subscales. (46) - Short Form-36 or -12: eight scaled scores assessing vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. (47)
f) Aerobic capacity:	- 6 MWT - VO2 max – Test starts with a self-selected speed and 0% gradient. Speed and gradient are increased according the protocol until participants reach voluntary exhaustion. The peak of consumption is determined based on the 20 s averages obtained during the final stage of the test - Blood oxidative stress and blood pressure
g) Joint health status, range of motion, strength	measured through recommended clinical tests to evaluate amplitude and muscle strength, from baseline and follow-up assessments;
f) Cognitive outcomes	measured through score differences in the recommended scales and tests, from baseline and follow-up assessments

Exclusion criteria:

(1) Non-English, French or Spanish publication.

Data Extraction

Before study selection, a data extraction form was developed, based on the checklist of guidelines for the design and report of clinical trials (SPIRIT and CONSORT statement) and on previous systematic reviews evaluating the efficacy of exercise in other populations. Five domains were analyzed:

1. General information (title, name and country of the corresponding author, language of publication, year and journal of publication, type of intervention, ethical approval and informed consent);
2. Methods (eligible criteria, type of study design, method of randomization, achievement of allocation concealment, type of blinding, total number of randomized patients and of patients per group, and duration of follow-up);
3. Intervention (type, duration and timing of treatment);
4. Data analysis (dropouts rate and sample size calculation, type of analysis, statistical methods used, pre-defined outcomes, assessment tools and groups comparability);
5. Results.

Quality assessment of the included studies

The risk of bias across included studies was assessed using the Cochrane risk of bias tool. All studies were classified with low, high or unclear risk of bias. Uncertainties were solved by discussion with a second reviewer. Studies were not excluded based on their quality of reporting.

Data analysis

Descriptive statistics were provided for continuous and categorical variables.

For statistical analysis and to derive forest plot showing the results of individual studies and pooled analysis, a meta-analysis using RevMan 5.3.5. was made.

Studies were analyzed according to the selected outcomes and included in meta-analysis if the outcome and respective assessment tool were present in at least two other studies. Also, only studies with a non-intervention control group were included. Non-exercise control group interventions included: sham intervention, no intervention, usual care and Qi-gong (when only restricted to meditation and relaxation).

For continuous data, mean difference (MD) and 95% confidence intervals (CI) of random-effects model were calculated for all eligible trials. Detailed subgroup analyses were conducted based on different follow-up periods and progression of exercise intensity. Intention-to-treat samples were used for this purpose.

Pooled odds ratio (OR) and 95% confidence interval (CI) were calculated for risk of dropout between intervention and control.

Heterogeneity across studies was tested using I^2. We used random effects model irrespective of the existence of substantial heterogeneity between study results ($I^2 \geq 50\%$)

III. Results

Study Selection

The electronic search identified 368 citations. After screening abstracts, 159 articles were deemed potentially eligible. The application of eligibility criteria excluded 107 studies. The main reasons for exclusion were: different study design (n=32), no exercise intervention assessed (n=48), only healthy control group (n=18), type of outcomes (n=2), language (n=1) and double publication (n=6). A total of 52 studies fulfilled the eligibility criteria and were included in this systematic review (Appendix 1)

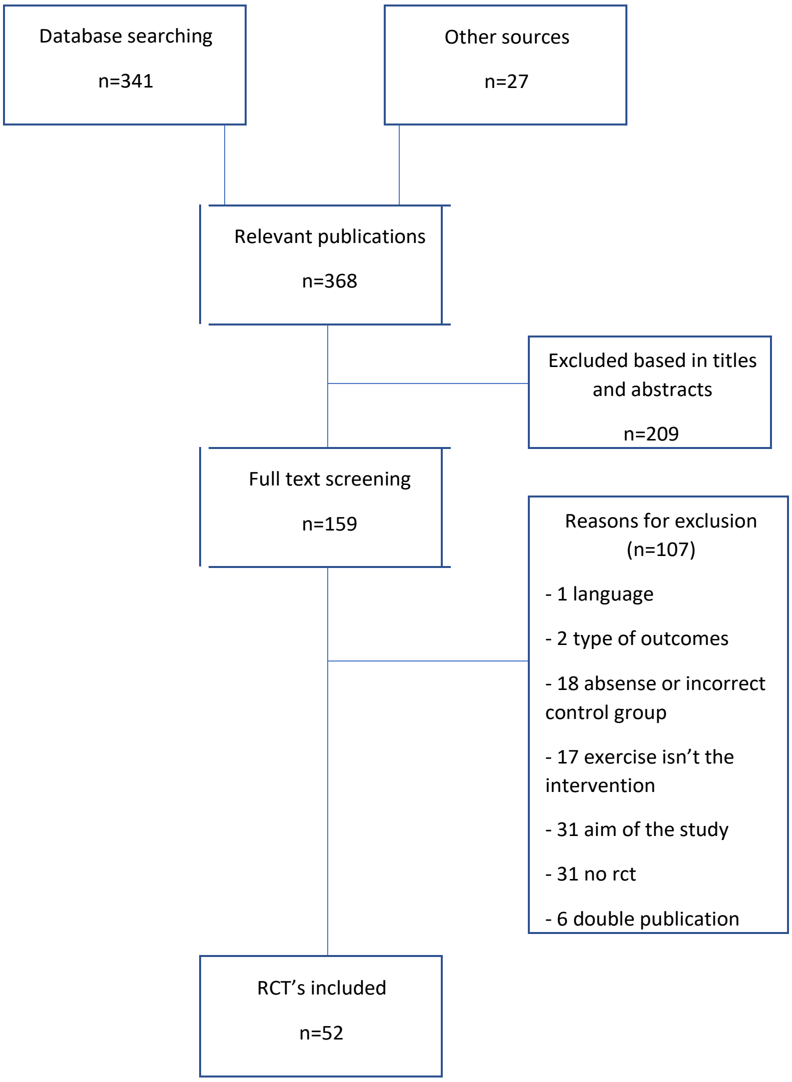


Figure 1: Flow chart of the selection process of included studies

Study Characteristics

The 52 included RCTs evaluated a total of 2374 participants with a mean age of 68.3±4.4 years, and a mean disease duration of 6.3±2 years.

Eligibility criteria varied considerably throughout studies. The most common criteria were: a Hoehn and Yahr scale score ≤ 3, to be under stable medication treatment, to have the capacityto perform the intervention, and to have the ability to understand and comply with the requirements of the study.

Only 26.9% (n=14) of included studies reported a sample size calculation. Of these, in 3.8% (n=2) the sample size in the trial did not match the sample size calculation. (Appendix 2)

In 13.5% (n=7) studies the dropout rate was higher than 20%. The main causes of attrition were symptom burden and clinical deterioration. Pooled results from studies that reported one or more dropouts (58.2%, n=32) showed a higher dropout rates among the control groups (OR = 0.8; 95% CI = [0.58, 1.1]), however the results were not statistically significant (Appendix 3)

Interventions

According to ACSM classification, 32.6% (n=17) of all interventions assessed aerobic/endurance training, 26.9% resistance training (n=14), 5.8% flexibility training (n=3), 9.6% balance training (n=5) and 55.8% multimodal training (n=29) (Appendix 4).

Duration and frequency of the intervention session and the duration of the program varied considerably between studies. The most common were three times per week, 45 to 60 minutes, for three months. (fig. 2 and 3)

Control group interventions included no intervention, usual care, stretching, resistance exercises, physical therapy, yoga, qigong and other exercise. Detailed characteristics of the interventions in active and control arms were summarized in table 1.

In 92.3% (n=48) of the included studies, the intervention and assessments were performed in ON medication state. Two studies (3.8%) evaluated the effect of intervention in both the ON and OFF states. (Appendix 2)

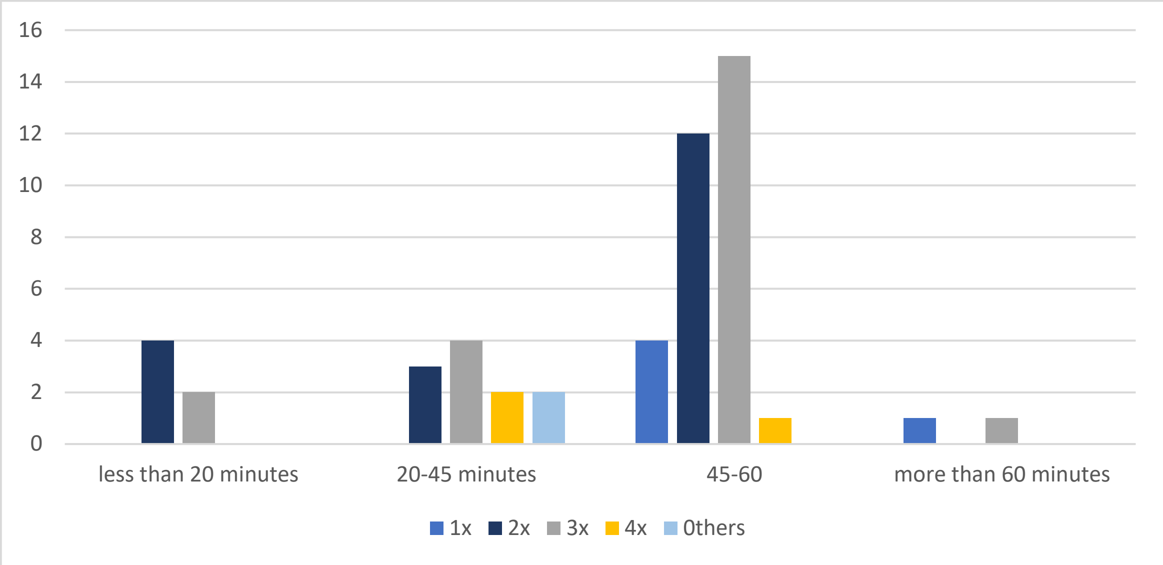


Figure 2: Duration and frequency of the intervention

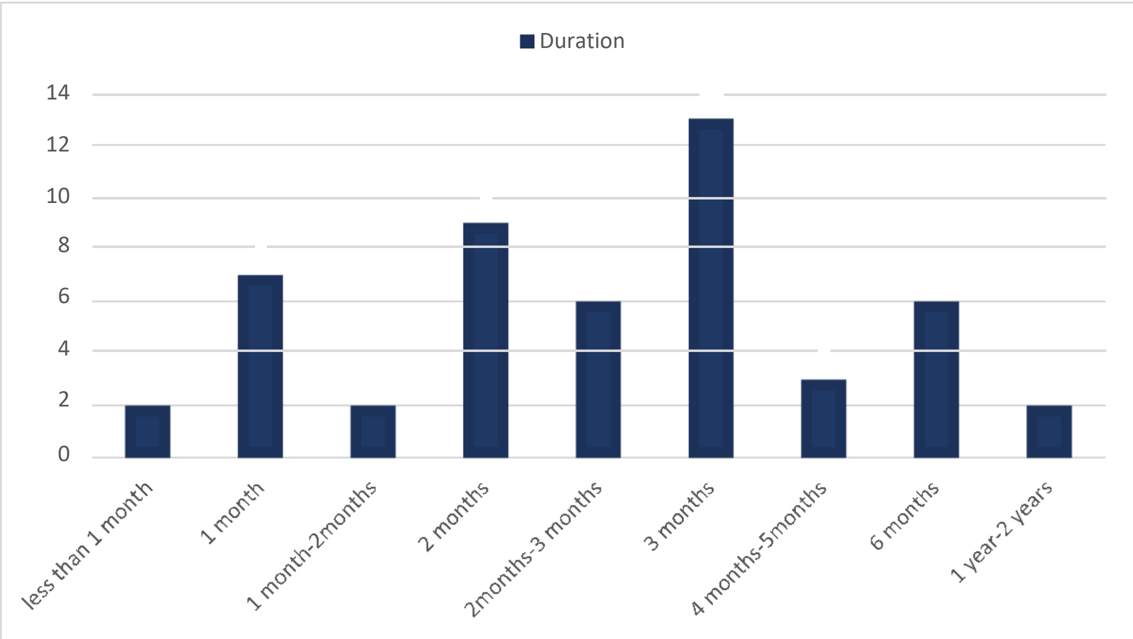


Figure 3: Duration of the program

Table 1: Type of exercise in intervention and control groups

Group	Type of exercise	Studies (n, %, authors)
Intervention group	Combined exercise (at least two: balance, strengthening, walking, cycling, boxing, exercises to improve range of motion)	22 (42.3%) (10,48,57–66,49,67,50–56)
	Tai Chi; Qi-gong	5 (9.61%) (68–72)
	Resistance training/eccentric training	5 (9.61%) (73–77)
	Walking/treadmill	8 (15.38%) (51,78–84)
	Aerobic exercises	7 (13.46%) (29,85–90)
	Dance	3 (5.77%) (91–93)
	Cued training; Stretching	2 (3.86%) (94,95)
Control group (only one CG or when we have more than 1 CG the "no" intervention	Usual care/no intervention	27 (50.94%) (16,29,64,65,67,68,71–73,77,79,80,49,81,86,92–94,96,50,51,53,57,60,62,63)
	Qigong	2 (3.77%) (68,85)
	Same intervention which differ in intensity, or "type"	8 (15.09%) (10,61,78,83,88–90,97)
	Not clear	1 (1.89%) (52)
	Other type of exercise	14 (26.42%) (54,55,87,91,95,98,56,58,59,66,69,70,76,82)
	Sham exercise	1 (1.89%) (75)

Control group (studies with 2 CG arms)	Healthy control group	2 (12.5%) (73,80)
	Physiotherapy	1 (6.25%) (87)
	Domestic exercise	2 (12.5%) (55)
	Same intervention which differ in intensity, or "type"	3 (18.75%) (79,81,92)
	Other type of exercise	8 (50%) (60,69,77,92,94)
Control group (studies with 3 CG arms)	Other type of exercise	1 (100%) (92)

Outcomes and assessment tools

The most reported primary outcome (Fig. 4) was motor impairment/disability (34.6%, n=18).

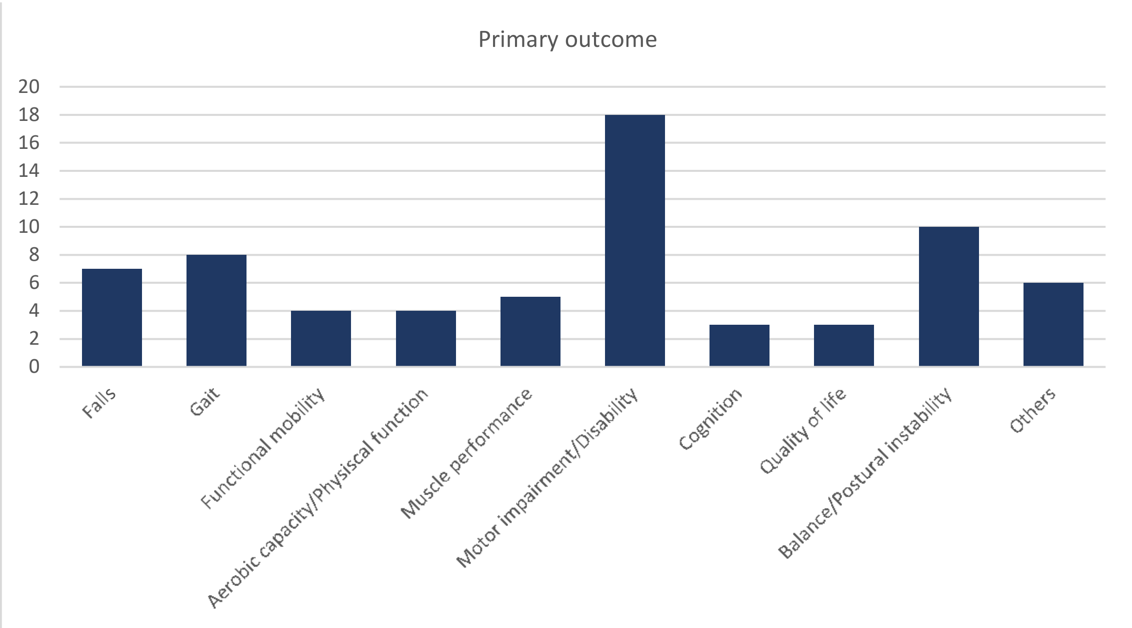


Figure 4: Distribution of the reported primary outcomes

Gait and quality of life were the most reported secondary outcomes followed by motor impairment, disability and balance. (Fig 5)

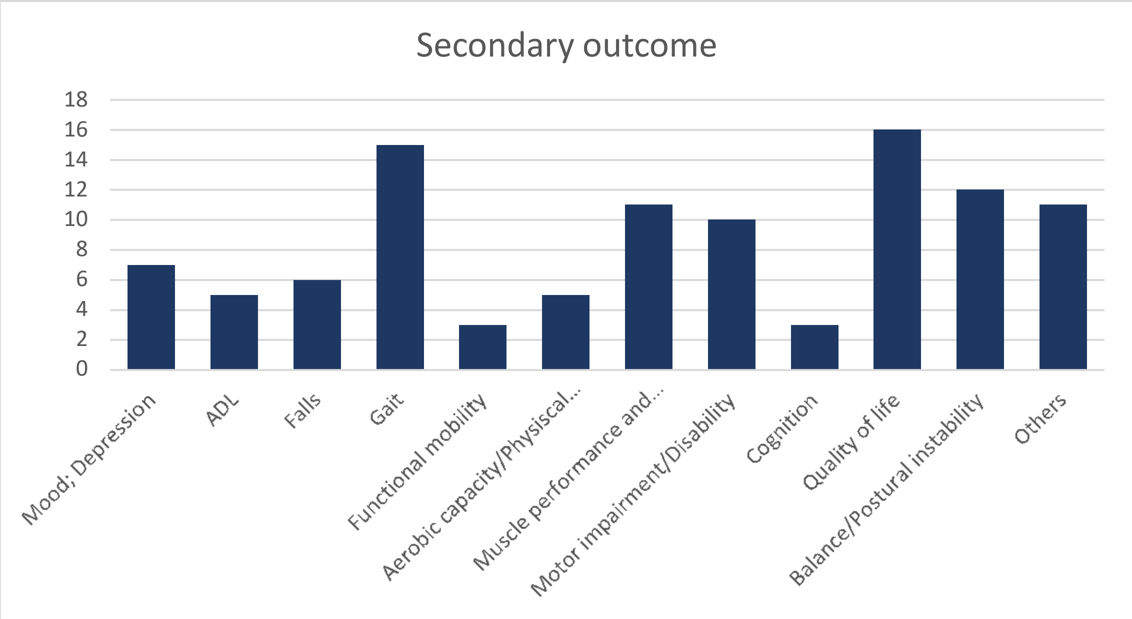


Figure 5: Distribution of the reported secondary outcomes

Many of the studies reported more than one secondary outcome (65.4%, n=34), while 30.8% (n=16) reported only one secondary outcome and 3.8% (n=2) of the studies did not report secondary outcomes. Tools used to assess primary and secondary outcomes are presented in table 2.

Quality of reporting analysis

The quality of the included studies is summarized in figure 6 and 7. In 53.8% of the studies (n=28) there was a low risk of bias in at least half of domains (4/7). 3.8% (n=2) presented high risk of bias, using the same reference. Only 53.8% (n=28) of the studies described randomization process in enough detail to allow an assessment of whether they should produce comparable groups.

Regarding allocation concealment, we found that 36% (n=20) of the studies describe the method used in sufficient detail to determine whether intervention allocations could have been foreseen in advance or during enrolment. In relation to blinding, the method most used was a blind evaluator (53.8%, n=28). Only in 3.6% studies (n=2) were the personnel and participants who were blind to the intervention. In 5.8% (n=3) of the studies the report of the outcomes was not clear, raising the possibility of a selective outcome reporting.

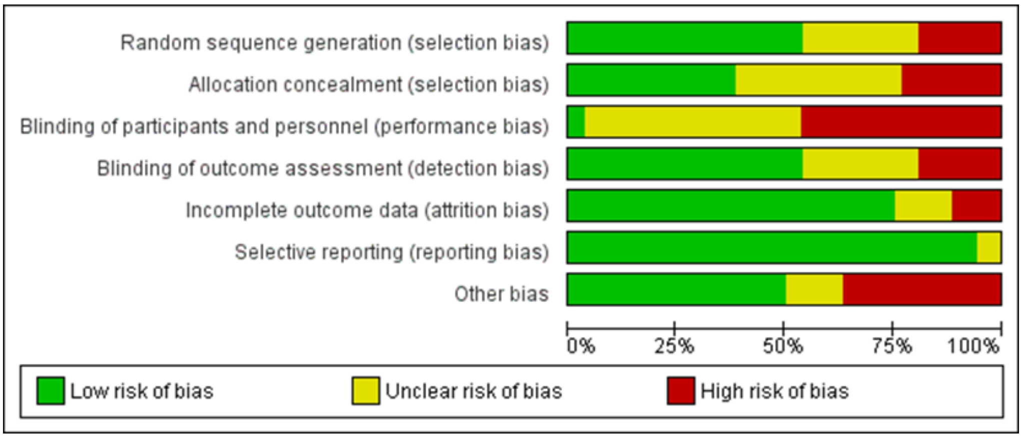


Figure 6: Risk of bias in included studies assessed using the Cochrane tool

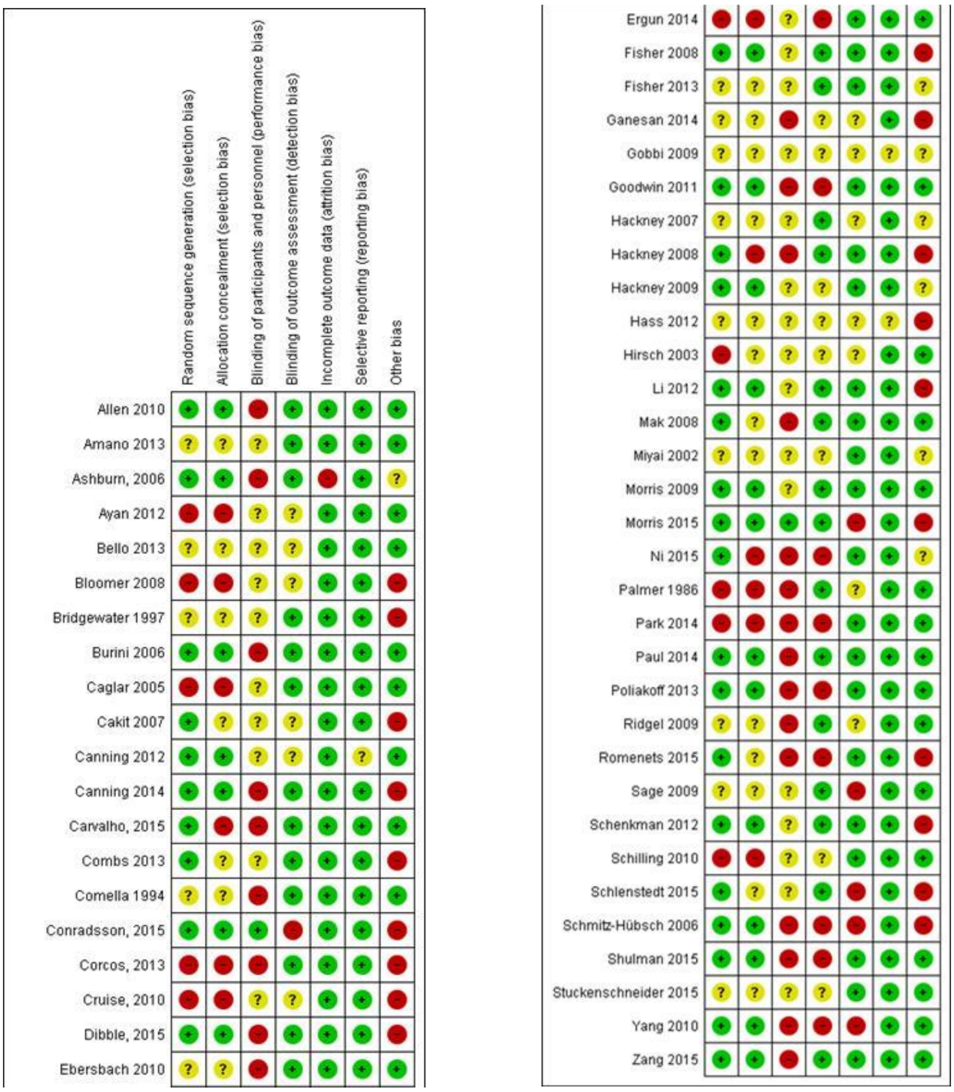


Figure 7: Risk of bias (domains) of included studies

Effects of intervention

1) Quantitative data synthesis

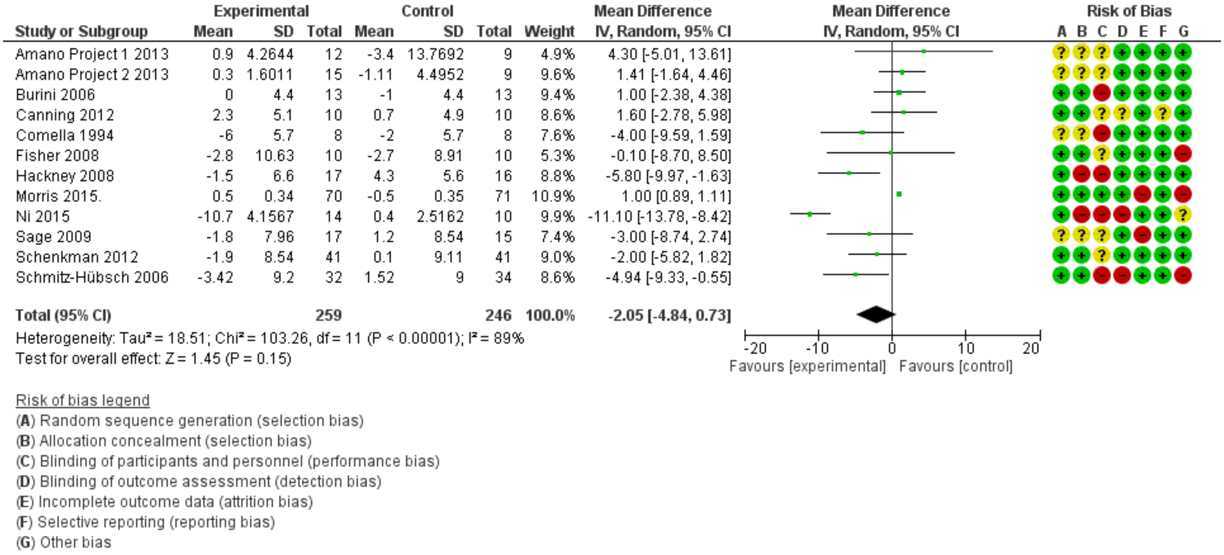
Quantitative analysis was performed only in studies where the comparator was a non-exercise intervention. Only 30 studies were eligible. A comparison was added for each outcome. Meta-analysis was divided according to the follow-up period for each comparison: until 3 months follow-up and study endpoint. Two subgroup analysis were undertaken. One for the changes in scores in UPDRS III with different types of exercise and the other for the effect of progressive increase on exercise intensity versus constant intensity.

a) Unified Parkinson's disease rating scale (UPDRS III)

Twelve studies using UPDRS part-III as outcome were included in the meta-analysis. UPDRS part-III results showed an improvement with exercise, however the improvement was not statistically significant (MD, -2.05; 95% CI, -4.84 to 0.73; p=0.15) (Fig. 8), at 3 months follow-up. At endpoint, the results were similar. (MD, -2.35; 95% CI, -4.72 to 0.03; p=0.05) (Fig. 9). A high heterogeneity was present in the two analyses (3 months follow-up analysis: I^2=89% and endpoint analysis I^2=85%). To overcome this limitation a model of random effect was used

The subgroup analysis according to the type of exercise, showed a higher improvement with multimodal training when compared with aerobic exercise training (MD, -2.69; 95% CI, -5.42 to 0.03; p=0.05 vs MD, 0.43; 95% CI, -1.91 to 2.76; p=0.72) (fig 10)

The subgroup analysis according to the type of training intensity (progressive vs unique) revealed a higher improvement in UPDRS III with progressive training intensity



(MD, -3.16; 95% CI, -7.56 to 1.24; p=0.16 vs MD, -1.81; 95% CI, -4.50 to 0.89; p=0.19) (fig 11). In both the improvement was not significative.

Figure 8: Forest plot showing the effect of exercise on UPDRS-III scores in changes from baseline to a maximum 3 months follow-up, in patients with PD

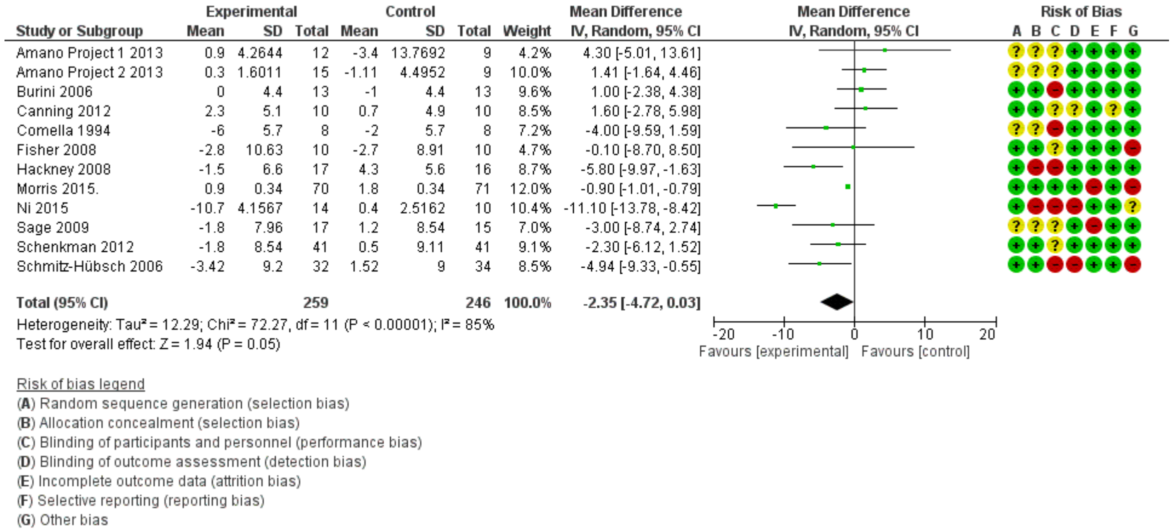


Figure 9: Forest plot showing the effect of exercise on UPDRS-III scores in changes from baseline to endpoint, in patients with PD

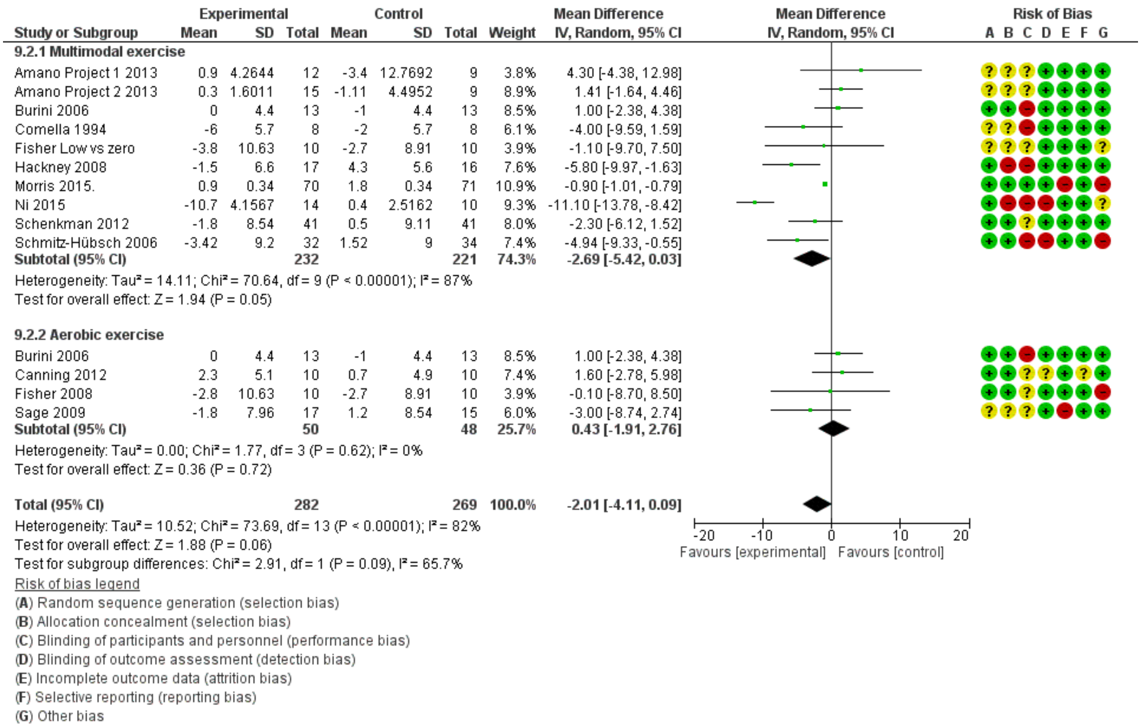


Figure 10: Forest plot showing the effect of exercise on UPDRS-III scores in changes from baseline to endpoint for two different interventions, in patients with PD

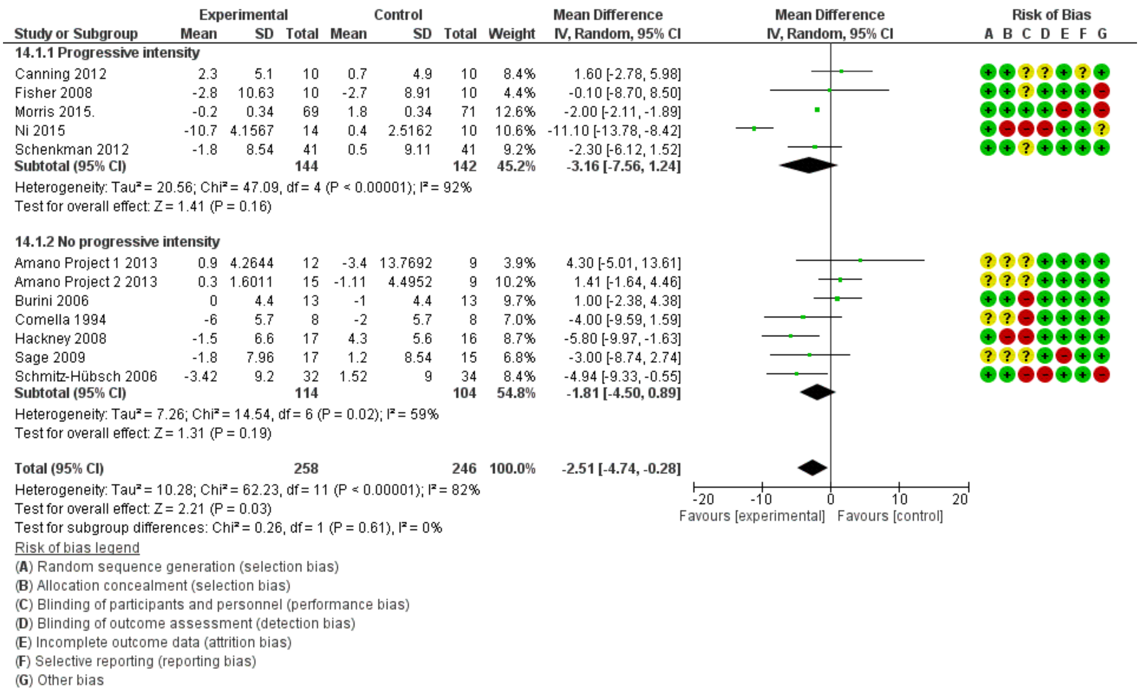


Figure 11: Forest plot showing the effect of exercise on UPDRS-III scores in changes from baseline to endpoint for progressive increase in exercise intensity vs unique intensity, in patients with PD

b) Balance – Berg Balance Scale (BBS)

Balance was assessed with BBS in 4 studies. Five different exercise interventions were included in meta-analysis. In both analysis (3 months follow-up and endpoint) the efficacy of exercise improving BBS score was not clear. A high heterogeneity was present in the two analyses (3 months follow-up: I^2=96% and endpoint I^2=96%) (fig 12 and 13)

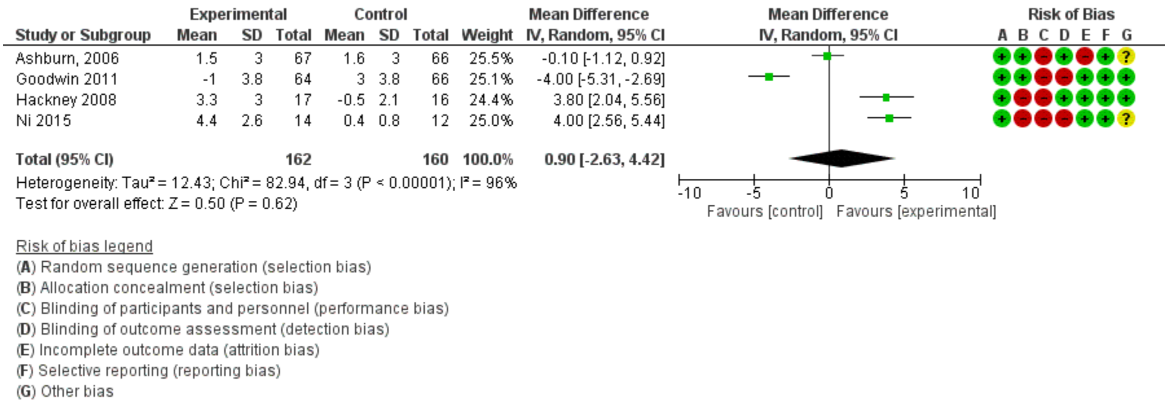


Figure 12: Forest plot showing the effect of exercise on Berg Balance Scale, from baseline to a maximum 3 months follow-up, in patients with PD

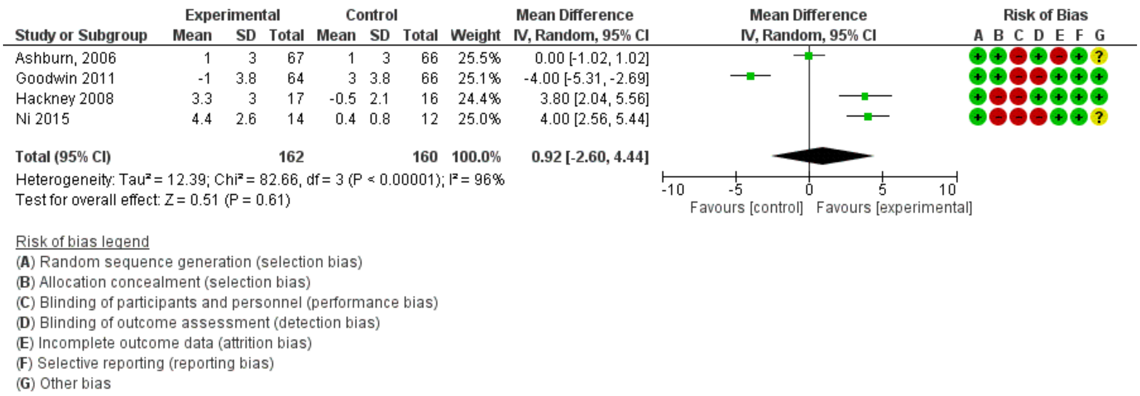


Figure 13: Forest plot showing the effect of exercise on Berg Balance Scale, from baseline to endpoint, in patients with PD

c) Quality of life – PDQ-39

Seven studies reporting quality of life were included in meta-analysis. Exercise did not prove to be effective improving quality of life in any of the performed analysis (3 months analysis: MD, 1.19; 95% CI, -2.57 to 4.96; p=0.54 (Fig. 14) and endpoint analysis: MD, -0.77; 95% CI, -4.42 to 2.88; p=0.68 (Fig. 15). Studies have low heterogeneity (baseline-3 months: I^2=55% and baseline-endpoint: I^2=49%)

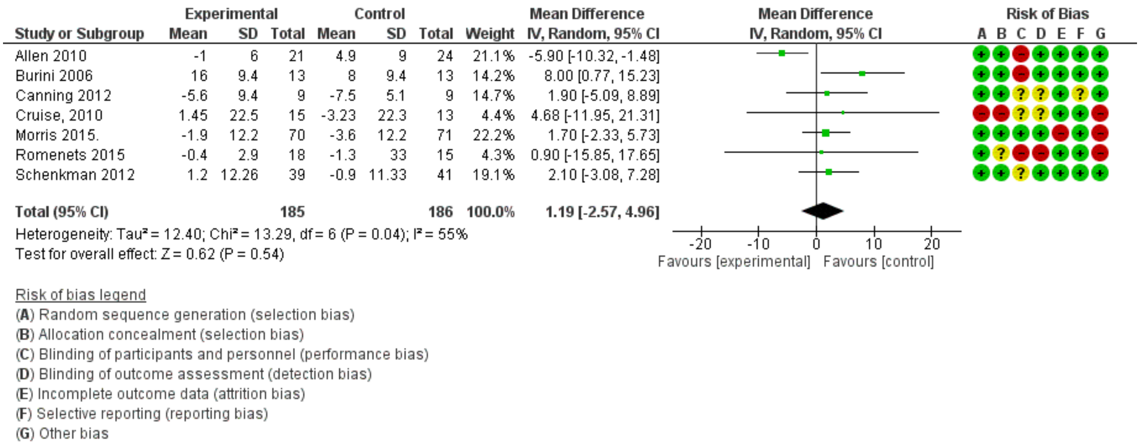


Figure 14: Forest plot showing the effect of exercise on PDQ-39, from baseline to a maximum 3 months follow-up, in patients with PD

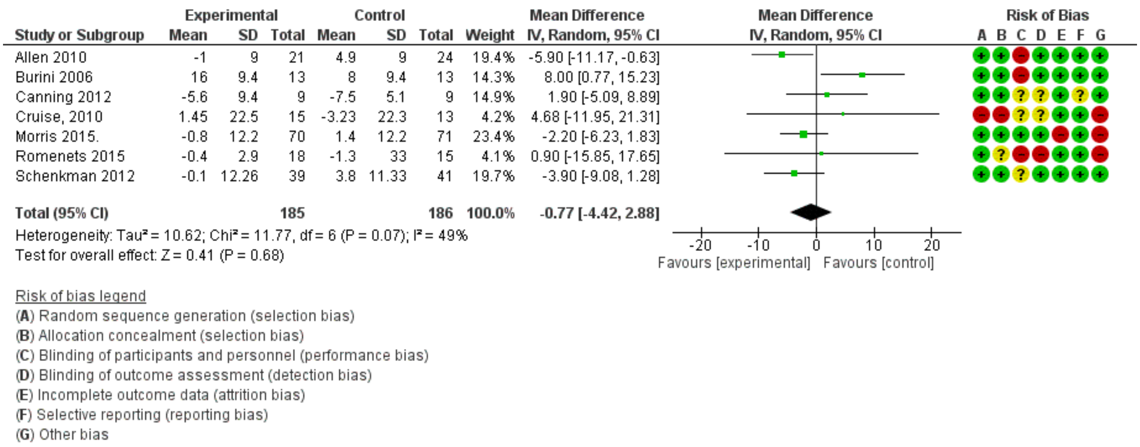


Figure 15: Forest plot showing the effect of exercise on PDQ-39, from baseline to endpoint, in patients with PD

d) Gait – 6MWT and gait parameters

Only 4 studies (51,63,72,85) used the same outcome tool to assess gait, the 6MWT. Exercise improved the distance in 6MWT (MD, 22.95; 95% CI, -0.69 to 46.6; p=0.06 (Fig. 16), but the improvement was not statistically significant.

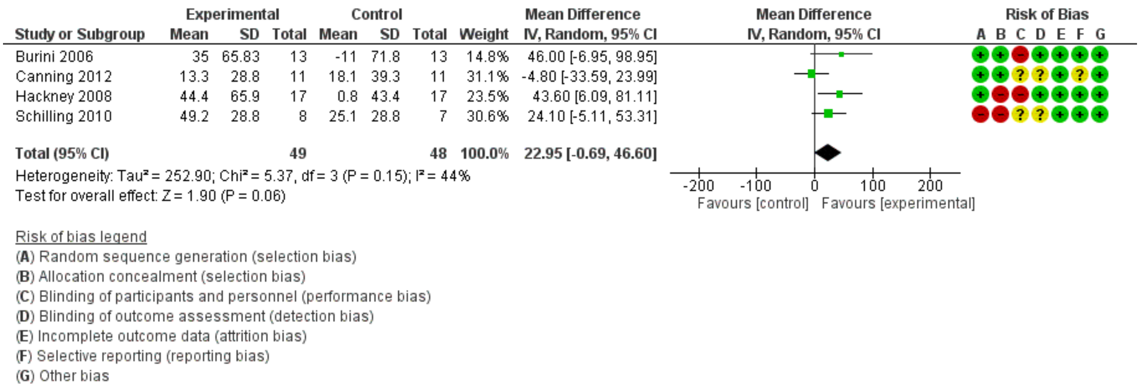


Figure 16: Forest plot showing the effect of exercise on 6MWT, in patients with PD

e) Falls – FES

Three studies (48,57,67) were included in meta-analysis. Results showed that exercise had a positive effect improving FES score (MD, -2.68; 95% CI, -4.99 to -0.37; p=0.02 (Fig. 17). Studies have low heterogeneity (I^2=27%).

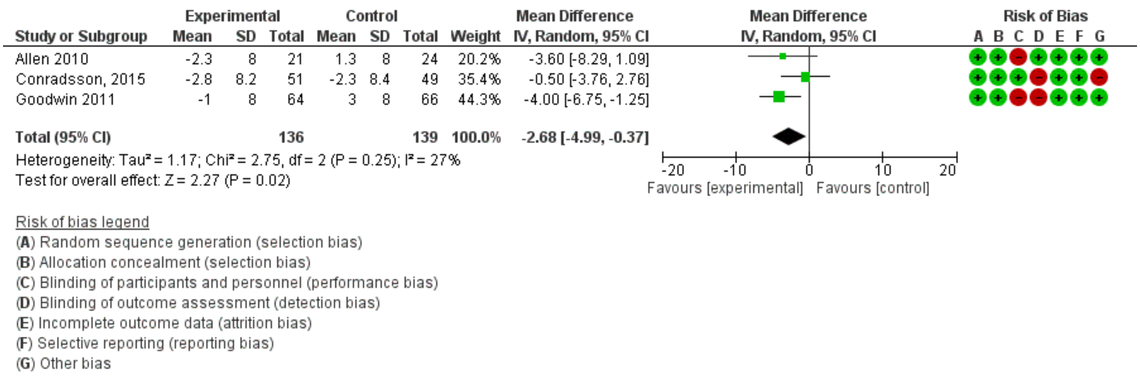


Figure 17: Forest plot showing the effect of exercise on FES, in patients with PD

2) Descriptive analysis

The results from the most frequently used outcomes were examined on a trial by trial basis (Tab. 2).

a. Motor impairment/Disability

Motor impairment/disability was assessed in 16 studies with UPDRS III, in one study with MDS-UPDRS (93) and one with the PD Motor Battery (95).

In six studies, no significative difference was found after the intervention (61,66,82,85,87,93) and in one study a small improvement was reported in both groups (79). Three studies reported a positive correlation between UPDRS part-III and training duration. One of the studies, comparing multimodal training with no exercise intervention, reported the loss of improvement, in UPDRS part-III, recorded in the end of the intervention after six months. (53) Schmitz-Hubsch compared Qigong with no intervention and found a statistically significant improvement in UPDRS part-III at 3 and 6 months. Although. after 12 months no significative improvement was found. (71) The third study reported a significant effect of time in UPDRS part-III improvement, in both groups (91)

One study in patients in off-state medication, compared the effect of resistance training with multimodal training. (10) Resistance training showed a higher improvement in UPDRS part-III score. These two types of exercise were compared in another study (77) with the no exercise control group intervention. Both, resistance and multimodal training, showed to be more effective improving UPDRS-part III.

Three studies (55,89) evaluate the effect of aerobic exercise in UPDRS part-III. Both reported a positive association between UPDRS part-III and training intensity. (55,89) One study that compared aerobic exercise with sensory attention focused exercise, reported that only in no aerobic exercise an improvement on UPDRS part-III was found. (65)

Two different studies evaluated the effect of tango (91) and Tai chi (72) in UPDRS part-III score. Both reported an improvement in the outcome, however only Tai chi had a statistically significant improvement.

The author of a study comparing movement strategies with multimodal exercise, reported that the improvement in UPDRS III was not dependent on the type of exercise but on movement strategies during exercise, such as external cues or attentional strategies. (59)

The only study using the improvement in PD Motor Battery as outcome compared flexibility training with karate. Flexibility was more effective. The author attributes the difference in score to the progressive component of flexibility training. (95)

Motor impairment/disability was also reported in 10 studies as secondary outcome. Only two studies reported an improvement in motor disability. (60,70) In one study, both groups (Tai Chi and multimodal exercise) had an improvement in UPDRS III (70) The other reported a higher benefit of a movement strategies intervention, when compared with multimodal exercise (60) (Table 2)

b. Balance/postural instability

Balance/postural instability was reported in 10 studies. Only one study did not report any improvement statistically significative. (56)

Five of the studies used Berg Balance Scale (BBS) as assessment tool. The other four used the Fullerton Advanced Balance scale (76), the mini BESTest (99), the functional reach test (69) and posturography (58).

Tango (91), Tai Chi (72), balance training (67) and aerobic exercise (52) showed an improvement in BBS score when compared with no exercise. One study (58) reported that balance training was more efficient improving balance, assessed by posturography, if combined with resistance training, than alone. Li, F. (69) found that Tai Chi improves more postural stability than resistance or stretching training. This superiority was not found when compared with another type of multimodal exercise focused on balance improvement. (70)

As a secondary outcome, balance improved in seven of the 12 studies. (52,57,59,77,78,93,97) The interventions tested included: aerobic training (52,78), multimodal training (59,77,93,97) and resistance training (57,77) (table 2)

c. Gait

Gait was more often used as a secondary outcome (15 studies) than as primary outcome (9 studies).

In three of the studies which reported gait as primary outcome, no significative difference in gait parameters was found. (51,65,68)

Aerobic training proved to be more effective than multimodal training in improving gait parameters in three studies. (62,64,84) Balance training showed to be more efficacious than no exercise improving gait parameters. (67) One study (83) compared two different treadmill intensities, reported a higher improvement in the 6MWT with a lower intensity. A similar study compared the effect of two different walking programs (treadmill vs overground) in gait parameters. The results showed that treadmill was only better than overground walking improving stride length. (78)

The main results of studies using improvement in gait parameters as secondary outcome are summarized in table 2. In seven studies there were no significative differences on gait outcomes while in eight studies some gait parameter was improved. The intervention in test, with an improvement in gait parameters, were: resistance and balance training (48), multimodal exercise (69,72,77,91), aerobic exercise (82) and multimodal and resistance training (77)

d. Falls

Falls were reported in seven studies as primary outcome and in six studies as secondary outcome. No significative differences were found in five of the seven studies which reported falls as primary outcome. (49,51,57,67,75) One study compared multimodal training with no intervention (52) and the other one (60), resistance with movement strategy training. Multimodal and resistance training reveal to be more efficacious decreasing the frequency of falls

As secondary outcome, an improvement in falls frequency was reported in four studies. (49,58,69,96) The intervention in these studies were multimodal exercise (49,69,96) and resistance and balance training (58) (table 2)

e. Quality of life

Quality of life was more often used as secondary outcome (16 studies) than as primary outcome (3 studies). Improvements in quality of life, assessed with PDQ-39, was found in one study, comparing Tango and Waltz/Foxtrot with Tai Chi and no intervention. (71)

As secondary outcome, nine studies (35,37,39,40,44,46,62,65,67) did not report any significative difference in quality of life and seven studies (51,52,61,68,72–74) reported some significative differences favorable to the intervention group (Tab. 2).

f. Adverse effects

Adverse effects were only reported in 11.5% (n=6) of the studies. The most reported adverse events were related to musculoskeletal injuries. (Appendix 2)

Table 2: Summary of the included studies

Studies	Exercise (n patients) vs control (n patients)	Primary outcome	Secondary outcome	Scales/assessment tools primary outcome	Scales/assessment tools secondary outcome	Relevant significative results
Allen, N. 2010(48)	Strengthening and balance exercises (n=24) vs usual care (n=24)	Falls	Standing balance, FOG and measures of physical ability, fear of falling, and quality of life	PD falls risk score	Swaymeter; Berg Balance Scale; FOG Questionnaire; Short Physical Performance Battery (SPPB) Sit-to-stand, Falls Efficacy Scale International questionnaire and Parkinson's Disease Questionnaire (PDQ-39)	a) FOG questionnaire improved in exercise group
Amano, S. 2013 (68)	Project 1 Tai Chi (n=12) vs Qi-gong (n=9) and Project 2: Tai Chi (n=15) vs no intervention (n=9)	Gait initiation (magnitude of posterior and lateral COP displacement; mean COP velocity in posterior and lateral directions) and Gait (Cadence; Gait velocity; Step length; Step duration; Swing time; Double limb support; Gait asymmetry)	Clinical motor score	Force platform; kinematic data captured by camera	UPDRS III	a) Qii-Gong Control group significantly shifted their COP more toward the initial swing limb after the 16-week period when compared to the TC group. (The same trend was observed in Project 2, but it did not reach significance)
Ashburn, 2006 (49)	6 levels and comprise muscle strengthening; range of movement; balance training; walking (n=70) vs usual care (n=72)	Falls	Balance; disability, quality of life	Self- reported falling or not at 8 weeks and 6 months from the falls diary	Functional Reach (in cm), the Berg Balance Test, TUG and the ''chair stand test''; Self-assessment Parkinson's Disease Disability Scale (SAS) and the Euro Quol EQ-5D24	a) At 6 months the exercise group had lower fall rates in the less severe subgroup while in the more severe subgroup the exercise group had higher fall rates b) Subjects in the exercises group maintained their ability to reach forward, subjects in the control group deteriorated over the 6 month follow-up period c) Participants in the exercises group maintained their perception of quality of life while participants in the control group scored worse over time: the difference between the groups was significant at 6 months

Studies	Exercise (n patients) vs control (n patients)	Primary outcome	Secondary outcome	Scales/assessment tools primary outcome	Scales/assessment tools secondary outcome	Relevant significative results
Ayan, C., 2012 (90)	low-intensity water-based exercise program (n=10) vs muscular resistance water-based exercise one (n=11)	Functional mobility	Quality of life and motor disability	FTSTS+E17	PDQ-39, UPDRS	a) Quality of life improve in group 2 (muscular resistance water exercise program) and participants in group 2 showed a significant change in functional mobility; b) Significant interaction moment programs was detected for the FTSTS Test, for the PDQ-39, and for the UPDRS part III.
Bello, O., 2013 (78)	Walking on treadmill (n=11) vs walking in overground (n=11)	Gait - speed, cadence and stride length	Strenght, balance and COP	Force sensitive switches placed in patients shoe and synchronized with photocells	TUG, knee extensors strenght test and static posturography	Significant differences for: a) Effect of time factor during the 4 minutes walking for speed, cadence, without a significant group effect b) (4minutes) stride length increase in the treadmill group c) (10 minutes) - group x time interaction for stride length in the treadmill group d) Group x time interactions for the total time to complete TUG test, time to stand up and sit (decrease in the treadmill group) e) Static posturography: group x time interaction for the area of COP (with eyes closed) with an increase in treadmill group and a decrease in overground group f) Improvement in the cognitive test for treadmill group
Bloomer, R., 2008 (73)	Resistance training (n=6) vs usual care (n=7) vs healthy group (n=9)	Blood oxidative stress		Blood sample collection - hydrogen peroxide and catalase activity were measured		a) Resistance training resulted in an 18% increase in leg press 1RM in the training group, with lower values for the resistance training group compared with the control group

Studies	Exercise (n patients) vs control (n patients)	Primary outcome	Secondary outcome	Scales/assessment tools primary outcome	Scales/assessment tools secondary outcome	Relevant significative results
Bridgewater, K., 1997 (29)	Exercise classes (warm-up, trunk muscles exercises; aerobic exercises) (n=13) vs normal activity (n=13)	Trunk muscle	Activities of daily living, range of motion, maximal isometric torque	Isostation B200	Northwestern University Disability Scale	a) Exercise group had significantly increased torque production over the period of their exercise classes, an improvement which was retained at the 4-week follow-up assessment
Burini, D., 2006 (85)	Aerobic training (n=13) vs Qi-gong (n=13)	Disease related disability	Mood state, quality of life and cardiorespiratory fitness	UPDRS-II and III, Brown's Disability scale (BDS)	6 MWT, Borg Scale, PDQ-39, spirometry test and maximum cardiopulmonary exercise test, Wpeak, VO2peak, VO2/kg rate, ventilation, respiratory exchange ratio, heart rate and double product	a) Time effects showed a significant increase in 6MWT after aerobic training within each subgroup b) Larger decrease in Borg score was observed after aerobic training than after Qigong, in both subgroups c) Quantitative parameters of cardiorespiratory fitness showed significant interaction effects between group and time for the Double Product peak, the VO_2 peak and the VO_2/kg ratio d) After aerobic training, a significant decrease in all the quoted measures was observed

Studies	Exercise (n patients) vs control (n patients)	Primary outcome	Secondary outcome	Scales/assessment tools primary outcome	Scales/assessment tools secondary outcome	Relevant significative results
Caglar, AT, 2005 (50)	Home exercise training (stretching, range of motion, walking) (n=15) vs no intervention (n=15)	Functional mobility	Compliance	10-m walking time (s), 20-m walking time (s), first pace length (cm), pace number at a 10-m distance, time to walk around a chair (s) and Nine Hole Peg Board test	Diary	a) All variables were significantly improved in the exercise group, from baseline to second month, whereas there was a significant impairment in the control group in 10-m and 20-m walking times b) Comparison of groups showed significant changes in 10-m, 20-m walking time and time taken to turn around a chair at first month assessment. The changes were significant in 10-m and 20-m walking time in the first month. The differences were not statistically significant in the second month when compared with the first month but were still significant when compared with baseline
Cakit, 2007 (52)	stretching, range of motion exercise and treadmill training (n=27) vs not described (n=27)	Postural instability and fear of failling	Balance and ability to adapt gait to changes in task demands	UPDRS III, FES	BBT, dynamic gait index, walking distance (m) and tolerated maximum speed on treadmill (km/h)	a) After the training program, walking distance and tolerated maximum speed on treadmill, BBT, Dynamic Gait Index and FES scores improved significantly
Canning, C., 2012 (51)	Treadmill walking (n=10) vs no instruction (n=10)	Walking capacity and feasibility	Exercise heart rate, quality of life, walking speed, walking consistency; motor examination and fatigue	6 MWT	Exercise heart rate, PDQ-39; walking speed, walking speed while performing a concurrent task(s); walking consistency during the 6-MWT; UPDRS III and fatigue	a) Reduction of 1.2 points on the 7-point fatigue scale was reported for the treadmill walking group b) Greater improvement in quality of life for the treadmill walking group

Studies	Exercise (n patients) vs control (n patients)	Primary outcome	Secondary outcome	Scales/assessment tools primary outcome	Scales/assessment tools secondary outcome	Relevant significative results
Canning, C., 2014 (96)	PD-WEBB program (progressive balance and lower limb strengthening exercises and cueing strategies to reduce freezing of gait) (n=115) vs usual care (n=116)	Number of falls and the proportion of fallers recorded during the 6-month intervention period.	Extensor muscle strength; coordinated stability test of balance; Physical Performance; FOG; quality of life and the positive affect subscale of the Positive and Negative Affect Schedule	Recorded using a "falls diary and PD Fall Risk score, FES	Mean knee extensor muscle strength of both legs; coordinated stability test of balance; the Short Physical Performance Battery, the FOG Questionnaire; mental and physical sub- scores of the SF-12v2 (Short Form 12 version 2), the SF-6D (Short Form 6 dimensions) utility score, PDQ-39; and the positive affect subscale of the Positive and Negative Affect Schedule	Significant differences for: a) In the lower disease severity subgroup, there were fewer falls in the exercise group compared with controls, while in the higher disease severity subgroup, there was a trend toward more falls in the exercise group b) Postintervention, the exercise group scored better than controls on the Short Physical Performance Battery, sit-to-stand, fear of falling, affect, and quality of life, after adjusting for baseline performance.
Carvalho, 2015 (87)	Aerobic training (n=5) vs strength training (n=8) vs physiotherapy (n=9)	Motor symptoms	Functional capacity; balance; walking speed and EEG	UPDRS III	Functional capacity (Senior Fitness Test)	No significative differences
Combs, S., 2013 (97)	Boxing (n=17) vs traditional exercise (n=14)	Function and quality of life	Balance	Parkinson's disease Quality of Life scale (PDQL), gait velocity and 6Minute Walk Test (6MWT)	Berg Balance Scale (BBS), Activities-specific Balance Confidence Scale (ABC), TUG, Dual-task TUG (dtug)	a) Traditional exercise group perceived a greater improvement in balance confidence after training b) Boxing group demonstrated an increase in median distance walked, while the traditional exercise group demonstrated a decrease in distance walked during the 6MWT. c) Both groups demonstrated improvements over time and large effect sizes with the BBS, TUG, dtug, and PDQL d) Boxing group showed a large effect size in gait velocity from pre- to post-test
Comella, C., 1994 (53)	repetitive exercises to improve range of motion, endurance, balance and gait, and fine motor dexterity (n=18) vs no specific intervention (n=18)	Physical disability/motor function	Depression	UPDRS and timed finger taps	Geriatric Depression Scale	a) In exercise group, total UPDRS and in the ADL and motor subsections improved b) Rigidity and bradykinesia factors improved following exercise c) Six months following the exercise phase, gains for total UPDRS and for the ADL and motor subsections returned to baseline.

Studies	Exercise (n patients) vs control (n patients)	Primary outcome	Secondary outcome	Scales/assessment tools primary outcome	Scales/assessment tools secondary outcome	Relevant significative results
Conradsson, D., 2015 (67)	Hibalance (n=51) vs no intervention (n=49)	Balance performance, Gait velocity and Concerns about falling	Performance of a cognitive task while walking, Physical activity level and Activities of daily living	Mini BESTest , 9-meter electronic walkway system, gaitrite; and FES International	Physical activity level (steps per day) was assessed during free-living conditions, using an accelerometer worn around the waist (Actigraph GT3X+, Pensacola, FL, USA) and UPDRS II	a) Improvements in the training group on the UPDRS-ADL at posttest; b)Balance and gait performance improved in the training group c) Cognitive task while walking improved in training group
Corcos, D., 2013(10)	Modified ftness counts exercise - MFC (stretches, balance exercises, breathing, and non-progressive strengthening) (n=24) vs Progressive resistance exercise - PRE (11 strengthening exercises) (n=24)	Change in the off-medication UPDRS-III score from baseline to 6, 12, 18 and 24 months	Changes in levodopa equivalent medication dosage, Off-medication elbow strength, Movement speed and Physical performance	Primary - UPDRS-III off medication;	UPDRS-III on medication; medication (LED), Elbow flexion, movement speed, Modified physical performance Test	a) Mean off-medication UPDRS-III score decreased more with PRE than with MFC b) The mean off-medication elbow flexion movement speed increased, at 24 months, in the PRE group was faster than the MFC group
Cruise, K, 2010 (86)	Progressive anabolia and aerobic exercise (n=17) vs usual lifestyle (n=17)	Cognition and Quality of life	Mood state, WAIS verbal IQ	MMSE, Cambridge Neuropsychological Test Automated Battery software and included the Pattern and Spatial Recognition Memory Spatial Working Memory; and Stockings of and PDQ-39	Geriatric Depression Scale, Australian National Adult Reading Test	No significative differences
Dibble, L, 2015 (54)	RENEW (similar to standard care+Resistance Exercise via Negative Eccentric Work) (n=20) vs standard care (n=21)	Quadricips force production	Thigh muscle cross sectional area; Body function; Activity domain (Dynamic stability during gait and Gait endurance); Participation domain	Kincon dynamometer;	MRI, UPDRS; Functional gait assessment (FGA), 6MW, PDQ-39	a) Time and Medication Main Effects in Average Force, UPDRS III, FGA and 6MWT b) Effect Sizes for Exercise and medication combined exceeded the effect sizes of either intervention in isolation)
Ebersbach, G., 2010 (55)	LSVT1BIG (n=20) vs nordic walk (n=20) vs home exercise (n=20)	Motor status	Quality of life, TUG, 20 and 10 time to walk 10 m	UPDRS III	PDQ-39, TUG, 20 and 10 time to walk 10 m (assessed with stopwatch)	a) UPDRS III was superior in LSVTBIG b) TUG was better in LSVTBIG

Studies	Exercise (n patients) vs control (n patients)	Primary outcome	Secondary outcome	Scales/assessment tools primary outcome	Scales/assessment tools secondary outcome	Relevant significative results
Ergun, Y., 2014 (88)	Continuous aerobic training (n=21) vs interval aerobic training (n=22)	Aerobic fitness and cognition	Cognition, Parkinsonism and Quality of life	Oxygen uptake was measured from expired air samples on a breath-by-breath basis during cycle ergometry and percent increase score (PIS) on flanker task	Wisconsin Card Sorting Test and Trail makingtest, visual perception using Judgment of Line Orientation and Complex Figure Test–Copy, verbal memory using Rey Auditory Verbal Learning Test, visual memory using Complex Figure Test–Recall, language using Controlled Oral Word Association Test and general cognition using Montreal Cognitive Assessment; UPDRS and timed motor tests, 7-m Walk and finger tapping, Functional Reach test for balance, total daily levodopa equivalents,and a patient diary; Fatigue Severity Scale (FSS), Geriatric Depression Scale, and PD Quality of Life Scale (PDQUALIF)	No significative differences between groups
Fisher, B., 2008 (79)	High (n=10) vs low (n=10) vs no intensity (n=10)	Motor performance and corticomotor excitability	Function walk and biomechanic structure	Motor performance UPDRS III and corticomotor excitability - cortical silent period durations (CSP) in response to single-pulse TMS	Biomechanic analysis of self-selected, fast walking, and sit-to-stand task	a) Small improvement in total and motor UPDRS was observed in all groups. High intensity group subjects demonstrated post exercise increases in gait speed, step and stride length, and hip and ankle joint excursion during self-selected and fast gait and improved weight distribution during sit-to-stand. b) Improvements in gait and sit-to-stand measures were not consistently observed in low- and zero-intensity groups. Importantly, the high-intensity group demonstrated lengthening in CSP
Fisher, B., 2013	Intensive treadmill (n=2) vs no intervention (n=2) vs healthy group (n=2)	DA-D2/D3 receptor BP	Postural control	Using fallypride, a radioligand with high affinity for D2/D3 receptors	Quantified as the peak distance between the center of pressure (COP) of the supporting foot and the extrapolated center of mass	a) Turning performance after intensive exercise improve, whereas minimal change was observed in the two non-exercise patients

Studies	Exercise (n patients) vs control (n patients)	Primary outcome	Secondary outcome	Scales/assessment tools primary outcome	Scales/assessment tools secondary outcome	Relevant significative results
Ganesan, M., 2014 (81)	Conventional gait training (CGT) (n=20) vs partial weight supported treadmill training (PWSTT) (n=20) vs no intervention (n=20)	Baroreflex sensitivity (BRS)	Blood pressure	The BRS values were derived using sequence method.	Mean systolic blood pressure (SBP), mean diastolic blood pressure, co-variation of SBP, low frequency component of SBP	a) PWSTT group showed significant improvement in BRS
Gobbi, L., 2009 (56)	multi-mode exercise program (Rhythmic activities, callisthenic gymnastics, stretching exercises, and recreational activities) (n=21) vs adaptive program (exercises related to flexibility, strength, motor coordination, and balance) (n=13)	Mobility and balance	Disease severity	Modified TUG; Berg's Functional Balance Scale (FBS)	UPDRS and the H&Y scale	a) Both programs were able to improve balance and mobility
Goodwin, V., 2011 (57)	10 min warm up, 40 min of strenght and balance training exercises and 10 min cool down (n=64) vs usual care (n=66)	Falls	Quality of life, physical activity and balance	Number of falls during the 10 week group intervention period and the 10 week follow-up period and FES	Euroqol-5D, Phone-FITT, BBS, TUG	No significative differences between groups
Hackney, M., 2007 (91)	Tango classes (n=9) vs breathing and stretching exercises, and progressed to resistance and dexterity exercises (n=10)	Motor symptoms and balance	Gait	UPDRS, BBS	TUG, velocity of walking and dual task walking	a) UPDRS - There was a significant main effect of time b) There was an improvement in the UPDRS for the tango participants and for the exercise participants c) BBS - effect of time; tango group improved more d) FOG – positive effect of time
Hackney, M., 2008 (72)	Tai Chi (n=17) vs no intervention (n=16)	Balance and mobility	Gait	UPDRS III, BBS, the tandem stance test (TST), the one leg stance test (OLS) and TUG	Examining standard forward and backward walking along an instrumented computerized gaitrite walkway (CIR Systems, Inc., Havertown, PA) and 6MWT	a) BBS, UPDRS III, tandem stance and 6MWT improved in Tai Chi group

Studies	Exercise (n patients) vs control (n patients)	Primary outcome	Secondary outcome	Scales/assessment tools primary outcome	Scales/assessment tools secondary outcome	Relevant significative results
Hackney, M., 2009 (92)	Tango (n=17) vs Waltz/Foxtrot (n=14) vs Tai Chi (n=13) vs untreated (n=17)	Health related quality of life	Disease severity fallers vs non-fallers	PDQ 39	UPDRS III	a) Main effect of time for Stigma and ADL but no differences between groups b) Tango group showed significant decreases in scores in Mobility, Social Support and PDQ-39 c) Mobility, Communication, and PDQ-39, had better scores in the Shorter Duration group
Hass, C., 2012 (74)	Progressive resistante training (PRT) (n=9) vs no intervention (n=9)	Displacement of the center-of-pressure (COP) during the anticipatory postural phase of GI	Initial stride length and velocity.	COP displacement	Stride length, swing limb step and the initial stance limb step and stride velocity	a) COP posterior displacement increase in PRT group
Hirsch, M., 2003 (58)	Combined (balance+resistance) (n=6) vs balance training (n=9)	Balance and muscle strenght	Falls	Balance: computerized dynamic posturography and muscle strength (knee flexion, and ankle plantarflexion)	Latency to falls	a) The combination of balance and resistance training improved balance scores more than did balance training alone. b) Latency to fall was longer after the treatment than before in both groups; c) Combined group was higher in strength; Posttreatment strength was higher than pretreatment strength and follow-up treatment strength d) The combined group was significantly higher in average strength of the 3 muscle groups than the balance group at posttreatment and follow-up testing.
Li, F., 2012 (69)	Tai Chi (n=65) vs resistance training (n=65) vs stretching (n=65)	Postural stability and physical performance	Gait, Strength of bilateral knee extensors and flexors, motor symptoms, falls	Functional reach test; TUG; falls	Gait (stride length and walking velocity): computerized 4.3m (14 ft) walkway (gaitrite, CIR Systems); Strength of bilateral knee extensors and flexors: isokinetic dynamometer; UPDRS III, fall calendars	a) Tai Chi group performed consistently better than the resistance-training and stretching groups in maximum excursion and in directional control. b) Tai chi group also performed better than the stretching group in all secondary outcomes and outperformed the resistance-training group in stride length and functional reach. c) Tai chi lowered the incidence of falls as compared with stretching but not as compared with resistance training.

Studies	Exercise (n patients) vs control (n patients)	Primary outcome	Secondary outcome	Scales/assessment tools primary outcome	Scales/assessment tools secondary outcome	Relevant significative results
Mak, M., 2008 (94)	Audio visual Cued training (AV) (n=21) vs conventional exercise (n=21) vs no intervention (n=18)	Improving sit to stand (STS)		VICON motion analysis system (System 370, Oxford Metrics, Oxford, UK) - to measure the vertical, antero-posterior, and medio-lateral components of ground reaction force at a frequency of 60 Hz.		a) Only AV group showed significant increases hip flexion joint torques b) AV group had a larger increase in peak horizontal velocity than in the Ex group at week2 and then the control group from week4 onward. Furthermore, the AV group had larger increases in peak vertical velocity than the Ex group had from week4 onward, and then the control group from week2 on c) STS movement time - AV group had larger decreases in movement time than the control group from week2 onward, and then the Ex group from week4 onward
Miyai, I, 2002 (82)	body weight supported treadmill training (n=11) vs conventional physical therapy (n=9)	Motor impairment	Gait speed and number of steps	UPDRS III	10MWT	a) BWSTT group had greater improvement than the PT group in ambulation speed at 1 month; and in the number of steps at 1, 2, 3 and 4 months.
Morris, M., 2009 (59)	Strategies (external cues, attentional strategies; aerobic training; practice functional mobility tasks and health education) (n=14) vs conventional exercise (n=14)	Disability	Walking speed, endurance, balance, and quality of life	UPDRS II and III	10 MW, TUG, 2 MW, balance pull test, PDQ-39	a) Improvement in UPDRS III was significative for the movement strategy group and UPDRS III score was marginally higher at the follow up, indicating greater disability b) Walking function, balance, 10 MWT and walking endurance better in movement strategy and did not improve in exercise group c) Quality of life improve in both groups
Morris, M., 2015 (60)	Progressive Resistance Strength Training (PRST) (n=70) vs Movement strategy training (MST) (n=69) vs life skill sessions (n=71)	Falls rate	Disability, mobility; changes in PD-related quality of life; number of injurious falls; and time to first fall	Number of falls per person over the period they remained in the study (exposure)	UPDRS II and III, 6MWT, time taken to perform the TUG test, PDQ39 and health-related quality of life using the visual analogue scale (VAS) of the Euroqol-5D; number of injurious falls; and time to first fall.	a) The strength training group had 85% fewer falls than controls b) The movement strategy training group had 61.5% fewer falls than controls c) For the 12-month follow-up test, the PRST and MST groups had greater improvements in their UPDRS activities of daily living scores compared with the life skills group. Over the 12-month follow-up the MST group had greater improvement in the UPDRS motor score compared with the LS group

Studies	Exercise (n patients) vs control (n patients)	Primary outcome	Secondary outcome	Scales/assessment tools primary outcome	Scales/assessment tools secondary outcome	Relevant significative results
Ni, M., 2015 (77)	Power training (n=14), Yoga (n=15) no exercise intrevention (n=12)	Motor impairment	Balance, Leg press strength and peak power, Gait speed.	UPDRS III	BBS, Mini-BEST, TUG, functional reach, single leg stance (SLS), postural sway test (PS), 10-m usual (Uwalk) and maximal walking speed tests, 1 repetition maximum (1RM), and peak power (PPW) for leg press.	a) Both training groups produced significantly better scores than control for the UPDRS MS, BBS , BEST, TUG, and FR on the less affected side, with no group differences detected between PWT and YOGA for any measurement b) Walking speed and leg press - PWT and YOGA groups showed significant improvements in all measures and significantly differed from control
Palmer, S., 1986 (95)	slow stretching exercise (n=7) vs Karate group (n=7)	Motor impairment	Activities of daily living, grip strength, motor coordination and speed; impressions of the benefits of the exercise program for specific Parkinson symptoms	Parkinson's disease motor battery	Nine-hole pegboard test, the Minnesota placing and turning test, a button board test, an arm swing test and a rapid alternating arm movement test; neurophysiologic tests	a) Karate group - progressive improvement in gait as indicated by declines in the walk index b) decrease in arm tremor in both groups
Park, A., 2014 (66)	Delayed start group (DSG) (n=15) vs early start group (ESG) (n=16)	Motor impairment	Balance, walk, depression and quality of life	UPDRS III	Tinetti, timed walk, BDI and PDQ-39	a) Beck Depression Index mean change from baseline values decreased more in the ESG than in the DSG
Paul, S., 2014 (75)	Muscle porwer training (n=20) vs sham exercise (n=20)	Peak power of four leg muscle groups	Maximal muscle strength and movement speed of lower limb muscles; mobility, balance and FOG; participants' perception of the effect of intervention; the number of falls, peak muscle power and maximal strength of the shoulder flexors and elbow extensors	Measured using pneumatic variable resistance equipment (Keiser A420, Keiser Sports Health Equipment, Fresno, CA)	Muscle strength - one repetition maximum; Movement speed - extracted from the muscle power tests and measured in two ways: (i) movement speed at peak power and (ii) the rate of power production; Muscle power and strength of the shoulder flexors and elbow extensors were measured using the seated chest press by the methods outlined above; Balance - tests of stepping maximum balance range and single leg stand	a) Power training group demonstrating significantly greater gains in hip muscle strength compared with the control group

Studies	Exercise (n patients) vs control (n patients)	Primary outcome	Secondary outcome	Scales/assessment tools primary outcome	Scales/assessment tools secondary outcome	Relevant significative results
Poliakoff, E, 2013 (61)	20-week biweekly gym training program (n=16) vs waiting list follow a 10-week program starting 10 weeks later (n=16)	Reaction time and motor performance	Quality of life and illness perceptions	Simple reaction time (SRT) task, UPDRS III	PDQ-39 and Brief Illness Perception Questionnaire	a) Simple Reaction time: The gym group's responses were significantly faster at T2 than T1 b) Reaction time: reduction for the gym group between T1 than T2, and for the control group between T2 and T3 c) Timed hand movements - for the control group, there was a decrease between T2 and T3. d) Chair test - the gym group, there was a increase in the number of stands performed from T1 to T2, whereas for the control group, there was a increase from T2 to T3
Ridgel, A., 2009 (89)	Forced exercise (FE) group exercised with a trainer on a stationary tandem bicycle (n=5) vs Voluntary exercise (VE) group exercised on a stationary single bicycle (n=5)	Motor function	Bimanual dexterity	UPDRS III	Interlimb coordination, as determined by the time interval between onset of grip force in manipulating and stabilizing hands and rate of grip-force production, were used to quantify bimanual dexterity	a) Average cadence during FE was greater (30%) than in the VE group b) UPDRS scores improved by 35% from baseline to end of treatment in FE group c) Interlimb coordination improved in the FE group d) A group-by-time interaction was present for the rate of grip force for the manipulating limb; the FE group increased the rate significantly, whereas a slight decrease was observed for the VE group e) FE resulted in as improvement in the consistency of digit placement for both limbs
Romenets, S., 2015 (93)	Argentine tango (n=18) vs usual care (n=15)	Motor severity	Other motor measures, balance, cognition, fatigue, apathy, depression and quality of life	MDS-UPDRS-III	Off fluctuations and dyskinesia, from the MDS-UPDRS; Mini-bestest; TUG; Dual-task TUG; Falls questionnaire (Canadian Community Health Survey; FOG Questionnaire; Purdue Pegboard for assessment of upper extremity function; Montreal Cognitive Assessment (MOCA), BDI; Apathy Scale, Krupp Fatigue Severity Scale; PDQ-39; Clinical Global Impression of Change (CGI-C) and an exit questionnaire ranking level of enjoyment	a) Dynamic balance improved in the tango group compared to controls b) there were improvements of balance during gait in favor of tango in the TUG and Dual Task TUG score c) After exclusion of the 9 protocol violations walking with pivot turns also demonstrated improvement in the tango group d) After exclusion of the 9 protocol violations, there was significant improvement of MOCA

Studies	Exercise (n patients) vs control (n patients)	Primary outcome	Secondary outcome	Scales/assessment tools primary outcome	Scales/assessment tools secondary outcome	Relevant significative results
Sage, M., 2009 (65)	Sensory Attention Focused Exercise (SAFEx program) (n=21) vs lower limb aerobic program (n=17) vs non-exercise (n=15)	Clinical symptom and spatiotemporal aspects of gait (velocity, step length, and cadence)	Gait included double support time, base of support, and step length variability	UPDRS-III and using the average of five trials of self-paced gait over a four-meter gaitrite1 carpet. Posture and gait score and TUG	Step length variability was calculated based on the variability between each individual step within a trial (within a participant), then averaged across all the participants.	a) UPDRS III - PD safex was the only group with a statistically significant score reduction. b) Posture and gait - PD safex group improving from pre to post exercise c) Only in the control group step length variability increased
Schenkman, M., 2012 (62)	Flexibility/balance/function exercise (FBF) (n=33) vs aerobic exercise (AE) (n=41) vs no intervention (n=41)	Physical function, balance, walking economy	ADL and motor impairment, quality of life	Continuous Scale Physical Functional Performance Test (CS-PFP), FRT, and walking economy (energy cost of walking, or oxygen uptake [V˙O_2] in ml/min/kg)	UPDRS ADL and motor sub-scales and PDQ-39	a) walking economy improved more in the AE group than in the FBF group b) UPDRS ADL - only the FBF group performed better than the control group at 4 months and at 16 months. c) FBF group demonstrated more favorable effects on the CS-PFP than the control group
Schilling, B, 2010 (63)	leg press, leg curl, and calf press (n=9) vs standard care (n=9)	Strength and function	Participants' confidence level of daily activities; ADL ability	Leg press machine, maximum weight lifted, after warm- up, for one repetition was recorded as the one repetition maximum (1-RM) and 6MWT	Activities-specific Balance Confidence (ABC) and TUG	a) Training resulted in an increase in relative leg press. Absolute strength also increased in the training group
Schlenstedt, C., 2015 (76)	Resistance training (RT) (n=20) vs balance training (n=20)	Balance	Center of mass (COM) displacement	FAB scale	Center of mass (COM) displacement	a) The RT-group improved from baseline to week 8 on average by 2.4points on the FAB scale
Schmitz-Hübsch, T., 2006 (71)	Qi-gong (n=32) vs no intervention (n=24)	Progression of motor symptoms	Depression and health related quality of life	UPDRS-III	MADRS and PDQ-39	a) UPDRS III was greater in the Qigong-treated group at 3 months reaching almost significance at 6 months and no significance at 12 months
Shulman, L., 2015 (83)	higher-intensity treadmill (n=26) vs lower intensity treadmill (n=26) vs Stretching and resistance (SR) (n=28)	Gait speed, cardiovascular fitness and muscle strength	Disability and physical activity, severity of PD, Depression, Fatigue, health-related quality of life, and Falls	6-minute walk, peak oxygen consumption per unit time [VO_2], and 1- repetition maximum strength	Beck Depression Inventory, the 16-item Parkinson Fatigue Scale, the Parkinson Disease Questionnaire (to determine health-related quality of life) and the FES	a) All 3 exercise groups improved distance on the 6MW, although only lower intensity treadmill and stretching and resistance reached statistical significance. Only lower-intensity treadmill training improved on all gait assessments. b) Peak VO_2 - both treadmill groups had better improvement than the SR group.

Studies	Exercise (n patients) vs control (n patients)	Primary outcome	Secondary outcome	Scales/assessment tools primary outcome	Scales/assessment tools secondary outcome	Relevant significative results
Stuckenschneider, T., 2015 (64)	active assistive forced exercise group (n=10) vs passive assistive forced exercise (n=12)	Gait analysis, tremor	Motor evaluation	Gait analysis - treadmill-analysis center FDM-T of the zebris. The measurement was conducted at this gait velocity for 20 s and evaluate velocity, stride length, monopedal and bipedal stance phase, and swing phase; Stride length was calculated after two steps; tremor - Kinesia Unit1	UPDRS III	a) the 2-intervention group with increased gait velocity, swing phase, monopedal stance phase, elongated stride lenght and decrease double stance phase b) postural and kinetic tremor were also reduced
Yang, Y., 2010 (84)	Downhill walking training (n=16) vs conventional therapy (n=17)	Gait and thoracic kypnotic curve	Strenght	Gait - walking speed (cm/sec), cadence (step/min) and stride length (cm) thoracic kypnotic curve – degree	Knee extensors and knee flexors	a) downhill walking training is more effective than conventional therapy in improving gait, muscle strength of knee extensors, and maintaining thoracic posture in patients with PD.
Zhang, T, 2015 (70)	Tai Chi (n=20) vs multimodal exercise (n=20)	Balance	Movement	BBS	UPDRS III, stride length, gait velocity, and TUG	a) Multimodal exercise training group - had better performance at 12 weeks than at baseline on the BBS, but the tai chi group, also increase in BBS. b) Significant differences were observed after 12 weeks of training in both groups on UPDRS III, stride length, gait velocity, and TUG

IV. Discussion

This systematic review supports and updates the findings of previous reviews (34,98,100,101) in which exercise showed to have a potential positive effect in falls frequency, motor impairment/disability and gait parameters. There was insufficient evidence to conclude on the benefits of exercise in PD patients' quality of life and balance.

Can all be considered exercise?

To evaluate the efficacy of exercise as a therapeutic intervention, interventions including exercise, which was defined as a structured and planned physical activity which aim is the improvement of physiological and motor function and is associated with an energy expenditure, were used as inclusion criteria.

Even though a high variability was found between the interventions in study in the included trial, most of them easily fit ACSM classification of types of exercise, while some are not so easy to classify. Tai Chi and Qigong can be considered a multimodal exercise training (or neuromotor or functional fitness training), a type of exercise that gathers different motor skills (balance, gait, motor coordination and proprioceptive training). (22) The classification of dance intervention in this group raises some doubts. Dance is a choreographed routine of movements with auditory, visual and sensory stimulation; memory and motor learning. (102) Although the definition of dance as an exercise does seem to fit in the definition of exercise, previous systematic reviews have considered dance as a complementary type of exercise (34) or an aerobic exercise (98) We included studies where dance was the intervention in our systematic review because the type of dance was in accordance with the definition of exercise: the dance was structured, involved energy expenditure and the aim in all studies was the improvement in PD symptoms.

Which Parkinson's disease patients benefit from exercise interventions?

A Hoehn and Yahr scale ≤3 was an inclusion criterion in all the included studies. Patients with mild to moderate PD were patients without significative cognitive impairment which is an advantage to understand instructions and correctly perform the exercise. The impairments in PD patients with Hoehn and Yahr scale>3 could be a barrier for the implementation of some type of exercise programs (98).

In advanced PD, postural instability and gait impairment can compromise the adherence to exercise and increase the number of adverse effects correlated to the exercise. The self-efficacy related to exercise (people's judgment of their capability to exercise successfully) can, also, contribute to the lower adherence and benefits with exercise(103).

So, it is concluded thatfurther work is needed to understand the effectiveness and the strategies needed to implement some exercise programs in PD patients with more severe cognitive impairment and/or more advanced disease stage. (34)

What are the most effective types of exercise?

Exercise appears to have benefits in improving UPDRS III score, falls frequency and gait measured through the 6-minutes walking test. However, due to the reduced number of studies, conclusions cannot be drawn about the significance of the improvement. Exercise has not shown to contribute to a relevant improvement in quality of life and balance of PD patients.

Previous systematic review (32,34,98,101) tried to answer this question but the number of studies were lower than the included in our systematic review, except in one case (32), which did not assess the effects of exercise exclusively but of all types of physical activity. The other studies did not answer the question as one evaluated the effects of long-term exercise (34), the other only synthetized the effects of aerobic exercise. (98) In our systematic review, to understand what are the most effective, all type of exercises were included.

We conclude that exercise appears to improve UPDRS III scores, although the improvement is not statistically significative. Of the 12 studies assessed in meta-analysis, the seven studies favorable to exercise (53,62,71,72,79,80,104) had a low risk of bias in at least half of the domains of Cochrane risk of bias. The studies, not included in meta-analysis, reported an improvement in the UPDRS III, which is in accordance with previous systematic reviews(32,34,98,101). The meta-analysis results reported highest benefits in longest interventions (>3 months).

This positive association between the duration of the intervention and the benefits in UPDRS III was also found in the systematic review above cited although no conclusions can be withdrawn, in our meta-analysis, about the association between the improvement in UPDRS III and disease-modifying effects. This point is an important question to further research, once UPDRS III scores were expected to deteriorate over time in patients with PD and so the improvements in scores could suggest possible disease-modifying effects

The seven studies that were favorable to exercise and had low risk of bias; had different interventions, time of follow-up and duration/frequency of the intervention. Multimodal exercise appears to have higher benefits than aerobic exercise.

One previous systematic review found that all multimodal programs result in improvement of the UPDRS III and that extended training periods (6 months in the case of dance, tai chi, aerobic exercise and 24 months of progressive resistance exercises) were associated with increased efficacy for achieving clinically meaningful improvement in UPDRS III scores. (34) Our meta-analysis also suggests that extended training periods and multimodal programs (when compared with aerobic training) were associated with increased efficacy. Although it is difficult to draw conclusions about which intervention would improve more UPDRS III, because of the high heterogeneity of studies.

The benefits in quality of life were an important question. Our study, such as previous reviews (32,98), did not find any significative improvement in quality of life, with exercise training. As PD is a long-term, neurodegenerative condition, it is important to study the impact of exercise in quality of life across the time and studies with a lower time of follow-up will not show positive differences in quality of life.

To find what type of exercise could be benefic to improve quality of life in PD, the studies need a longer follow-up time.

In studies where balance was assessed with BBS, no significative benefits of exercise were reported in meta-analysis. Previous systematic reviews reported a balance improvement, when measured with sensory organization test or functional reach test and no improvement when balance was assessed with BBS. The three studies not eligible for meta-analysis and not assessed by BBS, showed a statistically significative improvement. The improvement across time, only analyzed in one study, is not significative. The small number of studies and the high heterogeneity limits the conclusions we can withdraw from meta-analysis.

In gait, an improvement was found in some gait parameters. Regarding 6 MWT, the difference was not significative and the difference, in the distance in 6MWT, was less than the value defined as the minimal detectable change for the 6MWT in a previous study (105). Two previous systematic reviews found a significative improvement in gait parameters with exercise, which is in accordance with the known benefits of exercise, but the results need to be carefully interpreted. (32,106) The heterogeneity of studies (tools, parameters assessed, design) and the small number of studies included were a barrier to conclude if exercise is or not benefic to gait.

The studies included in our meta-analysis, which assessed frequency of falls, had low risk of bias and low heterogeneity, but the small number of studies was the limitation to conclude if exercise can reduce the risk of fall in PD.

According to previous studies, it is important to adequate the type of exercise to the goals we will want to achieve (22,94,101) and it is important in future research to evaluate that. The effect of time was also an important point for future research.

How to prescribe?

The studies reviewed in this paper targeted the same population (people with PD) using exercise as an intervention, although the length of follow-up, the outcomes and the type and intensity of the exercise varied widely. Some studies assessed outcomes at three-time points to establish any detraining effects after the intervention period had ceased, although others only assessed them before and after training.

PD patients are 70% more sedentary than healthy control matched for age (107) and 90% of PD patients reported that their physical activity is under the recommended level proposed by the ACSM. (17) It is recommended that PD patients should ideally integrate an exercise program that involves fitness, strength, balance and coordination training and the training should be adapted for each patient since it depends on the stage of disease and the characteristics of each.(107,108)

In most studies, included in our systematic review, the exercise was performed 3 times per week, 45-60 minutes for 3 months. It is known that there is a positive dose response of health/fitness benefits that results from increasing intensity. (17,22) Recommendations for healthy adults suggest that they should perform a minimum of 30 minutes of exercise per day, in bouts of minimal 10 minutes. (107) The studies included in this systematic review achieve these recommendations and were in accordance with the ACSM recommendations for older people. Our results also suggest that a progressive increase in the intensity could have benefits in exercise and it could be an important question to answer in future research. The small number of studies did not allow to evaluate the influence of intensity in the benefits achieved.

How to improve clinical trials testing exercise interventions in Parkinson's disease?

The clinical relevance of the question, comparators and outcomes chosen is very important to achieve significance in clinical trials. (86) In our systematic review, we can group comparators used in seven groups (Tab. 4). The European Medical Agency (EMA) supports that scientifically "efficacy is most convincingly established by demonstrating superiority to placebo in a placebo-controlled trial, by showing superiority to an active control treatment or by demonstrating a dose-response relationship." In 41.5% of the studies included in our systematic review we can only conclude that one exercise or exercise "dosage" has more effectiveness than the comparator used, but not if exercise has efficacy by itself because these studies choose as comparators other types of exercise or only differs from the active arm in intensity. The studies that have a non-exercise comparator can better answer the question "Has exercise efficacy in PD?". Eight (42,48,50,52,62,71,87,88) of the 52 studies (15.4%) have at least the three arms as suggested. EMA alerts that an appropriate active comparator would be a widely used therapy which efficacy in the relevant indication has been clearly established and quantified in well designed and well documented superiority trials and which can be reliably expected to exhibit similar efficacy in the contemplated active control trial. Most of the studies presented have as a comparator another exercise, which could be a limitation, since the efficacy of the exercise is not yet clearly defined and in some studies is the objective of the study itself. Another potential problem related with the comparators, in the included studies, is what the authors understand by usual care. In some studies, usual care is the exercise patients perform usually. We considered that it would not influence the size of the effect since effect size is used to translate "the before and after changes" in a "one group" and being physically active can influence the baseline characteristics but it is not a determinant for more pronounced improvements.

Another important point is the selection of the primary outcome which should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial. The International Consortium for Health Outcomes (ICHO) suggests that to better understand how to improve quality of life in PD it is important to measure the follow outcomes: health-related quality of life, cognitive and psychiatric functioning, non-motor and motor functioning, ability to work, hospital admissions and falls. A standard set of outcomes to monitor the quality of clinical management of patients with PD which include validated indicators of motor and non-motor symptoms and health status was developed. (89) Non-motor relevant symptoms are: depression, anxiety, impaired cognitive, urinary, gastrointestinal and sexual function, pain, sleep disorders and treatment complications (hemorrhages and behavior changes). Relevant motor symptoms in PD are related to mobility (ability to walk), activities of daily living, ability to self-care, tremor, speech, swallowing, among others. Some additional relevant outcomes are suggested such as ability to work, hospital admissions, overall PD-related health status and falls. In four studies (82,87,90,91), the primary outcome reported was not one of the relevant outcomes in PD defined by ICHO. In relation to the secondary outcomes, in one study (87), it was not used a relevant outcome, according to ICHO definition. In two studies (87,90) none of the outcomes were relevant as defined by ICHO. The benefits of exercise reported in these studies are, therefore, not clinically significative.

If the outcomes and comparators used in the studies are in accordance with the ones defined by EMA and ICHO, the effectiveness of the intervention should be associated to the intervention itself, and we could conclude about the effectiveness of exercise in PD. For that, only in 30 studies we can conclude about the effectiveness of exercise in PD. The other 22 studies, included in the systematic review, provided an overall direction of the effect although they could not precise about the estimated effects.

Another limitation to achieve conclusions was the fact that most studies provided an inadequate description of their methods to allow a full assessment of their methodological quality. In the included studies the major difficulty was to achieve participants and personnel blinding. This is a limitation of the trials included because empirical evidence suggests that blinding in trials does indeed make a difference. (109–112) Only in one study included in the meta-analysis (60) blinding is total. For example, among the studies that suggest an improvement in UPDRS III, only 38.5% (n=5 studies, 7 comparisons) present a low risk of bias in at least 50% of the domains.

Other limitation was the sample size. Studies must be adequately powered to achieve their aims, and appropriate sample size calculations should be carried out at the design stage of any study. To achieve a higher power in a study (the study has a higher chance of detecting a difference between groups if one exists), one of the important factors is increasing the sample size. (113,114). Only 26.9% of the studies included in the systematic review calculated the sample size which makes the interpretation of the effect size difficult.

One important conclusion is the low level of dropouts found. In this review a cut-off of ≤ 20% of losses to follow-up was used, as recommended by Evidence-Based Medicine (EBM). Of the seven studies which have a high number of dropouts, in three studies the number was similar within the two groups, in the other four studies the evidence of prevalent dropouts in control group is identified in three with the major cause of dropout being the loss of follow-up. One important finding observed is that studies that present a higher number of dropouts have unclear or high risk of bias in domains related to blinding and six of the seven studies have a high risk of bias in at least half domains. A systematic review suggests that there will be a correlation between the absence of blind and the number of attrition in the control group (112), but the heterogeneity in our systematic review is high which limit this affirmation, whether there is significance in the relation needs to be study. The low number of dropouts could also show that exercise in early PD stages had a high adherence and can show that supervised exercise enhances adherence. (22)

V. Conclusions

Exercise is an important tool in PD rehabilitation. However, it is difficult to establish a correlation between exercise and the benefits achieved. It is important for clinical practice to assess and determine the guidelines to achieve the benefits for these patients of using exercise.

Exercise appears to have positive effects on PD motor symptoms, especially in gait, motor symptoms as measured by the UPDRS Part III and frequency of falls. In quality of life and balance, the effectiveness appears to be lower, but the short duration of the follow-up is a limitation to achieve a possible improvement in quality of life and balance with the exercise. To achieve benefits in PD state, exercise should be performed at least five days per week, a minimum of 30 minutes of exercise per day, in bouts of minimal 10 minutes. Our results also suggest that a progressive increase in the intensity could have benefits in exercise.

This systematic review brings out the need for further research on the effects of exercise on some health parameters and the correlation between the type of exercise and the benefit achieved, to guide clinicians to choose the better exercise for each specific problem/symptom. Future clinical trials also need to be conducted to understand the benefit of exercise in advanced PD stages and to study the impact of early exercise in the progression of disease symptoms and its potential role in disease modifying. For that it is important the correct choice of comparators, sham intervention or no exercise that could answer better about the effectiveness of the exercise in PD.

The major limitations of existing studies include 1) small sample size; 2) most patients are in mild to moderate stage; 3) short term intervention (≤12 weeks) and 4) bias because studies had a lack of blinding of subjects and therapists (difficult in exercise interventions).

VI. References

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VII. Appendix

Appendix 1: Reasons for excluded studies

Autor	Year	Title	Reasons for exclusion
Baatile, J.	2000	Effect of exercise on perceived quality of life of individuals with PD	Quasi-experimental design
Baro, F.	2003	The influence of rotational exercises on freezing in PD	Exercise was not evaluated
Muller, T.	2008	Impact of endurance exercise on levodopa-associated cortisol release and force increase in patients with Parkinson's disease	no rct
Bello, O.	2008	Treadmill walking in PD patients: adaptation and generalization effect	Exercise was not evaluated
Bergen, J.	2002	Aerobic exercise intervention improves aerobic capacity and movement initiation in Parkinson's disease patients	no rct
Brauer, S.	2011	Single and dual task gait training in people with PD: a protocol for RCT	Study protocol
Canning, C.	2011	Exercise therapy for prevention of falls in people with PD: a prtocol for RCT and economic evaluation	Study protocol
Capato, T.	2015	RCT protocol: balance training with rythmical cues to improve and mantain balance control in PD	study protocol
Conradsson, D.	2012	A novel conceptual framework for balance training in PD-study protocol for a RCT	Study protocol
Crizzle, A.	2006	Is physical exercise beneficial for persons with PD?	no rct
David, F.	2015	Exercise Improves Cognition in Parkinson's Disease: The PRET-PD Randomized, Clinical Trial	duplicated
Tickle-Degne, L.	2010	Self-management rehabilitation and health-related quality of life in Parkinson's disease: A randomized controlled trial	exercise isn't the intervention

Dibble	2006	High-Intensity Resistance Training Amplifies Muscle Hypertrophy and Functional Gains in Persons With Parkinson’s Disease	no rct
Dibble	2009	High intensity eccentric resistance training decreases bradykinesia and improves quality of life in persons with PD: a preliminary study	duplicated
Duchesne, C.	2010	Comparison of the effects of a physiotherapistsupervised exercise programme and a self-supervised exercise programme on quality of life in patients with PD	Quasi-randomized trial
DiFrancisco-Donoghue	2009	Norepinephrine and Cardiovascular Responses to Maximal Exercise in PD On and Off Medication	healthy control group
Duchesne, C.	2015	Enhancing both motor and cognitive functioning in PD: aerobic exercise as a rehabilitive intervention	healthy control group
Earhart, G.	2015	Comparing interventions and and exploring neural mechanisms of exercise in PD: a study protocol for a RCT	Study protocol
Ebersbach, G.	2014	Impact of physical exercise on reaction time in patients with PD - data from the berlim big study	Duplicated
Ebersbach, G.	2015	Amplitude-oriented exercise in Parkinson’s disease: a randomized study comparing LSVT-BIG and a short training protocol	Control group and intervention group differ only in the duration of the intervention
Ellis,T.	2013	Feasibility of a Virtual Exercise Coach to Promote Walking in Community-Dwelling Persons with PD	Type of outcomes: feasibility, acceptability…
Filippin, N.	2010	Effects of treadmill-walking training with additional body load on quality of life in subjects with PD	Absence of control group

Frazzitta, G.	2009	Rehabilitation Treatment of Gait in Patients with Parkinson's Disease with Freezing: A Comparison Between Two Physical Therapy Protocols Using Visual and Auditory Cues with or Without Treadmill Training	Type of intervention
Frazzitta, G.	2015	Crossover versus Stabilometric Platform for the Treatment of Balance Dysfunction in Parkinson's Disease: A Randomized Study	Exercise was not evaluated
Galna, B.	2014	Retraining function in people with PD using the microsoft kinect: game design and pilot testing	Exercise was not evaluated
Ganesan, M.	2015	Partial Body weight support treadmill training in patients with PD: Impact on gait and clinical manifestations	Duplicated
Hackney, M.	2009	Short Duration, Intensive Tango Dancing for PD: An Uncontrolled Pilot Study	Uncontrolled
Harro, C.	2014	The effects of speed-dependent treadmill training and rhythmic auditory-cued overground walking on balance function, fall incidence, and quality of life in individuals with idiopathic PD: A RCT	Type of intervention
Hass, C.	2007	Resistance Training With Creatine Monohydrate Improves Upper-Body Strength in Patients With PD: A RT	Type of intervention
Hass, C.	2012	Quantitative Normative Gait Data in a Large Cohort of Ambulatory Persons with Parkinson's Diseas	Exercise was not evaluated
Heuvel, M.	2013	The effects of augmented visual feedback during balance training in PD: stydy design of a RCT	Study protocol
Heuvel, M.	2014	Effects of augmented visual feedback during balance training in PD: a pilot RCT	Exercise isn't an intervention

Hubble, R.	2014	Trunk muscle exercise as means of improving postural stability in people with PD: a protocol for RCT	Protocol
Kadivar, Z.	2011	Effect of Step Training and Rhythmic Auditory Stimulation on Functional Performance in Parkinson Patients	Type of intervention
Katzel, L.	2011	Repeatability of aerobic capacity measurements in PD	Exercise was not evaluated
King, L.	2015	Do cognitive measures and brain circuitry predict outcomes of exercise in Parkinson Disease: a RCT	Study protocol
King, L.	2015	Effects of Group, Individual, and Home Exercise in Persons With Parkinson Disease: A RCT	Exercise was not evaluated
Kolk, N	2015	Design of the Park-in-shape study: phase II double blind RCT evaluating the effects of exercise on motor and non-motor symptoms in PD	Study protocol
Kuroda, K	1992	Effect of physical exercise on mortality in patients with PD	no rct
Kurtais, Y.	2008	Does Treadmill Training Improve Lower-Extremity Tasks in PD? A RCT	Exercise was not evaluated
Lauhoff, P.	2013	A controlled clinical trial investigating the effects of cycle ergometry training on exercise tolerance, balance and quality of life in patients with PD	Absence of control group
Lee, K.	2011	Modified Constraint-Induced Movement Therapy Improves Fine and Gross Motor Performance of the Upper Limb in PD	Exercise was not evaluated
Li, F.	2014	A Randomized Controlled Trial of Patient-Reported Outcomes With Tai Chi Exercise in Parkinson's Disease	Duplicated

Li, F.	2015	Economic Evaluation of a Tai Ji Quan Intervention to Reduce Falls in People With PD	Exercise was not evaluated
Lopane, G.	2010	The Effect of a Clinically Practical Exercise on Levodopa Bioavailability and Motor Response in Patients With PD	Absence of control group
Mancini, C.	2012	Quantifying Freezing of Gait in PD during the Instrumented Timed Up and Go test	Exercise was not evaluated
Mansfield, A.	2015	Perturbation training to promote safe independent mobility post-stroke: study protocol for RCT	Study protocol
McKee, K.	2013	The Effects of Adapted Tango on Spatial Cognition and Disease Severity in PD	no randomized
Mirelman, A.	2013	V-Time a treadmill program augmented by virtual reality to decrease fall risk in older adults:study design of a RCT	Study protocol
Miyai, I.	2000	Treadmill Training With Body Weight Support: Its Effect on PD	Absence of control group
Moore, C.	2013	Study in Parkinson Disease of Exercise (SPARX): Translating high-intensity exercise from animals to humans	Exercise was not evaluated
Morbeg, B.	2014	The impact of high intensity physical training on motor and non-motor symptoms in patients withPD (PIP…	No randomization
Morris, M.	2011	Falls and mobility in Parkinson's disease: protocol for a randomised controlled clinical trial	Study protocol
Muller, T.	2008	Impact of endurance exercise on levodopa-associated cortisol release and force increase in patients with PD	Duplicated
Nakamura, T.	2010	Lowered Cardiac Sympathetic Nerve Performance in Response to Exercise in PD	healthy control group

Nascimento, C.	2011	Serum homocysteine and physical exercise in patients with PD	type of outcomes
Nieuwboer, A.	2007	Cueing training in the home improves gait-related mobility in Parkinson’s disease: the RESCUE trial	Exercise was not evaluated
Nimwegen, M.	2010	Design and baseline characteristics of the ParkFit study, a randomized controlled trial evaluating the effectiveness of a multifaceted behavioral program to increase physical activity in Parkinson patients	Study protocol
Nimwegen, M.	2011	Promotion of physical activity and fitness in sedentary patients with PD: randomized controlled trial	No exercise intervention
Nocera, J.	2009	Effects of Home-Based Exercise on Postural Control and Sensory Organization in Individuals with PD	no PD control group
Nozaki, T.	2013	Effect of subthalamic nucleus stimulation during exercise on the mesolimbocortical dopaminergic region in PD: a positron emission tomography study	Exercise was not evaluated
Onate, J.	2007	On-Field Testing Environment and Balance Error Scoring System Performance During Preseason Screening of Healthy Collegiate Baseball Players	Exercise was not evaluated
Palacios-Navarro, G.	2015	A Kinect-Based System for Lower Limb Rehabilitation in Parkinson’s Disease Patients: a Pilot Study	Absence of control group
Park, H.	2011	Development of a VR-based Treadmill Control Interface for Gait Assessment of Patients with PD	Exercise was not evaluated
Paul, F.	2006	Impact of an Exercise Program on Physical, Emotional, and Social Aspects of Quality of Life of Individuals With PD	Absence of control group

Peterson, D.	2014	Brain activity during complex imagined gait tasks in PD	Exercise was not evaluated
Picelli, A.	2012	Does robotic gait training improve balance in PD? A RCT	Type of intervention
Prodoehl	2014	Two Year Exercise Program Improves Physical Function in Parkinson's Disease: the PRET-PD Study	Duplicated
Protas, E.	1996	Cardiovascular and Metabolic Responses to Upper- and Lower-Extremity Exercise in Men with Idiopathic	no Parkinson CG
Protas, E.	2005	Gait and step training to reduce falls in PD	Type of intervention
Qui, F.	2013	Effects of Textured Insoles on Balance in People with PD	Exercise was not evaluated
Ridgel, A.	2012	Active-assisted cycling improves tremor and bradykinesia in PD	Exercise was not evaluated
Ridgel, A.	2013	Variability in Cadence During Forced Cycling Predicts Motor Improvement in Individuals with PD	Exercise was not evaluated
Rocchi, L.	2012	Effects of deep brain stimulation in subthalamic nucleus or globus pallidus internus on step initiation in PD	Exercise isn't an intervention
Rose, M.	2013	Effects of training and weight support on muscle activation in PD	Absence of control group
Rose, M.	2013	Improved clinical status, quality of life and walking capacity in PD after body weight supported high intensity locomotor training	Absence of control group
Rosenfeldt, A.	2015	The cyclical lower extremity exercise for Parkinson's trial: methodology for RCT	Study protocol
Sage, M.	2010	A Positive Influence of Vision on Motor Symptoms During Sensory Attention Focused Exercise for PD	exercise is not the intervention
Sale, P.	2013	Robot-assisted walking training for individuals with PD: a pilot RCT	exercise is not the intervention

Shanahan, J.	2015	Is Irish set dance feasible for people with PD in Ireland?	Exercise was not evaluated
Shaojuan, G.	2013	Effect of PD-WEBB training on balance impairment and falls in people with PD	Language
Sanpablo, A.	2014	Familiarización de la marcha en banda sinfín de individuos con enfermedad de Parkinson	Exercise was not evaluated
Scandalis, TA	2001	Resistance Training and Gait Function in Patients with PD	healthy control group
Schenkman, M.	1998	Exercise to Improve Spinal Flexibility and Function for People with Parkinson's Disease: A Randomized, Controlled Trial	Type of intervention
Sheard, J.	2014	Improved nutritional status is related to improved quality of life in PD	Exercise was not evaluated
Shen, X.	2012	Repetitive step training with preparatory signals improves stability limits in patients with PD	Exercise was not evaluated
Steffen, T.	2008	Test-Retest Reliability and Minimal Detectable Change on Balance and Ambulation Tests, the36-Item Short Form Health Survey, and the UPDRS in People with Parkinsonism	Exercise was not evaluated
Sterling, N.	2015	Dopaminergic modulation of arm swing during gait among PD patient	No exercise intervention
Stocchi, F.	2014	Comparison of IPX066 with cardidopa-levodopa plus entacapone in advanced PD patient	No exercise intervention
Su, M.	2015	Depth-Sensor-Based Monitoring of Therapeutic Exercises	Exercise was not evaluated
Summa, S.	2015	Adaptive training with full-body movements to reduce bradykinesia in persons with PD: a pilot study	Absence of control group
Tanaka	2009	Benefit of physical exercise on executive function in older people with PD	no randomized
Thaut, M.	1996	Rhythmic Auditory Stimulation in Gait Training for PD Patients	Type of intervention

Trigueiro, LCL	2015	Effects of Treadmill Training with Load on Gait in PD	Exercise was not evaluated
Tunik, E.	2007	Dopamine replacement therapy does not restore the ability of Parkinsonian patients to make rapid adjustments in motor strategies according to changing sensorimotor contexts	No exercise intervention
Uygur	2015	Immediate effects of high-speed cycling intervals on bradykinesia in PD	Exercise was not evaluated
Volpe, D.	2013	A comparison of iris set dancing and exercises for people with PD: a phase II feasibility study	Exercise was not evaluated
Watts, J.	2008	Cost effectiveness of preventing falls and improving mobility in people with PD: protocol for an economic evaluation alongside a clinical trial	Study protocol
Weiss, A.	2014	Objective Assessment of Fall Risk in PD Using a Body-Fixed Sensor Worn for 3 Day	Exercise was not evaluated
White, D	2009	Changes in walking activity and endurance following rehabilitation for people with PD	Exercise was not evaluated
Wong-Yu, I.	2015	Task- and Context-specific Balance Training Program Enhances Dynamic Balance and Functional Performance in Parkinsonian Non-fallers: A RCT with 6-month Follow-up	No exercise intervention
Wu, S	2011	Running exercise protects the substantia nigra dopaminergic neurons against inflammation-induced degeneration via activation of BDNF signaling pathway	animal models
Xu, Q.	2010	Physical activities and future risk of PD	no rct
Yang, Y	2015	The effectiveness of Tai Chi for patients with PD: study protocol for a RCT	Study protocol

Yousefi, B.	2009	Exercise therapy, quality of life, and activities of daily living in patients with PD: a small scale quasi-randomised trial	no randomized
Zigmond, M.	2012	Neurorestoration by physical exercise: Moving forward	no rct
Zoladz, J.	2014	Moderate-intensity interval training increases serum brain-derived neurotrophic factor level and decreases inflammation in PD patients	Absence of control group

Appendix 2: Characteristics of included studies

Studies included	Disease duration	Hoehn and Yar	Age	ON/OFF medication	Adverse effects
Allen, N. 2010 (48)	8	Mild to moderate	67 ± 8.5	On state	Not reported
Amano, S. 2013 (68)	8	Mild to moderate	67.3 ± 9.9	On state	Not reported
Ashburn, 2006 (49)	A	Moderate	71.1 ± 9.2	On state	Not reported
Ayan, C., 2012 (90)	6,8	Mild to moderate	70.4 ± 7.4	On state	Not reported
Bello, O., 2013 (78)	5	Mild to moderate	58.7 ± 10,4	On state	Not reported
Bloomer, R., 2008 (73)	A	Mild	59.0 ± 2.5	On state	Not reported
Bridgewater, K., 1997 (29)	4	Mild to moderate	66.6 ± 7.05	On state	Not reported
Burini, D., 2006 (85)	11	Mild to moderate	65.2 ± 6.5	On state	Not reported
Caglar, AT, 2005 (50)	5	Mild to moderate	65.9 ± 8.67	On state	Not reported
Cakit, 2007 (52)	6	Mild to moderate	71.8 ± 6.4	On state	Ventricular extrasystole (2 patients) but not relevant
Canning, C., 2012 (51)	6	Not clear	61.8 ± 7.9	On state	Not reported
Canning, C., 2014 (96)	8	Mild to moderate	70.6 ± 8.7	On state	Not reported
Carvalho, 2015 (87)	5	Mild to moderate	68.1 ± 15.4	On state	Not reported
Combs, S., 2013 (97)	6	Mild to moderate	Mediana	On state	Not reported
Comella, C., 1994 (53)	10	Mild to moderate	66.0 ± 8.0	On state	Not reported
Conradsson, D., 2015 (67)	6	Mild to moderate	73.2 ± 5.7	On state	Not reported
Corcos, D., 2013(10)	7	Mild to moderate	58.8 ± 5.1	On and off state	Not reported
Cruise, K, 2010 (86)	6	Mild to moderate	60.0 ± 9.4	On state	Not reported
Dibble, L, 2015 (54)	7	Mild to moderate	68.4 ± 11.9	On and off state	Not reported
Ebersbach, G., 2010 (55)	7	Mild to moderate	67.3 ± 6.9	On state	Not reported
Ergun, Y., 2014 (88)	6	Mild to moderate	65.4 ± 6.2	On state	Not reported
Fisher, B., 2008 (79)	1	Mild	62.9 ± 11.9	On state	Not reported
Fisher, B., 2013	1	Mild to moderate	55,1±2.2	Off state	Not reported
Ganesan, M., 2014 (81)	5	Mild to moderate	58.2 ± 8.7	On state	Not reported
Gobbi, L., 2009 (56)	A	Mild to moderate	67.8 ± 8.6	On state	Not reported
Goodwin, V., 2011 (57)	9	Mild to moderate	71.0 ± 8.4	On state	Not reported

Hackney, M., 2007 (91)	5	Mild to moderate	71.0 ± 2.1	On state	1 knee pain
Hackney, M., 2008 (72)	7	Mild to moderate	63.8 ± 9.2	On state	Not reported
Hackney, M., 2009 (92)	8	Mild to moderate	66.6 ± 2.3	On state	Not reported
Hass, C., 2012 (74)	9	Mild to moderate	65.5 ± 7.5	On state	1 muscle soreness and 1 shoulder pain
Hirsch, M., 2003 (58)	7	Mild to moderate	73.7 ± 2.4	On state	1 inguinal hernia
Li, F., 2012 (69)	7	Mild to moderate	68.7 ± 8.7	On state	Not reported
Mak, M., 2008 (94)	6	Mild to moderate	64.1 ± 7.9	On state	Not reported
Miyai, I, 2002 (82)	4	Mild to moderate	69.6 ± 1.7	On state	Not reported
Morris, M., 2009 (59)	A	Mild to moderate	67.0 ± 1.9	On state	Not reported
Morris, M., 2015 (60)	7	Mild to moderate	67.9 ± 9.6	On state	Not reported
Ni, M., 2015 (77)	7	Mild to moderate	72.4 ± 7.0	On state	Not reported
Palmer, S., 1986 (95)	A	Mild to moderate	64.9 ± 5.8	On state	Not reported
Park, A., 2014 (66)	3	Mild to moderate	59.9 ± 6.3	On state	Not reported
Paul, S., 2014 (75)	8	Mild to moderate	66.3 ± 6.5	On state	Not reported
Poliakoff, E, 2013 (61)	6	Mild to moderate	69.5 ± 3.2	On state	1 panic attack; 1 mildly sprained ankle whilst exercising in the gym
Ridgel, A., 2009 (89)	6	Mild to moderate	61.0 ± 4.6	On state	Not reported
Romenets, S., 2015 (93)	6	Mild to moderate	63.7 ± 9.1	Not clear	Not reported
Sage, M., 2009 (65)	4	Mild to moderate	65.9 ± 9.5	On state	Not reported
Schenkman, M., 2012 (62)	5	Mild to moderate	64.7 ± 10.7	On state	Injurious falls (1 per group); soreness pain (2 in AE group); 24 non serious adeverse events (2 sprain/strain: 1 in the FBF group and 1 in the AE group; 22 soreness/pain: 9 in the FBF group, 9 in the AE group, and 4 in the control group)
Schilling, B, 2010 (63)	A	Mild to moderate	59.3 ± 7.9	On state	Not reported

Schlenstedt, C., 2015 (76)	10	Mild to moderate	75.7 ± 5.9	On state	Not reported
Schmitz-Hübsch, T., 2006 (71)	6	Mild to moderate	63.6 ± 8.0	On state	Not reported
Shulman, L., 2015 (83)	6	Mild	65.8 ± 10.8	On state	No serious adverse events
Stuckenschneider, T., 2015 (64)	A	Mild to moderate	71.3 ± 5.1	On state	Not reported
Yang, Y., 2010 (84)	5	Mild to moderate	67.2 ± 9.1	On state	Not reported
Zhang, T, 2015 (70)	6	Mild to moderate	65.2 ± 11.2	On state	Not reported

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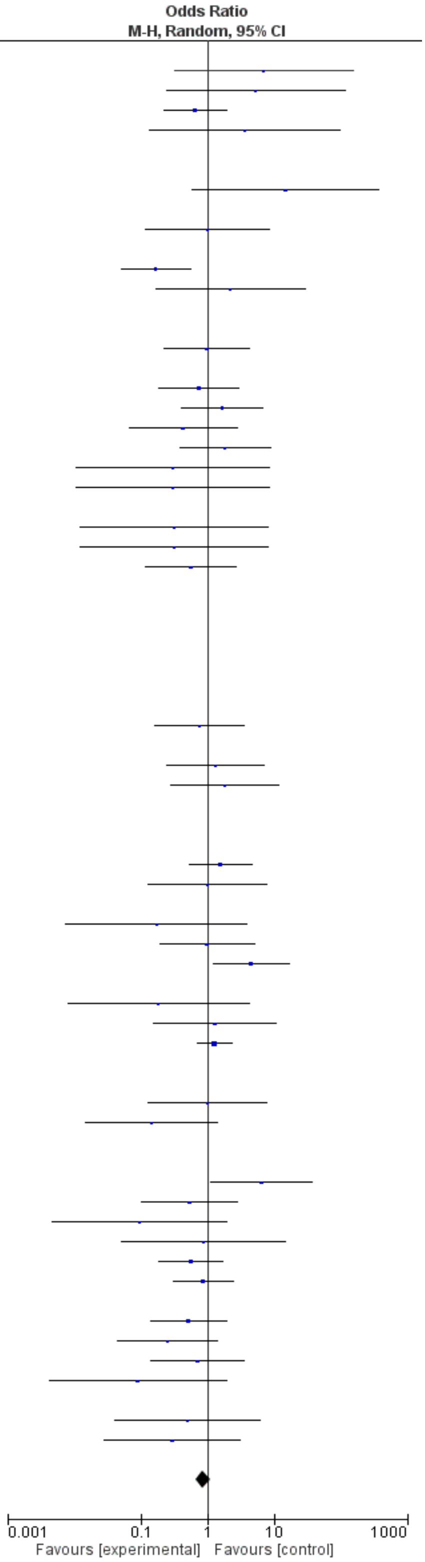
Appendix 3: Forest plot comparing dropouts between intervention and control group

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Allen 2010	0	24	0	24		Not estimable
Amano Project 1 2013	3	12	0	9	0.8%	7.00 [0.32, 154.87]
Amano Project 2 2013	3	15	0	9	0.8%	5.32 [0.24, 115.86]
Ashburn, 2006	6	70	9	72	5.0%	0.66 [0.22, 1.95]
Ayan 2012	1	10	0	11	0.7%	3.63 [0.13, 99.85]
Bello 2013	0	11	0	11		Not estimable
Bergen 2002	0	4	0	4		Not estimable
Bloomer 2008	3	6	0	7	0.7%	15.00 [0.60, 376.70]
Bridgewater 1997	0	13	0	13		Not estimable
Burini 2006	2	13	2	13	1.5%	1.00 [0.12, 8.42]
Caglar 2005	0	15	0	15		Not estimable
Cakit 2007	6	27	17	27	4.3%	0.17 [0.05, 0.56]
Canning 2012	2	10	1	10	1.1%	2.25 [0.17, 29.77]
Canning 2014	0	115	0	116		Not estimable
Carvalho, 2015	0	5	0	8		Not estimable
Combs 2013	6	17	5	14	3.0%	0.98 [0.22, 4.30]
Comella 1994	0	18	0	18		Not estimable
Conradsson, 2015	4	51	5	49	3.4%	0.75 [0.19, 2.97]
Corcos, 2013	6	24	4	24	3.2%	1.67 [0.40, 6.87]
Cruise, 2010	2	17	4	17	2.0%	0.43 [0.07, 2.76]
David 2015	5	23	3	23	2.7%	1.85 [0.39, 8.87]
Dibble 2006	0	10	1	10	0.7%	0.30 [0.01, 8.33]
Dibble 2009	0	10	1	10	0.7%	0.30 [0.01, 8.33]
Dibble, 2015	0	20	0	21		Not estimable
Ebersbach 2010	0	20	1	20	0.7%	0.32 [0.01, 8.26]
Ebersbach 2014	0	20	1	20	0.7%	0.32 [0.01, 8.26]
Ergun 2014	3	21	5	22	2.7%	0.57 [0.12, 2.74]
Fisher 2008	0	10	0	10		Not estimable
Fisher 2013	0	2	0	2		Not estimable
Fisher Low vs zero	0	2	0	2		Not estimable
Ganesan 2014	0	20	0	20		Not estimable
Ganesan 2015	0	20	0	20		Not estimable
Ganesan PWSTT	0	20	0	20		Not estimable
Gobbi 2009	0	21	0	13		Not estimable
Goodwin 2011	3	64	4	66	2.8%	0.76 [0.16, 3.55]
Hackney 2007	0	9	0	10		Not estimable
Hackney 2008	4	17	3	16	2.4%	1.33 [0.25, 7.17]
Hackney 2009	4	17	2	14	2.0%	1.85 [0.28, 11.98]
Hass 2012	0	9	0	9		Not estimable
Hirsch 2003	0	6	0	9		Not estimable
Li 2012	0	65	0	65		Not estimable
Li 2014	9	65	6	65	5.0%	1.58 [0.53, 4.73]
Mak 2008	2	21	2	21	1.6%	1.00 [0.13, 7.85]
Miyai 2002	0	11	0	9		Not estimable
Morris 2009	0	14	2	14	0.7%	0.17 [0.01, 3.94]
Morris 2015	3	70	3	69	2.5%	0.99 [0.19, 5.06]
Morris PRST	12	71	3	69	3.7%	4.47 [1.20, 16.63]
Nascimento 2011	0	24	0	17		Not estimable
Ni 2015	0	14	2	15	0.7%	0.19 [0.01, 4.24]
Ni Yoga 2015	2	12	2	15	1.5%	1.30 [0.16, 10.90]
Nimwegen 2013	26	299	20	287	11.2%	1.27 [0.69, 2.33]
Palmer 1986	0	7	0	7		Not estimable
Park 2014	0	15	0	16		Not estimable
Paul 2014	2	20	2	20	1.6%	1.00 [0.13, 7.89]
Poliakoff 2013	1	16	5	16	1.4%	0.15 [0.01, 1.44]
Prodoehl 2014	0	24	0	24		Not estimable
Ridgel 2009	0	5	0	5		Not estimable
Romenets 2015	9	18	2	15	2.2%	6.50 [1.13, 37.48]
Sage 2009	3	21	4	17	2.4%	0.54 [0.10, 2.84]
Sage PDSAFEx	0	15	4	17	0.8%	0.10 [0.00, 1.97]
Schenkman 1998	1	27	1	24	0.9%	0.88 [0.05, 14.96]
Schenkman 2012	6	39	10	41	4.8%	0.56 [0.18, 1.74]
Schenkman FBF 2012	9	41	10	41	5.5%	0.87 [0.31, 2.44]
Schilling 2010	0	9	0	9		Not estimable
Schlenstedt 2015	6	20	9	20	3.7%	0.52 [0.14, 1.92]
Schmitz-Hübsch 2006	2	32	5	24	2.2%	0.25 [0.04, 1.44]
Shulman 2015	3	26	4	26	2.6%	0.72 [0.14, 3.58]
Stuckenschneider 2015	0	10	4	12	0.8%	0.09 [0.00, 1.92]
Tanaka 2009	0	10	0	10		Not estimable
Yang 2010	1	16	2	17	1.1%	0.50 [0.04, 6.12]
Zang 2015	1	20	3	20	1.3%	0.30 [0.03, 3.15]
Total (95% CI)		**1875**		**1835**	**100.0%**	**0.87 [0.66, 1.14]**
Total events	161		173			

Heterogeneity: Tau² = 0.08; Chi² = 46.58, df = 42 (P = 0.29); I² = 10%
Test for overall effect: Z = 1.01 (P = 0.31)



Appendix 4: Intervention characteristics

Studies	Description	Study Design	Type of exercise: Aerobic traning	Type of exercise: Resistance training	Type of exercise: Flexibiity training	Type of exercise: Balance training	Type of exercise: Multimodal training	Intensity	Duration of exercise	Frequency	Primary Outocome	Duration of intervention
Allen et al. (2010) (48)	40 to 60 min program of progressive lower limb strengthening and balance exercises	Open RCT		x		x		Unk	40-60 min	Group classes: 1x/month, home-based exercise program: 3x/week	Falls rate	24 weeks
Amano et al. (2013) (68)	Tai Chi (the first eight movements of the Yang-style short forms)	Open RCT					x	Unk	60 min	2x or 3x/week	Changes in postural control during gait initiation and gait performance	16 weeks
Ashburn et al. (2006) (49)	Home based exercise and strategy programme (muscle strengthening, range of movement, balance training, walking, strategies for falls prevention and movement initiation and compensation)	Single-blinded RCT					x	Unk	60 min	1x/week	Falls rate	24 weeks
Ayan et al. (2012) (90)	Water-based exercise program (gentle walking in different directions, Static exercises of the limbs, coordination and proprioceptive group exercises)						x	Low-intensity	60 min: 10 min warm-up, 20 min static exercises (2 sets, 12 repetitions of 35-40 sec, 1.5 min rest between sets), dynamic exercises (3 sets , 35-40 sec/exercise, 5 min)	2x/week	Changes in motor-cognitive abilities, functional capacity and fitness level	12 weeks

Studies (cont)	Description	Study Design	Type of exercise					Intensity	Duration of exercise	Frequency	Primary Outocome	Duration of intervention
			Aerobic traning	Resistance training	Flexibiity training	Balance training	Multimodal training					
Bello et al. (2013) (78)	Treadmill training	Open RCT	x					Individual preferred speed	4 sets of 4 min of walking, with 3 min rest between bouts. Each week additional 4 min bout was added.	3x/week	Changes in motor performance	5 weeks
Bloomer et al. (2008) (73)	Resitance training	Open RCT		x				Unk. Progression: weight increase of 5% to 10%.	3 sets of 5-8 repetitions	2x/week	Changes in oxidative status	8 weeks
Bridgewater et al. (1997) (29)	Trunk function exercise clases training (aerobic class with trunk muscle training emphasised in the warm-up)	Open RCT					x	Strengthening exercises: 10 repetitions of 7 sec isometric contractions, 7 sec rest; stretch position was held for 20-30 sec.	15 min warm-up (strengthening exercises), aerobic exercises and 5-10 min cool-down (stretching exercises)	2x/week	Changes in range of motion, torque and velocity of trunk flexors, extensors and rotators	12 weeks
Burini et al. (2006) (85)	Aerobic trainning sessions or Qigong (breathing exercises associated with stretching, neck and trunk rotation exercises and balance training in the upright position)	Randomized controlled cross-over trial	x				x	Aerobic training: 50-60% HRRmax	50 min. Aerobic training: warm-up: 10 min; endurance: 30 min; cool-down 10 min.	3x/day	Changes in fitness, disability and patient’s well-being	7 weeks
Caglar et al. (2005) (50)	Home exercise training programme (relaxation, range-of-motion, stretching, functional and balance exercises, breathing and facial muscle exercises)	Single-blinded Cross-over trial					x	Unk	60 min, 10 repetitions/exercise	3x/day	Changes in range of motion, functional activity, balance, gait and fine motor dexterity	8 weeks
Cakit et al. (2007) (52)	Speed-dependent treadmill training programme (stretching, range-ofmotion exercise and treadmill training)	Single-blinded RCT	x					Maximum tolerated walking speed with increments of 0.6 km/h every 5 minutes, 0% inclination.	30 min	Unk	Changes in postural instability, dynamic balance and fear of falling	8 weeks

Studies (cont)	Description	Study Design	Type of exercise					Intensity	Duration of exercise	Frequency	Primary Outocome	Duration of intervention
			Aerobic traning	Resistance training	Flexibiity training	Balance training	Multimodal training					
Canning et al. (2012) (51)	Home-based treadmill walking training	Single-blinded RCT	x					50% of the average speed maintained during the pre-test 6-minute walk test; progressions: 80% of the average 6-minute walk test speed	30–40 min	4x/weeks	Changes in MDS-UPDRS Part III	6 weeks
Canning et al. (2014) (96)	PD-WEBB program (progressive balance, lower limb strengthening exercises, cueing strategies to reduce freezing of gait)	Single-blinded RCT					x	Unk	40-60 min	3x/week	Falls rate	24 weeks
Carvalho et al. (2015) (87)	Strength training, aerobic training (treadmill walking)	Single-blinded RCT	x	x				Strength training: 70-80% of 1RM; Aerobic training: 60% VO2max or 70% Hrmax.	Strength training: 2 sets of 8-12 repetitions, rest intervals of 30-60 seconds; Aerobic training: 30 min, preceded by 5 min of warming and 5 min of postexercise recovery	2x/week	Changes in MDS-UPDRS Part III	12 weeks
Combs et al. (2013) (97)	Boxing training (stretching, boxing, resistance exercises, and aerobic training) or traditional group exercise (stretching, resistance exercises, aerobic training, and balance activities)						x	Unk	90 min	Unk	Changes in function and quality of life	12 weeks

Studies (cont)	Description	Study Design	Type of exercise					Intensity	Duration of exercise	Frequency	Primary Outocome	Duration of interventio n
			Aerobic traning	Resistance training	Flexibiity training	Balance training	Multimodal training					
Comella et al. (1994) (53)	Physical therapy program (69 repetitive exercises to improve range of motion, endurance, balance and gait, and fine motor dexterity)	Randominzed, single-blinded cross-over trial					x	Unk	60 min	3x/week	Changes in UPDRS total score and timed finger taps	24 weeks
Conradsson et al. (2015) (67)	HiBalance program (exercises where the participants were forced, intermittently, to use reactive postural adjustments to control their balance during single-tasking. Balance components worked: sensory integration, anticipatory postural adjustments, motor agility, stability limits)	Open RCT				x		Week 1-2: single-task exercises of each balance component separately emphasizing quality of movement and the objectives of the exercises; Weeks 3-5: 40% of the session with basic dual-task exercises and increased level of difficulty for each balance component; Weeks 6-10: 60% of the session with dual-task exercises, exercises of higher level of difficulty, combining several balance components.	60 min	3x/week	Changes in postural control	10 weeks
Corcos et al. (2013) (10)	Modified ftness counts exercise (stretches, balance exercises, breathing, and non-progressive strengthening) or Progressive Resistance Exercise (11 strengthening exercises)	RCT		x			x	Unk	60 min	2x/week	Change on UPDRS Part-III	96 weeks

Studies (cont)	Description	Study Design	Type of exercise					Intensity	Duration of intervention	Frequency	Primary Outocome	Duration of intervention
			Aerobic traning	Resistance training	Flexibiity training	Balance training	Multimodal training					
Cruise et al. (2010) (86)	Exercise intervention program (combination of strength and cardiovascular training)						x	Aerobic trainig: 60–85% of HRmax; Streghtening trainig: to work past the specific RM prescribed. Progression: increasing of 5–10%	60 min: 5 min warm up (low-level aerobic activity such as walking, stationary cycling and stretching), strenghtening exercises and 25–30 min aerobic training	2x/week	Changes in cognitive functioning, mood and disease-specific QoL	12 weeks
Dibble et al. (2015) (54)	Strengthening and fitness exercises and Resistance Exercise via Negative Eccentric Work (RENEW)	RCT					x	RPE: 13	Strengthening and fitness exercises: 45 min; Resistance Exercise via Negative Eccentric Work (RENEW): 15 min	2-3x week	Changes in muscle force production and muscle cross-sectional area, mobility and helath status	12 weeks
Ebersbach et al. (2010) (55)	LSVT®BIG (high-amplitude movements, multiple repetitions, high intensity, and increasing complexity) or Nordic walking or domestic training programs (stretching, high-amplitude movements, muscular power and posture exercises)	Single-blinded RCT	x				x	LSVT®BIG: 80% of their maximal energy	60 min	LSVT®BIG: 4x/week; Nordic walking: 2x/week;	Changes in motor performance (UPDRS Part-III)	LSVT®BIG: 4 weeks; Nordic walking: 8 weeks

Studies (cont)	Description	Study Design	Type of exercise					Intensity	Duration of exercise	Frequency	Primary Outocome	Duration of intervention
			Aerobic traning	Resistance training	Flexibiity training	Balance training	Multimodal training					
Fisher et al. (2008) (79)	High-intensity exercise using body weight–supported treadmill training (10% of the participant's body weight) or low-intensity multi-model exercise	Open RCT	x				x	High-intensity exercise: greate than 3.0 METS and/or 75% of an age-adjusted Hrmax; Low-intensity exercise: 3.0 or less METs and/or a Hrmax of 50% or less	45 min within the respective intensity level	Unk (24 sessions)	Changes in functional performance and corticomotor excitability	8 weeks
Ergun et al. (2014) (88)	Aerobic walking (continuous vs interval)	2 x 2 randomized trial	x					Continuous training: 70% to 80% of Hrmax; Interval trainees: alternated every 3 minutes between slower (60%–70% of HRmax) and faster (80%–90% of HRmax)	45 min	3x/week	Changes in motor function, cognition and quality of life	Bouts 6 months during three years
Fisher et al. (2013) (80)	intensive treadmill exercise	Open RCT	x					Greater than 3.0 METS and/or 75% of an age-adjusted Hrmax during 45 minutes	60 min	3x/week	Changes in DA-D2R binding potential	8 weeks
Ganesan et al. (2015) (115)	Conventional gait training or partial weight supported treadmill gait training (20% of the participant's body weight)	Open RCT	x					Training speed and progression were individualized to subject's own comfortable walking speed	30 min	4x/weeks	Changes in gait and postural stability	4 weeks

Studies (cont)	Description	Study Design	Type of exercise					Intensity	Duration of exercise	Frequency	Primary Outocome	Duration of intervention
			Aerobic traning	Resistance training	Flexibiity training	Balance training	Multimodal training					
Gobbi et al. (2009) (56)	A multi-mode exercise program (including rhythmic activities, callisthenic gymnastics, stretching exercises, and recreational activities) or an adaptive program (low complexity flexibility, strength, motor coordination, and balance exercise)	Open RCT					x	Multi-mode exercise: Unknow initial load. Every 12 sessions, load progressively increased. Adaptive program: Incremental load changes were not applied	60 min	Multi-mode exercise: 3x/week; Adaptive program: 1x/week	Changes in functional balance and mobility	24 weeks
Goodwin et al. (2011) (57)	Strength and balance training programme with supplementary home exercises	Open RCT		x		x		Unk	60 min: 10 min warm up, 40 min of strenght and balance training exercises and 10 min cool down	2x/week	Falls rate	10 weeks
Hackney et al. (2007) (91)	Progressive tango dance lessons or structured strength/flexibility exercise classes	Single-blinded RCT		x	x		x	Low-intensity exercise training	60 min	2x/week	Changes in functional mobility	13 weeks
Hackney et al. (2008) (72)	Partner and nonpartner tango dance classes	Single-blinded RCT					x	Unk	60 min	2x/week	Changes in postural stability, motor ability and gait	13 weeks
Hackney et al. (2009) (92)	Partner and nonpartner tango dance classes	Single-blinded RCT					x	Unk	60 min	2x/week	Changes in postural stability	10 weeks
Hass et al. (2012) (74)	Progressive resistance training	Open RCT		x				Moderate-intensity level: 70% of 1 RM. Progression: increased of 10% from the last workout	2 sets of 12–20 repetitions to volitional fatigue.	Unk	Changes in peak strength and performance of gait initiation.	10 weeks

Studies (cont)	Description	Study Design	Type of exercise					Intensity	Duration of exercise	Frequency	Primary Outocome	Duration of intervention
			Aerobic traning	Resistance training	Flexibiity training	Balance training	Multimodal training					
Hirsch et al. (2003) (58)	Combined balance and resistance training or balance training only	Open RCT		x		x		High-intensity level: 60% of 4 RM. Progression: 80% of 4 RM	Resistance training: 15 min, 12 sets of 6-9 repetitions with a 2-min rest between exercises.; Balance training: 30 min	3x/week	Changes in muscle strength and postural stability	10 weeks
Li et al. (2012) (69)	Tai Chi	Open RCT					x	Unk	60 min	2x/week	Changes in postural stability and physical performance	24 weeks
Mak et al. (2008) (94)	Conventional mobility and strengthening exercises for flexors and extensors of trunk, hips, knees, and ankles.	Open RCT		x	x			Unk	20 min	3x/week	Changes in sit to stand task	4 weeks
Miyai et al. (2012) (82)	Body weight–supported treadmill training ou Physiotherapy program (range-of-motion exercise, ADL training, and gait training)	Open RCT	x					Body weight support: 20% for 10 minutes, 10% for 10 minutes, 0% for 10 minutes. Treadmill speed: 3.0km/h by increments of 0.5km/h as tolerated.	45 min	3x/week	Changes in UPDRS total score and 10-m walk	4 weeks
Morris et al. (2009) (59)	Lower limb and trunk strengthening exercises, spinal and lower limb flexibility exercises and receiving feedback on optimal postural alignment for a range of positions.	Single-blinded RCT					x	Unk	45 min	2x/week	Changes in UPDRS Part-II and III	2 weeks

Studies (cont)	Description	Study Design	Type of exercise					Intensity	Duration of exercise	Frequency	Primary Outocome	Duration of intervention
			Aerobic traning	Resistance training	Flexibiity training	Balance training	Multimodal training					
Morris et al. (2015) (60)	Progressive Resistance Strength Training or Movement Strategy Training	single-blind, parallel group randomized controlled clinical trial					x	Exercises were progressed by increasing: repetitions to a maximum of 15; sets to a maximum of 3; or weights by 2% of the person's body weight.	2 hours	1x/week	falls rate	8 weeks
Ni et al. (2015) (77)	Power Training or High-speed yoga program	Open RCT		x			x	Power training: 50 and 75% of 1 RM. Progression: weekly increases of load based on participants' reaching power plateaus	60 min. Power traning: 3 sets of 10–12 repetitions	2x/week	Changes in motor symptoms, balance, mobility, and muscle performance	12 weeks
Palmer et al. (1986) (95)	United Parkinson Foundation exercise program (stretch exercises) or upper body karate training program (warm-up stretching exercises, upper body karate techniques in a seated position and cool-down stretching exercises)	Single-blinded RCT			x			Unk	60 min	3x/week	Changes in grip strength, motor coordination and speed, and neurophysiologic determinations of long-latency stretch responses	12 weeks

Studies (cont)	Description	Study Design	Type of exercise					Intensity	Duration of exercise	Frequency	Primary Outocome	Duration of intervention
			Aerobic traning	Resistance training	Flexibiity training	Balance training	Multimodal training					
Park et al. (2014) (66)	Exercise program (cardiovascular, core strength, and joint integrity work with and without formal strength training exercise plan)	Single-blinded Cross-over trial					x	Cardiovascular training: 75%–85% of Hrmax	60 min	3x/week	Changes in MDS-UPDRS toal score	48 weeks
Paul et al. (2014) (75)	Muscle power training (the leg extensors, knee flexors, hip flexors and hip abductors) and self-directed in-home exercise program (exercises for the trunk, leg flexors, leg extensors and hip abductors at an intensity thought to be insufficient to achieve a training effect)	Open RCT		x				1 set at 40%, 1 set at 50%, 1 set at 60%. Porgression: when able to perform 10 repetitions in 3º set, with good form and speed of movement, an increase of 5% 1 RM.	45 min: 3 sets of 8 repetitions	2x/week	Changes in peak power of four leg muscle groups	12 weeks
Poliakoff et al. (2013) (61)	Gym training programme (cardiovascular activity, including treadmill, recumbent bikes, bikes, cross trainers and rowers) or Studio exercise program (gait and agility and some cardiovascular exercise)	Delayed start trial	x					Unk	120 min: 60 min in the training in the studio and 60 min in the gym	2x/week	Changes in motor function	20 weeks
Ridgel et al. (2009) (89)	Forced (stationary tandem bicycle) or voluntary (stationary single bicycle pedaling at their preferred voluntary rate) exercise intervention	Open RCT	x					60%-80% of the individualized target HR. Progression: increases of 5% HR every 2 weeks	60 min: 10-min warm-up, a 40-min exercise set, and a 10-min cool- down	3x/week	Changes in motor function	8 weeks
Romenets etal. (2015) (93)	Partnered tango classes	Open RCT					x	Unk	60 min	2x/week	Changes in overall motor severity	12 weeks

Studies (cont)	Description	Study Design	Type of exercise					Intensity	Duration of exercise	Frequency	Primary Outocome	Duration of intervention
			Aerobic traning	Resistance training	Flexibiity training	Balance training	Multimodal training					
Sage et al. (2009) (65)	Lower-limb aerobic program (Bio-Step Semi-Recumbent Ellipticals - the machine was primarily leg driven with the arms moving in a coordinated pattern similar to walking) or PD SAFEx program (nonaerobic gait exercises and sensory attention exercises)	Single-blinded RCT	x					Lower-limb aerobic intervention: 60–75% Hrmax and RPE < 5	Lower-limb aerobic intervention: 5 min of warm-up, 20 min of aerobic training, and 5 min of cool-down. PD SAFEx program: 20–30 min of nonaerobic gait exercises focused on body coordination and 20–30 min of sensory attention exercises utilizing latex Thera-bands attached to the arm rests of standard office chairs	3x/week	Changes in UPDRS Part-III	12 weeks
Schenkman et al. (2012) (62)	Flexibility/balance/function exercise program (individualized spinal and extremity flexibility exercises followed by group balance/functional training) or supervised aerobic exercise (using a treadmill, bike, or elliptical trainer) or home-based exercise (using the National Parkinson Foundation Fitness Counts program, with 1 supervised, clinic-based group session/month)	Single-blinded RCT					x	Supervised aerobic exercise: 65% to 80% of Hrmax	Aerobic exercise: 5 to 10 min of warm-up, 30 min of aerobic exercise, and 5 to 10 min of cool-down.	3x/week	Changes in physical function, balance and walking economy	16 weeks
Sage et al. (2009) (65)	Lower-limb aerobic program (Bio-Step Semi-Recumbent Ellipticals - the machine was primarily leg driven with the arms moving in a coordinated pattern similar to walking) or PD SAFEx program (nonaerobic gait exercises and sensory attention exercises)	Single-blinded RCT	x					Lower-limb aerobic intervention: 60–75% Hrmax and RPE < 5	Lower-limb aerobic intervention: 5 min of warm-up, 20 min of aerobic training, and 5 min of cool-down. PD SAFEx program: 20–30 min of	3x/week	Changes in UPDRS Part-III	12 weeks

									nonaerobic gait exercises focused on body coordination and 20–30 min of sensory attention exercises utilizing latex Thera-bands attached to the arm rests of standard office chairs			
Schilling et al. (2010) (63)	Resistance training intervention	Open RCT		x				When 8 repetitions could be completed for all 3 sets, the weight was increased 5%–10%	3 sets of 5–8 repetitions	2x/week	Changes in strength and function	8 weeks
Schlenstedt et al. (2015) (76)	Resistance training or balance training	Single-blinded RCT		x		x		Unk	60 min: 10 min to warm-up followed by 50 min resistance or balane training. Resistance training: 3 sets of 15–20 repetitions to volitional fatigue of each exercise. Balance exercises: Each exercise lasted for 45 sec and was performed 3 times, followed by a break of 2 min.	2x/week	Changes in Fullerton Advanced Balance scale	7 weeks
Schmitz-Hübsch et al. (2006) (71)	Qigong exercise (low-energy exercises with sustained movements of limbs, trunk, face, and tongue as well as breathing coordination)	Single-blinded RCT					x	Low-intensity	60 min	1x/week	Changes in UPDRS Part-III	16 weeks

Studies (cont)	Description	Study Design	Type of exercise					Intensity	Duration of exercise	Frequency	Primary Outocome	Duration of intervention
			Aerobic traning	Resistance training	Flexibiity training	Balance training	Multimodal training					
Shulman et al. (2015) (83)	Higher-intensity treadmill exercise or lower-intensity treadmill exercise or stretching and resistance exercises	Single-blinded RCT	x	x				High-intensity: 70%-80% of HRR; low-intensity: 40%-50% of HRR	High-intensity: 30 min; low-intensity: 50 min; stretching and resistance exercises: 2 sets of 10 repetitions on each leg on 3 resistance machines	3x/week	Changes in 6-minute walk, VO2 and 1RM	12 weeks
Stuckenschneider et al. (2015) (64)	Active forced exercise training or in-home passive forced exercise training	Open RCT	x					Starting intensity: 30 rounds/min.Progression: 30%, with a maximum of 90 rounds/min.	40 min: 5-min warm-up phase with a successive increase of cadence, a main phase of 30 min at training cadence and a 5-min cool-down phase with a successive reduction of cadence	3x/week	Change in UPDRS Part-III	12 weeks
Yang et al. (2010) (84)	Downhill walking training or conventional therapy (flexibility exercises, strengthening exercises, proprioceptive neuromuscular facilitation, coordination training, balance training, and overground walking training)	Open RCT	x				x	Initially, the downhill grade was set at 3%. Progression: 1% per training session.	30 min	3x/week	Changes in gait, thoracic kyphosis, and muscle strength	4 weeks
Zang et al. (2015) (70)	Tai Chi (Yang style 24-posture short-form) or the multimodal exercise training group (core muscle training,crossing obstacle training, standing on ankle joint correcting board, and cycle ergometer)	Open RCT					x	Unk	60 min	2x/week	Changes in the Berg Balance Scale	12 weeks