UNIVERSIDADE FEDERAL DO PARÁ – UFPA
CAMPUS UNIVERSITÁRIO DE CASTANHAL
FACULDADE DE EDUCAÇÃO FÍSICA

Brena Ester Silva Miranda

EFICÁCIA DO EXERCÍCIO FÍSICO NOS SINTOMAS MOTORES E RISCO DE QUEDAS EM PESSOAS COM DOENÇA DE PARKINSON: UM PROTOCOLO DE REVISÃO SISTEMÁTICA COM METANÁLISE DE REDE

Castanhal - Pará

2022

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Trabalho de Conclusão de Curso apresentado a Universidade Federal do Pará, como requisito parcial para obtenção do título de Licenciatura em Educação Física.

Orientadora: Profª. Drª Elren Passos-Monteiro

Castanhal

2022

UNIVERSIDADE FEDERAL DO PARÁ
FACULDADE DE EDUCAÇÃO FÍSICA

A comissão examinadora, abaixo, aprova/reprova o trabalho de conclusão de curso:

EFICÁCIA DO EXERCÍCIO FÍSICO NOS SINTOMAS MOTORES E RISCO DE QUEDAS EM PESSOAS COM DOENÇA DE PARKINSON: UM PROTOCOLO DE REVISÃO SISTEMÁTICA COM METANÁLISE DE REDE

Elaborado por

BRENA ESTER SILVA MIRANDA

Orientado por

PROFESSORA DOUTORA ELREN PASSOS-MONTEIRO

Como requisito parcial para obtenção de título de Licenciatura Plena em Educação Física.

Aprovado/Reprovado com conceito:

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Castanhal – PA

2022

DEDICATÓRIA

Dedico essa pesquisa a minha orientadora Elren Passos-Monteiro, por ter desempenhado tal função com dedicação e amizade.

AGRADECIMENTOS

A finalização dessa etapa do Trabalho de Conclusão de Curso consiste em sentimentos de alegria e dever cumprido, sou grata a todas as experiências vividas no Campus Castanhal da Universidade Federal do Pará da Faculdade de Educação Física, foram anos de ensinamentos, dedicação e descobertas que proporcionam o desenvolvimento da minha formação em Educação Física.

Agradeço a minha orientadora Elren Passos-Monteiro pela oportunidade de participar do grupo de pesquisa PENDULUM como bolsista de extensão, me proporcionando muito aprendizado e o direcionamento para área tema do meu TCC, professora agradeço por toda sua dedicação desempenhada a mim para o desenvolvimento desse estudo e todas as orientações online e presenciais disponibilizadas durante esse período, que foram essenciais para a pesquisa, você foi muito além do seu papel de professora, foi amiga e família na Universidade Federal do Pará.

Agradeço ao apoio logístico e intelectual do grupo de pesquisa PENDULUM, onde todos os membros tiveram um papel essencial para os meus estudos. As reuniões semanais, apresentações e discussões de diversos artigos e conceitos envolvendo Doença de Parkinson, Dança, Caminhada Nórdica e Treinamentos Aeróbios foram de suma importância para a construção dessa pesquisa.

A todos professores, os quais tive oportunidade de ser aluna durante esse período de graduação, agradeço todas as correções, ensinamentos e conselhos, guiando o meu aprendizado e me permitindo apresentar um melhor desempenho no meu processo de formação profissional ao longo do curso.

RESUMO

Introdução: A prática regular de exercícios físicos em pessoas com Parkinson (PcP) é benéfica para reduzir a velocidade da progressão dos sintomas motores e não motores. Entretanto, ainda não há evidências sobre qual o exercício físico é mais efetivo para os sintomas motores e risco de quedas nesta população. **Objetivo:** O objetivo do presente estudo, é apresentar a publicação do Protocolo de Revisão Sistemática com Metanálise em Rede, que tem por propósito identificar o tipo de exercício mais eficaz para os sintomas motores da doença de Parkinson (DP). **Métodos:** O presente estudo é estruturado em três partes, as quais consistem em uma parte composta por uma introdução, escrita na língua Portuguesa, e abrange o conceito geral sobre a DP, descrição dos sintomas motores da doença, e a relação benéfica da prática de exercícios físicos e pessoas com Parkinson (PcP). Dando continuidade, o trabalho apresenta os Procedimentos Metodológicos do Protocolo de Revisão Sistemática com Metanálise em Rede em sua versão extensa na língua inglesa. Seguido pela apresentação do Resultado Final do Protocolo de Revisão Sistemática com Metanálise em Rede publicado na base PROSPERO. E por fim consiste o desenvolvimento das considerações finais e indicações futuras para os próximos estudos, descrito na língua Portuguesa

Palavravas – Chave: Doença de Parkinson; Exercício; Protocolo; Sintomas Motores; Risco de quedas.

ABSTRACT

Introduction: Regular exercise in people with Parkinson's disease (PwP) is beneficial in reducing the speed of progression of motor and non-motor symptoms. However, there is still no evidence on which exercise is more effective for motor symptoms and risk of falls in this population. **Objective:** The purpose of this study, is to present the publication of the Systematic Review Protocol with Network Meta-Analysis, which aims to identify the most effective type of exercise for the motor symptoms of Parkinson's disease (PD). **Methods:** The present study is structured in three topics, described below: Topic 1 consists of an introduction, written in Portuguese, and covers the general concept about PD, description of the motor symptoms of the disease, and the beneficial relationship of physical exercise and people with Parkinson's disease (PwP). Next, topic 2 presents the Methodological Procedures of the Systematic Review with Network Meta-Analysis Protocol in its extended English version. Followed by topic 3, which covers the Final Result of the Systematic Review Protocol with Network Meta-analysis published in the PROSPERO database. And finally, topic 4, described in Portuguese, consists of the final considerations and future indications for further studies.

Keywords: Parkinson’s Disease; Exercise; Protocol; Motor Symptoms; Risk of Falls.

LISTA DE ABREVEATURAS E SIGLAS

Português

B.E.S.M	Brena Ester Silva Miranda
DP	Doença de Parkinson
I.C.G	Igor Conterato Gomes
PcP	Pessoa com Parkinson
TCC	Trabalho de Conclusão de Curso
UFPA	Universidade Federal do Pará

Inglês

CENTRAL	*Cochrane Central Register of Controlled Trials*
CI	*Confidence Interval*
DIC	*Deviance Information Criterion*
DM	*Differences in Means*
IBECS	*Índice Bibliográfico Español de Ciencias de la Salud*
ICr – 95%	*Credibility Intervals for 95%*
LILACS	*Latin American and Caribbean Health Science Information Database*
MD	*Mean Difference*
PD	*Parkinson's Disease*
PROSPERO	*International Prospective Register of Systematic Reviews*
ROB2	*Version 2 of the Cochrane risk-of-bias tool for randomized trials*
RR	*Risk Rates*
SMD	*Standardized Mean Difference*
UPDRS	*Unified Parkinson's Disease Assessment Scale*

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1. APRESENTAÇÃO DO TRABALHO DE CONCLUSÃO DE CURSO

O presente estudo é referente ao Trabalho de Conclusão de Curso (TCC) da graduação em Licenciatura Educação Física da Universidade Federal do Pará (UFPA), com orientação da Professora Elren Passos-Monteiro. Este trabalho foi desenvolvido com apoio logístico e Intelectual do Grupo de Pesquisa em Fisiomecânica da Locomoção e Reabilitação Neurofuncional, PENDULUM – UFPA, e apresenta um protocolo de revisão sistemática com metanálise em rede, publicado na plataforma *International Prospective Register of Systematic Reviews* (PROSPERO), uma base de registros de protocolos de revisões sistemáticas mantida pelo *Centre for Reviews and Dissemination*, da Universidade de York. Esse protocolo tem como autores Brena Ester Silva Miranda, Igor Conterato Gomes, Vagner Deuel Tavares, Nelson Carvas Júnior e Elren Passos-Monteiro.

Esse estudo teve como motivação o contato com o grupo de pesquisa PENDULUM, do qual fui bolsista de extensão, e pesquisa a estudos relacionados a DP e as avaliações para pessoas com Parkinson (PcP). A partir do contato com as avaliações e estudos utilizados no projeto, surgiram alguns questionamentos acerca de qual tipo de exercício físico seria mais eficaz para os sintomas motores da DP e o risco de queda nesta população. No primeiro momento, a pesquisa seria realizada com algumas modalidades de exercício físico, mais específicas como a Caminhada Nórdica, a dança e o treinamento aeróbio, as quais seriam desenvolvidas no projeto de Extensão para Pessoas com Parkinson, no Campus Universitário de Castanhal, na Faculdade de Educação Física. No entanto, em função da pandemia da COVID-19, não foi possível realizar a pesquisa experimental, e criação e publicação do Protocolo de Revisão Sistemática com Metanálise de Rede foi uma possibilidade viável de conseguirmos responder à pergunta de pesquisa em questão de acordo com os parâmetros e objetivos do estudo.

2. INTRODUÇÃO

A doença de Parkinson (DP) é uma doença neurodegenerativa que provoca a morte dos neurónios dopaminérgicos na substância *nigra* localizada no mesencéfalo (BEITZ., 2014). A redução da produção dopaminérgica nos Núcleos da Base provoca desordens do movimento que se caracterizam por sintomas motores clássicos da doença de Parkinson (POEWE, et al., 2017).

Dez por cento dos diagnósticos da DP ocorrem até os 45 anos de idade, entretanto, com o crescente aumento da expectativa de vida, cresce a prevalência e a incidência de novos casos de forma exponencial, principalmente a partir dos 60 anos. E atualmente é considerado como uma pandemia (ZINGMOND e SMEYNE, 2014; MARRAS et al., 2018). Relacionado principalmente ao envelhecimento é provável que os números de diagnósticos da DP cheguem a 12 milhões em 2040, contudo esse número tem potencial para chegar a 17 milhões em função do aumento dos índices de tabagismo e da industrialização alimentícia (DORSEY, et al., 2018).

Considerando os sinais clínicos da doença, existem múltiplos sintomas da DP, classificados em não-motores, que muitas vezes são apresentados antes do diagnóstico, e os motores (GRANZIERA, et al., 2020). Os principais sintomas motores são: tremor, rigidez, bradicinesia e instabilidade postural, considerados cardinais. A instabilidade postural e as quedas são características complexas e incapacitantes da DP, ocorrem com frequência e têm velocidade de progressão rápida (OPARA, et al., 2017).

A prática regular de exercícios físicos em pessoas com Parkinson (PcP) é benéfica para reduzir a velocidade da progressão dos sintomas motores e não motores (FENG, et al., 2020). Uma revisão sistemática mostrou que exercícios que envolvem equilíbrio, melhoram a instabilidade postural, o equilíbrio, e consequentemente, reduzem a taxa de quedas. E estes efeitos prolongam-se pelo menos até 12 meses após o final da intervenção. O mesmo estudo, apresenta que o Tai Chi realizado durante 6 meses, a terapia de dança durante 12 meses e o treino resistido progressivo durante 24 meses alivia os sintomas motores da DP, sugerindo que estas modalidades de exercícios podem desacelerar a progressão da doença (MAK e WONG-YU., 2019).

Outra modalidade de exercício que tem sido bastante investigada para melhora clínica de PcP é o treinamento de força, seja com maquinas, peso corporal e com uso de elásticos (BARBALHO et al, 2019). Por exemplo um treinamento progressivo praticado durante 9 meses pode reduzir a bradicinesia e melhorar o desempenho funcional em pessoas com DP (VIEIRA

DE MORAES FILHO, et al., 2020). Mesmo quando o treinamento de força acontece em doses mínimas semanais, observa-se um incremento na força, na velocidade da marcha, e na mobilidade funcional (BARBALHO et al., 2019). Práticas de intervenções complementares, tais como a dança, artes maciais, caminhada nórdica, treinamento de marcha, melhoram os sintomas motores da DP (MONTEIRO et al., 2016; FRANZONI et al., 2018; RADDER, et al., 2020).

Diante do exposto, PcP devem ser incentivadas a manterem-se ativas, através da prática de exercícios físicos. Entretanto, embora a literatura apresente os benefícios do exercício físico na melhora de parâmetros clínicos da DP, ainda não há evidências sobre qual o exercício físico é mais efetivo para os sintomas motores e risco de quedas nesta população. Neste sentido, há uma necessidade contundente de avaliar a eficácia das intervenções de exercício para melhorar os sintomas motores, a estabilidade postural e diminuir o índice de quedas na população com DP. Portanto, o objetivo do presente estudo consiste em apresentar o protocolo de revisão sistemática com metanálise em rede, publicado na plataforma PROSPERO.

3. RESULTADO: PROTOCOLO NA FORMA EXTENSA E NA LÍNGUA INGLESA

Background

Symptoms of Parkinson's Disease (PD) are classified as motor and non-motor symptoms, and motor symptoms are tremor, stiffness, bradykinesia and postural instability (OPARA, et al., 2017). Among these, postural instability may promote falls, that are complex characteristics and closely linked to immobility and functional disability in people with PD. Also, besides occurring frequently and having rapid rate of progression (POEWE, et al., 2017). Therefore, it is necessary to search for effective pharmacological and non-pharmacological therapies to reduce the symptoms and their consequences of PD. Therefore, non-pharmacological therapies, physical exercise are most used to improve motor symptoms and postural stability, and consequently reduce the incidence of falls in the patients with PD (SHEN, WONG-YU and MAK., 2015).

The practice of exercises involving static and dynamic balance may reduce the risk of falls, and these effects are prolonged for at least 12 months after the end of the training period (FENG, et al., 2020). In addition to balance training, can be utilized some modalities, such as Tai Chi, dance therapy, nordic walking, martial arts and progressive resistance training. For this reason, they are able to attenuate the motor symptoms of PD, suggesting that they can slow disease progression (MAK and WONG-YU., 2019; RADDER, et al., 2020).

Thus, it is understood that people with PD should be encouraged to remain active, performing the practice of physical exercises, so that they can attenuate symptoms, improve quality of life. Although the literature already presents the benefits of physical exercise in improving clinical PD parameters, to date, there is no evidence on the most effective physical exercise for motor symptoms and risk of falls in this population. In this way, the aim of this study is to evaluate and quantify systematically the rank to best intervention with physical exercises to reduce motor symptoms and the risk of falls in people with PD.

Methods

Criteria for considering studies for this review

Type of studies

Studies that have been randomized clinical trials (including parallel-group design, within-person design, cluster design or the first phase of cross-over trials), evaluated and

compared exercises or training programs for Parkinson's disease. We will exclude non-randomized clinical trials, cohort studies, control cases, case reports, systematic review and meta-analyses studies. There will be no language restriction for studies and without data restrictions.

Study of participants

Articles were eligible for inclusion if they met the following criteria: 1) participants over 40 years of age (40 to 59 years; 60 to 74 years; over 75 years) diagnosed with Idiopathic Parkinson's disease will be included; 2) The classification of the disease stage from the Hoehn and Yahr scales should ranging scores from 1 to 4, to at least 1 year of the time of diagnosis of the disease; 3) Studies in which participants have experience and practice with any type or modality of physical exercise when compared non-exercise; 4) evaluation of the effects of exercises on the reduction of motor symptoms, assessed by the Unified Parkinson's Disease Assessment Scale (UPDRS), number of falls (risk of falls or fear of falling) and functional mobility.

Type of interventions

Randomized clinical trial studies with all types of exercises will be included. Aerobic resistance exercises (e.g., walking, water aerobics, swimming and running); muscle endurance exercises (e.g., strength exercises, functional training, cross-fit); flexibility exercises (e.g., stretching, yoga); multimodal or multi-component exercises (e.g., Tai Chi Chuan), dance and speed exercises (e.g., sprints or running).

Type of outcome measures

Primary outcomes

Reduction of motor symptoms measured for UPDRS scale: (https://www.movementdisorders.org/MDS-Files1/Education/Rating-Scales/MDS-UPDRS_Portuguese_Official_Translation_FINAL.pdf)

1 - Improvement muscle stiffness;

2 - Decreased bradykinesia;

3 - Reduction of freezing occurrence;

4 - Improves balance;

5 - Adverse Events.

Secondary outcomes

1 - Reduction of risk and number of falls;

2- Increased functional mobility.

Search methods for identification of studies

Electronic searches

A search will be carried out using the following electronic databases:

- LILACS (Latin American and Caribbean Health Science Information Database);
- IBECS (Índice Bibliográfico Español de Ciencias de la Salud);
- MEDLINE via PUBMED (1966 to present);
- EMBASE via Elsevier (1974 to present);
- CENTRAL (Cochrane Central Register of Controlled Trials) in the Cochrane Library (2020).

Additional research will be added for potential randomized clinical trials on online platforms as follows:

- https://www.clinicaltrials.gov/ (United States National Library of Medicine);
- https://www.who.int/ictrp/en/ (International Clinical Trials Registry Platform - World Health Organization);
- Rebec

Searching other resources

The search for tests will be performed using a list of references of the studies included in the second selection phase.

Data extraction and management

Two reviewers (B.E.S.M. and I.C.G.) will track titles and abstracts after the removal of duplicates and identify potentially eligible studies according to our eligibility criteria from the defined databases. In the event of a conflict between the decisions, we will resolve them by consensus with a third reviewer. After this phase, we will acquire the full text and evaluate once again the eligibility of these trials for inclusion:

P= Parkinson’s Disease;

I = Exercise;

C = Exercise;

O = Reduction of motor symptoms;

S = Randomized Clinical Trials.

If necessary, we will contact the authors of the studies for more information. Finally, we will merge published reports from the same study.

Assessment of risk of bias in included studies

The risk of bias will be assessed by two reviewers (B.E.S.M and I.C.G), this assessment will be made according to the recommendations of the Cochrane Manual for systematic reviews of interventions. Version 2 of the Cochrane Bias Risk Assessment (RoB2) tool will be used. Any disagreement will be resolved by consensus and the following definitions will be used to assess the risk of bias: bias resulting from the randomization process; bias due to deviations from the intende d interventions; bias due to lack of result data; bias in measuring the result; and bias in the selection of the result. Within each domain composed of the series of signaling questions, one of the five answer options offered by the RoB2 tool ("Yes", "Probably Yes", "Probably No", "No" and "No Information") will be provided assigning one of the three levels to the judgment and risk of bias "Low risk of bias", "Some concerns" or "High risk of bias", according to the result of the algorithm. The less favorable assessment in all domains will serve for the general analysis of bias risk for each result.

Measures of treatment effect

The continuous primary results (e.g., UPDRS scores), we will measure the mean difference (DM) with a 95% confidence interval (CI). First, when the study no provide data on the same scale, the standardized mean difference (SMD), there were used. Second, for dichotomous primary results (e.g., adverse events), we will calculate risk rates (RR) with 95% CI. For all secondary results, we will measure the mean difference (MD) with a 95% confidence interval (CI) if all recovered records provide data of the same scale, and as a standardized mean difference (MDS) if different scales were used during reporting.

Unit of analysis issues

We will consider individuals as a unit of analysis for the design of parallel groups and the first phase of cross-over studies, to minimize the carry-over effect. Multiple-arm studies will extract data related to exercise to perform network meta-analyses.

Assessment of heterogeneity

Statistical heterogeneity will be evaluated using Cochran's Q test which will determine whether the heterogeneity of the evidence is true. The value limit considered will be $P<0.1$ as an indicator of the presence of heterogeneity. We will perform a test, examining the I^2 statistic, and will be interpreted as follows: <25% (low heterogeneity); 25% to 49% (low heterogeneity); 50% to 74% (moderate heterogeneity); ≥ 75% (high heterogeneity).

Assessment of reporting biases

If we obtain the inclusion of 10 or more clinical trials in the systematic review, the bias of publication in inspection funnel plot charts will be investigated, followed by the Egger Test.

Data synthesis

A Bayesian network meta-analysis will be performed using the "gemtc" version 0.8-8 package implemented in the R version 4.0 program for Mac iOS. The mtc.run function will be used to generate samples through Monte Carlo simulations in Markov Chains. We will start in 10.000 simulations for each chain as a "Burn-in" period. The convergence of the model will be evaluated using the Brooks-Gelman graphical methods.

Differences in means (DM) with credibility intervals for 95% (ICr-95%) calculated for each comparison pair. Additionally, the probability rank will be calculated.

Random effects and fixed-effect models will be conducted, but the choice of the most parsimonious model will be made using the deviance information criterion (DIC), giving preference to the model that presents the lowest DIC (a difference of 3 between the DICs of the models showed that the smaller one is more parsimonious). We will also evaluate the incoherence between direct and indirect evidence by the node splitting method.

Geometric network

The network graph will be built to describe and show the geometry of the network of treatment comparations between studies to ensure that it will be a feasible network meta-analysis. Trials that are not connected by treatments will be excluded from the analysis. The

size of the nodes and the thickness of the lines will be associated with the sample sizes in the interventions and the number of studies between the differences.

We will categorize the nodes of the network as follows: aerobic exercises (walking, water aerobics, swimming, running, and nordic walking); muscle resistance exercises (e.g., strength exercises, functional training, bodyweight exercises, elastic, thera band exercises, cross-fit); flexibility exercises; multimodal or multi-component exercises; balance exercises and dance.

For the publication bias, we will use a funnel plot adjusted for multiple comparisons on package "netmeta" to investigating if there is effect of small samples on the network. (LU and ADES., 2004).

Publication Bias

To evaluate publication bias, we will build a funnel graph adjusted for comparisons with the "netmeta" package version 1.3-0 implemented in R version 4.0 for Mac IOS in order to investigate whether there is an effect of small samples on the network.

Certainty of evidence

Two trained methodologists will use the GRADE structure to assess the certainty of the evidence and classify it as high, moderate, low, or very low. The starting point of clinical trials is high but can be reduced down based on limitations of the risk of bias, inconsistency, presence of indirect evidence, and publication bias. We will grade the certainty of the evidence of each comparison according to the recommendations already established (BRIGNARDELLO-PETERSEN, et al., 2019).

Subgroup analysis and investigation of heterogeneity

If possible, we intend to perform a subgroup analysis in case of heterogeneity considering the following variables:

Sensitivity analysis

The following sensitivity analyses will be performed, if possible:

• Influence of unpublished studies, excluding summaries-only trials;

• Influence of sponsorship by excluding industry-funded studies;

• Effects of the risk of bias, excluding studies with high or uncertain risk of bias.

4. RESULTADO FINAL DO PROTOCOLO PUBLICADO NA BASE PROSPERO

A partir desse momento, iremos apresentar neste tópico o resultado deste Trabalho de Conclusão de Curso que consiste na publicação do Protocolo de Revisão Sistemática com Metanálise em Rede, publicado na base PROSPERO e pode ser acessado pelo seu número de registro **CRD42021238358** e pelo link a seguir:

https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=238358

Systematic review

This record cannot be edited because it has been marked as out of scope

Please select one of the options below to edit your record. Either option will create a new version of the record - the existing version will remain unchanged.

1. * Review title.

Give the title of the review in English

Physical exercise on parkinson disease: a systematic review and network meta-analysis protocol

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

Exercício físico na Doença de Parkinson: um protocolo de revisão sistemática e meta-análise de rede

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

04/01/2021

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

01/02/2022

5. * Stage of review at time of this submission.

This field uses answers to initial screening questions. It cannot be edited until after registration.

Tick the boxes to show which review tasks have been started and which have been completed.

Update this field each time any amendments are made to a published record.

The review has not yet started: Yes

Review stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

The review has not yet started: No
The review has not yet started: No

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Elren Passos-Monteiro

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:
Dr Passos-Monteiro

7. * Named contact email.

Give the electronic email address of the named contact.

elren.monteiro@ufpa.br

8. Named contact address

PLEASE NOTE this information will be published in the PROSPERO record so please do not enter private information, i.e. personal home address

Give the full institutional/organisational postal address for the named contact.

Av. dos Universitários - Jaderlandia, CEP: 68746-360
Castanhal - PA

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+55 91 984801027

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

UFPA

Organisation web address:
https://www.portal.ufpa.br/

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.
NOTE: email and country now MUST be entered for each person, unless you are amending a published record.

Dr Elren Passos-Monteiro. Federal University of Pará (UFPA)
Miss Brena Ester Miranda. Federal University of Pará (UFPA)
Dr Igor Conterato Gomes. Shchool of public health - University of São Paulo
Mr Nelson Carvas Júnior. Evidence-Based Health Program, Universidade Federal de São Paulo
Mr Vagner Deuel Tavares. Federal University of Rio Grande do Norte

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

None

Grant number(s)
State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

Dr Elren Passos-Monteiro. Federal University of Pará (UFPA)

Miss Brena Ester Miranda. Federal University of Pará (UFPA)

Dr Igor Conterato Gomes. Shchool of public health - University of São Paulo

Mr Nelson Carvas Júnior. Evidence-Based Health Program, Universidade Federal de São Paulo

Mr Vagner Deuel Tavares. Federal University of Rio Grande do Norte

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

Whats the rank to best intervention with physical exercises to reduce motor symptoms and the risk of falls in people with PD?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

The sources to be searched are:
- LILACS (Latin American and Caribbean Health Science Information Database);
- IBECS (Índice Bibliográfico Español de Ciencias de la Salud);
- MEDLINE via PubMed;
- EMBASE via Elsevier;
- CENTRAL (Cochrane Central Register of Controlled Trials) in the Cochrane Library (2020).

The surveys will be carried out in April (2021), with no publication date limitations. Research published in all languages will be accepted.

Additional research will be added for potential randomized clinical trials on online platforms as follows:
- https://www.ClinicalTrials.gov/ (United States National Library of Medicine);
- https://www.who.int/ictrp/en/ (International Clinical Trials Registry Platform - World Health Organization);
- Rebec

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible.

Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

https://www.crd.york.ac.uk/PROSPEROFILES/238358_STRATEGY_20210220.pdf

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Articles were eligible for inclusion if they met the following criteria: 1) participants over 40 years of age (40 to 59 years; 60 to 74 years; over 75 years) diagnosed with Idiopathic Parkinson's disease will be included; 2) The classification of the disease stage from the Hoehn and Yahr scales should ranging scores from 1 to 4, to at least 1 year of the time of diagnosis of the disease; 3) Studies in which participants have experience and practice with any type or modality of physical exercise when compared non-exercise; 4) evaluation of the effects of exercises on the reduction of motor symptoms, assessed by the Unified Parkinson's Disease Assessment Scale (UPDRS), number of falls (risk of falls or fear of falling) and functional mobility.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Articles were eligible for inclusion if they met the following criteria: 1) participants over 40 years of age (40 to 59 years; 60 to 74 years; over 75 years) diagnosed with Idiopathic Parkinson's disease will be included; 2) The classification of the disease stage from the Hoehn and Yahr scales should ranging scores from 1 to 4, to at least 1 year of the time of diagnosis of the disease; 3) Studies in which participants have experience and practice with any type or modality of physical exercise when compared non-exercise; 4) evaluation of the effects of exercises on the reduction of motor symptoms, assessed by the Unified Parkinson's Disease Assessment Scale (UPDRS), number of falls (risk of falls or fear of falling) and functional mobility.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Randomized clinical trial studies with all types of exercises will be included. Aerobic resistance exercises (e.g., walking, water aerobics, swimming and running); muscle endurance exercises (e.g., strength exercises, functional training, cross-fit); flexibility exercises (e.g. stretching, yoga); multimodal or multi-component exercises (e.g. Tai Chi Chuan), dance and speed exercises (e.g. sprints or running).

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

another intervention of exercise

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

Studies that have been randomized clinical trials (including parallel-group design, within-person design, cluster design or the first phase of cross-over trials), evaluated and compared exercises or training programs for Parkinson's disease. We will exclude non-randomized clinical trials, cohort studies, control cases, case reports, systematic review and meta-analyses studies. There will be no language restriction for studies and without data restrictions.

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

Symptoms of Parkinson's Disease (PD) are classified as motor and non-motor symptoms. The motor symptoms are known as tremor, stiffness, bradykinesia, and postural instability. Among these, postural instability may promote falls, that are complex characteristics and closely linked to immobility, including functional disability in people with PD. Also, besides occurring frequently and having a rapid rate of progression. Therefore, it is necessary to search for effective pharmacological and non-pharmacological therapies to reduce the symptoms and their consequences of PD. Non-pharmacological therapies, physical exercise are most used to improve motor symptoms and postural stability, and consequently, reduce the incidence of falls in patients with PD. The practice of exercises involving static and dynamic balance may reduce the risk of falls, and these effects are prolonged for at least 12 months after the end of the training period. In addition to balance training, can be utilized some modalities, suggesting that they can slow disease progression. Although the literature showed the benefits of physical exercise in improving clinical PD parameters, to date, there is no evidence on the most effective physical exercise for motor symptoms and risk of falls in this population. In this way, the aim of this study is to evaluate and quantify systematically the rank to best intervention with physical exercises to reduce motor symptoms and the risk of falls in people with PD.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Primary outcomes
Reduction of motor symptoms measured for UPDRS scale: (https://www.movementdisorders.org/MDS-Files1/Education/Rating-Scales/MDS-UPDRS_Portuguese_Official_Translation_FINAL.pdf)

1 - Improvement muscle stiffness;
2 - Decreased bradykinesia;
3 - Reduction of freezing occurrence;
4 - Improves balance;
5 - Adverse Events.

Measures of effect
The continuous primary results (e.g., UPDRS scores), we will measure the mean difference (DM) with a 95% confidence interval (CI). First, when the study no provide data on the same scale, the standardized mean difference (SMD), there were used. Second, for dichotomous primary results (e.g., adverse events), we will calculate risk rates (RR) with 95% CI. For all secondary results, we will measure the mean difference (MD) with a 95% confidence interval (CI) if all recovered records provide data of the same scale, and as a standardized mean difference (MDS) if different scales were used during reporting.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

Secondary outcomes
1 - Reduction of risk and number of falls;
2- Increased functional mobility.

Measures of effect
The continuous primary results (e.g., UPDRS scores), we will measure the mean difference (DM) with a 95% confidence interval (CI). First, when the study no provides data on the same scale, the standardized mean difference (SMD), there were used. Second, for dichotomous primary results (e.g., adverse events), we will calculate risk rates (RR) with 95% CI. For all secondary results, we will measure the mean difference (MD) with a 95% confidence interval (CI) if all recovered records provide data of the same scale, and as a standardized mean difference (MDS) if different scales were used during reporting.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Two reviewers (B.E.S.M. and I.C.G.) will track titles and abstracts after the removal of duplicates and identify potentially eligible studies according to our eligibility criteria from the defined databases. In the event of a conflict between the decisions, we will resolve them by consensus with a third reviewer. After this phase, we will acquire the full text and evaluate once again the eligibility of these trials for inclusion:
P= Parkinson's Disease;
I = Exercise;
C = Exercise;
O = Reduction of motor symptoms;
S = Randomized Clinical Trials.

If necessary, we will contact the authors of the studies for more information. Finally, we will merge published reports from the same study.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

The risk of bias will be assessed by two reviewers (B.E.S.M and I.C.G), this assessment will be made according to the recommendations of the Cochrane Manual for systematic reviews of interventions. Version 2 of the Cochrane Bias Risk Assessment (RoB2) tool will be used. Any disagreement will be resolved by consensus and the following definitions will be used to assess the risk of bias: bias resulting from the randomization process; bias due to deviations from the intended interventions; bias due to lack of result data; bias in measuring the result; and bias in the selection of the result. Within each domain composed of the series of signaling questions, one of the five answer options offered by the RoB2 tool ("Yes", "Probably Yes", "Probably No", "No" and "No Information") will be provided assigning one of the three levels to the judgment and risk of bias "Low risk of bias", "Some concerns" or "High risk of bias", according to the result of the algorithm. The less favorable assessment in all domains will serve for the general analysis of bias risk for each result.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data.
If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

A Bayesian network meta-analysis will be performed using the "gemtc" version 0.8-8 package implemented in the R version 4.0 program for Mac iOS. The mtc.run function will be used to generate samples through Monte Carlo simulations in Markov Chains. We will start in 10.000 simulations for each chain as a "Burn-in" period. The convergence of the model will be evaluated using the Brooks-Gelman graphical methods.
Differences in means (DM) with credibility intervals for 95% (ICr-95%) calculated for each comparison pair. Additionally, the probability rank will be calculated.
Random effects and fixed-effect models will be conducted, but the choice of the most parsimonious model will be made using the deviance information criterion (DIC), giving preference to the model that presents the lowest DIC (a difference of 3 between the DICs of the models showed that the smaller one is more parsimonious).
We will also evaluate the incoherence between direct and indirect evidence by the node splitting method.
Geometric network
The network graph will be build to describe and show the geometry of the network of treatment comparations between studies to ensure that it will be a feasible network meta-analysis. Trials that are not connected by treatments will be excluded from the analysis. The size of the nodes and the thickness of the lines will be associated with the sample sizes in the interventions and the number of studies between the differences.
We will categorize the nodes of the network as follows: aerobic exercises (walking, water aerobics, swimming, running, and nordic walking); muscle resistance exercises (e.g., strength exercises, functional training, bodyweight exercises, elastic, thera band exercises, cross-fit); flexibility exercises; multimodal or multi-component exercises; balance exercises and dance.
For the publication bias, we will use a funnel plot adjusted for multiple comparisons on package "netmeta" to investigating if there is effect of small samples on the network.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

If possible, we intend to perform a subgroup analysis in case of heterogeneity considering the following variables:

Sensitivity analysis
The following sensitivity analyses will be performed, if possible:
• Influence of unpublished studies, excluding summaries-only trials;
• Influence of sponsorship by excluding industry-funded studies;
• Effects of the risk of bias, excluding studies with high or uncertain risk of bias.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness	No
Diagnostic	No

Epidemiologic	No
Individual patient data (IPD) meta-analysis	No
Intervention	Yes
Living systematic review	No
Meta-analysis	No
Methodology	No
Narrative synthesis	No
Network meta-analysis	Yes
Pre-clinical	No
Prevention	No
Prognostic	No
Prospective meta-analysis (PMA)	No
Review of reviews	No
Service delivery	No
Synthesis of qualitative studies	No
Systematic review	Yes
Other	No

Health area of the review

Alcohol/substance misuse/abuse	No
Blood and immune system	No
Cancer	No
Cardiovascular	No
Care of the elderly	Yes
Child health	No
Complementary therapies	No
COVID-19	No
Crime and justice	No
Dental	No
Digestive system	No

Ear, nose and throat	No
Education	No
Endocrine and metabolic disorders	No
Eye disorders	No
General interest	No
Genetics	No
Health inequalities/health equity	No
Infections and infestations	No
International development	No
Mental health and behavioural conditions	No
Musculoskeletal	No
Neurological	Yes
Nursing	No
Obstetrics and gynaecology	No
Oral health	No
Palliative care	No
Perioperative care	No
Physiotherapy	Yes
Pregnancy and childbirth	No
Public health (including social determinants of health)	No
Rehabilitation	Yes
Respiratory disorders	No
Service delivery	No
Skin disorders	No
Social care	No
Surgery	No
Tropical Medicine	No
Urological	No
Wounds, injuries and accidents	No

Violence and abuse	No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Brazil

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them.
If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

No I do not make this file publicly available until the review is complete

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Parkinson's disease
bradykinesia
freezing of gait
falls
motor symptoms
functional mobility

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

Don´t exist.

38. * Current review status.

Update review status when the review is completed and when it is published.
New registrations must be ongoing so this field is not editable for initial submission.

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

Certainty of evidence
Two trained methodologists will use the GRADE structure to assess the certainty of the evidence and classify it as high, moderate, low, or very low. The starting point of clinical trials is high but can be reduced down based on limitations of the risk of bias, inconsistency, presence of indirect evidence, and publication bias.

We will grade the certainty of the evidence of each comparison according to the recommendations already established.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission).
List authors, title and journal details preferably in Vancouver format.

Após a publicação do Protocolo de Revisão Sistemática com Metanálise em Rede foram desenvolvidas as estratégias de buscas e termos MeSH de duas bases de dados, descritas no quadro 1.

QUADRO 1. Estratégia de Busca que será realizada na Revisão Sistemática com Metanálise em Rede.

BASE DE DADOS	TERMOS MeSH
PUBMED	Symptomatic Parkinsonism OR Symptomatic Parkinson Disease OR Secondary Parkinson Disease OR Paralysis Agitans OR Primary Parkinsonism OR Lewy Body Parkinson Disease OR Parkinson Disease OR Idiopathic Parkinson's Disease OR Lewy Body Parkinson's Disease Idiopathic OR Parkinson's Disease OR Idiopathic Parkinson Disease Aerobic Exercise OR Isometric Exercise OR Acute Exercise OR Physical Exercises OR Physical Exercise OR Exercise OR Exercises OR Physical Activity OR Circuit-Based Exercise OR Exercise Therapy OR Remedial Exercise OR Exercise Therapies OR Rehabilitation Exercise OR Rehabilitation Exercises Muscle Stretching Exercises OR Muscle Stretching Exercise OR Static Stretching OR Passive Stretching OR Relaxed Stretching OR Static-Passive Stretching OR Static Passive Stretching OR OR Isometric Stretching OR Active Stretching OR Static-Active Stretching OR Static Active Stretching OR Ballistic Stretching OR Dynamic Stretching OR Proprioceptive Neuromuscular Facilitation OR Stretching High-Intensity Interval Training OR High Intensity Interval Training OR High-Intensity Interval Trainings OR High-Intensity Intermittent Exercise OR High-Intensity Intermittent Exercises OR Sprint Interval Training OR Sprint Interval Trainings Plyometric Exercise OR Exercises Plyometric OR Plyometric Drill OR Drills Plyometric OR Plyometric Training OR Plyometric Trainings OR Stretch-Shortening Exercise OR Exercises Stretch-Shortening OR Stretch Shortening Exercise OR Stretch-Shortening Exercises OR Stretch-Shortening Cycle Exercise OR Cycle Exercises Stretch-Shortening OR Exercise Stretch-Shortening Cycle OR Exercises Stretch-Shortening Cycle OR Stretch Shortening Cycle Exercise OR Stretch-Shortening Cycle Exercises OR Stretch-Shortening Drill OR Drills Stretch-Shortening OR Stretch Shortening Drill Dancing OR Ballet OR Square Dance OR Hip-Hop Dance OR Jazz Dance OR Tap Dance OR Modern Dance OR Salsa Dancing OR Line Dancing OR Dance Therapy OR Dance Therapies Resistance Training OR Strength Training OR Weight-Lifting Strengthening Program OR Strengthening Programs Weight-Lifting OR Weight-Lifting Strengthening Programs OR Weight-Lifting Exercise Program OR Exercise Programs, Weight-

	Lifting OR Weight-Bearing Strengthening Program OR Strengthening Programs Weight-Bearing OR Weight-Bearing Exercise Program OR Exercise Programs Weight-Bearing
BVS	(Symptomatic Parkinsonism OR Symptomatic Parkinson Disease OR Secondary Parkinson Disease OR Paralysis Agitans OR Primary Parkinsonism OR Lewy Body Parkinson Disease OR Parkinson Disease OR Idiopathic Parkinson's Disease OR Lewy Body Parkinson's Disease Idiopathic OR Parkinson's Disease OR Idiopathic Parkinson Disease) AND (Aerobic Exercise OR Isometric Exercise OR Acute Exercise OR Physical Exercises OR Physical Exercise OR Exercise OR Exercises OR Physical Activity OR Circuit-Based Exercise) OR (OR Exercise Therapy OR Remedial Exercise OR Exercise Therapies OR Rehabilitation Exercise OR Rehabilitation Exercises) OR (Muscle Stretching Exercises OR Muscle Stretching Exercise OR Static Stretching OR Passive Stretching OR Relaxed Stretching OR Static-Passive Stretching OR Static Passive Stretching OR OR Isometric Stretching OR Active Stretching OR Static-Active Stretching OR Static Active Stretching OR Ballistic Stretching OR Dynamic Stretching OR Proprioceptive Neuromuscular Facilitation OR Stretching) OR (High-Intensity Interval Training OR High Intensity Interval Training OR High-Intensity Interval Trainings OR High-Intensity Intermittent Exercise OR High-Intensity Intermittent Exercises OR Sprint Interval Training OR Sprint Interval Trainings) OR (Trainings Plyometric OR Stretch-Shortening Exercise OR Exercise Stretch-Shortening OR Exercises Stretch-Shortening OR Stretch Shortening Exercise OR Stretch-Shortening Exercises OR Stretch-Shortening Cycle Exercise OR Cycle Exercise Stretch-Shortening OR Cycle Exercises Stretch-Shortening OR Exercise Stretch-Shortening Cycle OR Exercises Stretch-Shortening Cycle OR Stretch Shortening Cycle Exercise OR Stretch-Shortening Cycle Exercises OR Stretch-Shortening Drill OR Drill Stretch-Shortening OR Drills Stretch-Shortening OR Stretch-Shortening OR DrillsTraining Plyometric OR Plyometric Trainings OR Plyometric Training OR Drills Plyometric OR Drill Plyometric OR Plyometric Drill OR Plyometric Exercises OR Plyometric Exercise OR Exercise Plyometric OR Exercises Plyometric)

5. CONSIDERAÇÕES FINAIS E INDICAÇÕES FUTURAS

Tendo em vista os aspectos apresentados, é possível afirmar que a DP é uma doença neurodegenerativa e incapacitante ao longo da progressão dos seus sintomas, classificados em não-motores, os quais muitas vezes aparecem antes do diagnóstico, e motores. Os principais

sintomas motores da DP são: tremor, rigidez, bradicinesia e instabilidade postural, os quais contribuem para o aumento do índice de quedas em PcP.

Compreende-se a partir de diversos estudos, que a prática de qualquer tipo de exercício físicos é benéfica para a desaceleração dos sintomas motores da DP e melhora da estabilidade postural, e assim consequentemente a redução do risco de quedas nessa população. Nesse sentido, nota-se a importância de apontar a partir da literatura o tipo de exercício mais eficaz para a redução dos sintomas motores da DP.

O protocolo de Revisão Sistemática com Metanálise em Rede, foi publicado na Plataforma PROSPERO, e encontra-se disponível ao público para consulta. As etapas seguintes deste Estudo serão referentes a produção e publicação da revisão sistemática com metanálise de rede.

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