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Effect of exercise on motor symptoms in patients with Parkinson's disease

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Journal of Geriatric Physical Therapy

Effect of exercise on motor symptoms in patients with Parkinson's Disease: a network meta-analysis.

--Manuscript Draft--

Manuscript Number:	JGPT-D-21-00011R1
Full Title:	Effect of exercise on motor symptoms in patients with Parkinson's Disease: a network meta-analysis.
Article Type:	Systematic Reviews
Keywords:	ageing, effectiveness, exercise rehabilitation
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	Ana I Torres-Costoso
	Malcolm Price
	Ruben Fernandez-Rodriguez
	Vicente Martinez-Vizcaino
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Manuscript Region of Origin:	SPAIN
Abstract:	I ntroduction: The pharmacological approach to motor symptoms in Parkinson's disease (PD) has not proven to be fully effective. Thus, for the treatment of PD motor symptoms, physical activity has been proposed as an effective intervention. Methods: A systematic search in MEDLINE, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials databases was conducted to identify randomized controlled trials testing the effectiveness of exercise interventions on motor symptoms of PD. Physical exercise interventions were divided into nine categories: endurance, resistance, combined, balance, dance, alternative exercises, body weight supported, sensorimotor interventions, including endurance exercise, and sensorimotor interventions, not including endurance exercise. A pairwise meta-analysis for direct and indirect comparisons between intervention and control/non-intervention groups was carried out. Results : Fifty-six studies met the inclusion criteria, including 2,740 participants, aged between 57.6 and 77.7 years.Results of our analyses showed that sensorimotor training, including endurance (effect size [ES]: -1.09; 95% CI: -1.68, -0.50), resistance (ES: -0.82; 95% CI:-1.23, -0.41), and dance (ES: -0.64; 95% CI: -1.24, -0.05) were the most effective physical activity interventions for mitigating PD motor symptoms. Conclusion: Physical activity interventions are an effective strategy for the management of motor symptoms in PD patients. Among the different exercise intervention programs, those including more complex and demanding activities,

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	(sensorimotor training, including endurance, resistance, and dance) seem to be the most effective physical activity interventions.
Response to Reviewers:	Dr. Dr. Kerstin Palombaro May 6, 2021 Associate Editor Journal of Geriatric Physical Therapy Enclosed you will find a revision of our manuscript: "Effect of exercise on motor symptoms in patients with Parkinson's Disease: a network meta-analysis." Manuscript ID: JGPT-D-21-00011 We would like to thank you for giving us the opportunity to revise and improve our manuscript; we also thank the reviewers for their thoughtful and constructive comments. We have considered all of the suggestions and incorporated them into the revised manuscript. Changes to the original manuscript are marked in red, and we believe our manuscript is stronger as result of these modifications. An itemized point-by-point response to the reviewers' comments is presented below. In addition, we have updated the literature search to provide the readers the most recent evidence. In order to ask the check list for re-submission requirements we would like to state that: This manuscript has not been published elsewhere and is not under consideration by another journal. All the authors have revised and approved the final version of the manuscript. The authors have no conflicts of interest to declare, and the funding sources h financial support have been properly described. Yours sincerely, Ivan Cavero Redondo Reviewer Comments: Associate Editor: Specific comment In your background section, I am in agreement with reviewer two regarding your presentation of pharmacology for PD. Perhaps in line 55-57 you might state something on the order of "Pharmacological interventions do not completely address motor symptoms of PD." Authors We would like to thank the Associate Editor's comment. We have modified the sentence as follows: "Background: Although the pharmacological approach may help with motor symptoms in Parkinson's disease (PD), they are clearly not the complete solution…." "Introduction: Pharmacological and surgical treatments may help in the management of PD symptoms, but they do not completely address motor symptoms of PD as it is an incurable and progressive neurodegenerative disease.3" Specific comment Please include a brief description of the types of exercise included in your paper. Authors We would like to thank the Associate Editor's comment. As suggested, we have included additional information on the types of exercises included in this paper. "Data synthesis and analysis. To perform the meta-analysis, physical exercise interventions were classified into nine categories: endurance (aimed at increasing heart rate and energy expenditure), resistance (aimed at increasing muscle strength and muscle power), combined (including only aerobic exercise and resistance training), stretching (aimed at increasing muscle's elasticity and achieve comfortable muscle tone), dance (interventions with target balance and complex gait tasks in coordination with music), balance (aimed at improving postural reactions, by the strengthening of muscles that help keep you upright), body weight-supported (aimed at maintain the lower-limb trajectories, while increasing the motor activation and motor function by reducing the patient's weight) alternative exercises ([Tai-Chi, Yoga, Qui-Gong, and Ai-Chi] understood as a modality of exercise that combines body movement, mental focus, and controlled breathing for improving strength, balance, and flexibility), and

sensorimotor training (aimed at improving the neuromuscular system by the emphasis on postural control and progressive challenges to the sensorimotor system, using aerobic, relaxation, postural and stretching exercises, and gait and balance training) including endurance and sensorimotor training not including endurance."
Specific comment
You discuss sensorimotor interventions. Reviewer 1 questions if all interventions are sensorimotor whereas I think of LSVT BIG. Could you operationally define this.
Authors
We really appreciate the Associate Editor's comment. As suggested, we have included the definition of "sensorimotor training" interventions in the methods section.
"sensorimotor training (aimed at improving the neuromuscular system by the emphasis on postural control and progressive challenges to the sensorimotor system, using aerobic, relaxation, postural and stretching exercises, and gait and balance training)."
Specific comment
I am in agreement of reviewer 1 re Lines 70-71: The purpose of the study was to provide evidence regarding the effectiveness of exercise programs on relieving motor symptoms of PD by comparing different types of exercise programs. Different exercise program may improve different motor symptoms in PD. How did the authors ensure fair comparisons? Also, what types of motor symptoms did the authors examined? What were the functional outcomes that the authors focus on and why?
Authors
We would like to thank the Associate Editor's comment. As suggested, we have included information regarding the motor symptoms studied and the outcomes of interest.
"Frequently, PD symptoms have been measured using the Unified Parkinson's Disease Rating Scale (UPDRS), which ensure fair comparisons among studies and include a specific section for PD motor symptoms that consist of a combination of the following motor symptoms: speech, facial expression, rigidity, finger tapping, hand movements, pronation-supination movements of hands, toe tapping, leg agility, arising from chair, gait, freezing of gait, postural stability, posture, global spontaneity on movement, postural tremor of the hands, rest tremor amplitude and constancy of the rest tremor."
Specific comment
In the methods, please discuss please describe how the GRADE was used to ensure quality.
Authors
Thank you for the comment. We have included this information.
"Literature search, data extraction, risk of bias assessment, and grading the quality of evidence were independently performed by two researchers (CAB and ICR), and disagreements were resolved by consensus or involving a third researcher (VMV)."
Specific comment
I am in agreement with reviewer #2's comments regarding adding a sentence or two regarding the effect size and confidence interval of the dance intervention. Only a few studies included dance and while the effect size was meaningful, the confidence interval was extremely wide (CI: -1.24, -0.05). Wide enough, in fact, that it may not be a useful intervention. Additionally, the dance reviewed was quite heterogeneous.
Authors
We would like to thank the Associated Editor's comment. As suggested, we have included some information on dance interventions.
"Additionally, because the scarcity of studies and the width of the CI, the small, but significant, effect estimated for dance should cautiously be interpreted."
Specific comment
Inclusion of articles-it would be nice to have a figure demonstrating the number of articles at the start and why each set of articles were excluded. To reduce 9.298 studies to 56 required extensive culling; knowing how many were eliminated due to using the same study sample, having another intervention as a control etc would improve understanding of your methodology.
Authors
We would like to thank the reviewer's comment. As suggested, we have modified the figure 1 in supplementary material to properly reflect the study selection process.
Specific comment
Page 8, line 219 it would be helpful to explain the rationale behind removing these two studies.
Authors
We would like to apologize for the misunderstanding. These two papers are part of the

sensitivity analysis and are the only two which modified the pooled effect size after their exclusion. We have modified the methods and results sections for better understanding.
“vii) Sensitivity analyses were performed excluding studies one by one from the pooled estimates, in order to evaluate whether any particular study significantly modified the original summary estimate.”
“The sensitivity analysis after removing one by one the studies from the pooled estimates showed that they were substantially modified only after removing the data from…”
Specific comment
I am in agreement of reviewer 2 re: Line 253 - I suggest adding a sentence or two regarding the effect size and confidence interval of the dance intervention. Only a few studies included dance and while the effect size was meaningful, the confidence interval was extremely wide (CI: -1.24, -0.05). Wide enough, in fact, that it may not be a useful intervention. Additionally, the dance reviewed was quite heterogeneous.
Authors
We would like to thank the Associated Editor’s comment. As suggested, we have included some information on dance interventions.
“Additionally, the slightly effect observed for dance should cautiously interpreted.”
Specific comment
This may just be my personal preference but rather than listing the limitations as i through vii, I find it easier to read as separate sentences.
Authors
Thank you for the suggestion. We have properly modified the limitation section.
Specific comment
Please make a section specific for conclusion to be consistent with the subheading in your abstract.
Authors
Done. Thank you.
Specific comment
Please revisit lines 286-294 after addressing the conflicting statements in the discussion session.
Authors
We really thank the comment. As suggested, we have modified this section as follows.
“Among the different intervention programs, sensorimotor training including endurance, resistance, dance, sensorimotor training not including endurance, alternative exercise, and endurance training seems to be the most effective physical activity interventions.”
Minor comments
Please go through your manuscript and change PD patients to patients with PD as this journal uses person-first language.
Authors
Done.
Specific comment
Change the word introduction in the abstract to background.
Authors
Done.
Specific comment
I am in agreement with reviewer 1 re: Line 68: There is no consistent evidence showing which is the "most" effective one for the PD motor symptoms. Different exercises may benefit different motor symptoms. The use of the word "most" seems to be too general and too strong. I suggest revision and provide more detail background.
Authors
We really thank the Associated Editor’s comment. As suggested, we have modified the sentence.
“Although so far, there is no consistent evidence on which type of exercise shows the greater effects for the PD motor symptoms.”
Specific comment
Page 5, line 122 add the word “The” to the beginning of the sentence.
Authors
Done.
Specific comment
Page 5 line 167 remove the comma after studies and remove the word “these” before estimates to improve readability.
Authors

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Done.
Specific comment
Please reference I^2 classification.
Authors
Thank you for the comment. As suggested, we have provided a reference for I2 classification.
Specific comment
Page 5, line 200, remove the word finally. Move this paragraph to the end of the previous paragraph or the beginning of the following paragraph, whichever makes the most sense to you.

Authors
Done.
Specific comment
I am in agreement with reviewer 1 that complex physical activity needs to be operationally defined.
Authors
We really thank the Associate Editor's comment. As suggested, we have included the definition of "complex intervention".
"From our results, complex or multi-faceted physical activity program that emphasize on fine motor tasks like holding a pencil or gross motor tasks like getting up from the bed, could improves walking, self-care and other tasks by helping people to modify and adjust how they perceive their movements "
Specific comment
Page 9, line 269, begin the sentence with Limitations.
Authors
Done.
Specific comment
References
Only the first word of an article title should be capitalized, excluding proper nouns.
Authors
Done.
Specific comment
Reference 4 needs addressing.
Authors
Done.
Specific comment
The articles used in this study should be included in the references.
Authors
Done.

Reviewer #1: This manuscript presents a systematic review and meta-analysis to provide evidence regarding the effectiveness of exercise programs on relieving motor symptoms of PD by comparing different types of exercise programs. The methodology section was well written, and the study can contribute to the field of geriatric rehabilitation. My comments are as follows:

Specific comment
Line 48: Replace "Background" to "Introduction" to be consistent with the subheadings in the abstract. In general, the introduction section was concise and easy to follow. However, I feel some important background of the study was missing. My specific concerns are listed in the following points.
Authors
We would like to thank the reviewer's comment. As suggested, we have replaced "Background" to "Introduction"
Specific comment
Lines 65 - 67: I recommend the authors to briefly describe the exercise programs included in your review (e.g., indication, contraindication, etc). The readers may not be familiar with all the exercise programs.
Authors
We would like to thank the reviewer's comment. As suggested, we have included additional information on the indications and contraindications of the exercise programs included.
"Several types of exercise have been included in these PD-adapted programs, such as body weight support exercises, adapted dance, tai chi, yoga, endurance, and strength physical activity programs.7-9 Specific PD-adapted programs have shown benefits in physical functioning, HRQOL, strength, balance and gait speed, although there is insufficient evidence on their efficacy on reducing falls or depression in people with PD."
Specific comment
Line 68: There is no consistent evidence showing which is the "most" effective one for the PD motor symptoms. Different exercises may benefit different motor symptoms. The use of the word "most" seems to be too general and too strong. I suggest revision and provide more detail background.
Authors
We really appreciate the reviewer's comment. we have modified the sentence to accurately write.
""…. Although so far, there is no consistent evidence on which type of exercise shows the greater effects for the PD motor symptoms"
Specific comment
Lines 70-71: The purpose of the study was to provide evidence regarding the effectiveness of exercise programs on relieving motor symptoms of PD by comparing different types of exercise programs. Different exercise program may improve different motor symptoms in PD. How did the authors ensure fair comparisons? Also, what types of motor symptoms did the authors examined? What were the functional outcomes that the authors focus on and why?
Authors
We would like to thank the reviewer's comment. As suggested, we have included information regarding the motor symptoms studied and the outcomes of interest.
"Frequently, PD symptoms have been measured using the Unified Parkinson's Disease Rating Scale (UPDRS), which ensure fair comparisons among studies and include a specific section for PD motor symptoms that consist of a combination of the following motor symptoms: speech, facial expression, rigidity, finger tapping, hand movements, pronation-supination movements of hands, toe tapping, leg agility, arising from chair, gait, freezing of gait, postural stability, posture, global spontaneity on movement, postural tremor of the hands, rest tremor amplitude and constancy of the rest tremor."
Specific comment
Line 73: Methods was generally well written, but I have some clarifications. How many researchers involved in the study selection process? If multiple, how was the agreement reached? Similarly, how many researchers evaluate the quality of the study using GRADE? If multiple, was the grading results consistent?
Authors
We thank the reviewer's comment. we have included some information on the researchers involved in the process.
"Literature search, data extraction, risk of bias assessment, and grading the quality of evidence were independently performed by two researchers (CAB and ICR), and disagreements were resolved by consensus or involving a third researcher (VMV)."
Specific comment
Lines 154-155: Could the authors provide references for I^2 classification?
Authors
Thank you for the comment. As suggested, we have provided a reference for I2

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classification.
Specific comment
Line 180: Results section was nicely written. I have no comments.
Authors
We really appreciate the reviewer's comment.
Specific comment
Lines 234-235: Please check these sentences - they are a bit confusing, especially the "including endurance" and "not including endurance" part.
Authors
We appreciate the reviewer's comment. We have modified the sentence to properly write the publication bias section.
"Publication bias was found for the direct comparison of sensorimotor training not including endurance versus resistance (p = 0.066)"
Specific comment
Line 246-248: Please define "complex physical activity." Is resistance training or endurance training considered complex or not complexed? Also, I am confused the relationship between life style interventions and exercise programs.
Authors
We really thank the reviewer's comment. As suggested, we have included the definition of "complex intervention".
"From our results, complex or multi-faceted physical activity program that emphasize on fine motor tasks like holding a pencil or gross motor tasks like getting up from the bed, could improves walking, self-care and other tasks by helping people to modify and adjust how they perceive their movements "
Specific comment
Lines 250-252: I am not sure if I am convinced by this sentence "The absence of described side effects of physical activity programs makes them a potentially useful adjunct to medication." The absence of described side effects could simply because they were not reported in the study.
Authors
Thank you for the comment. We have modified the mentioned sentence.
"The absence of reported side effects of physical activity programs makes them a potentially useful adjunct to medication,22 although patients might be closely followed as side effects could occur based on patient's stage or severity of the health condition."
Specific comment
Lines 253 -255: "In our study, most types of exercise confirmed these previous findings, although we did not find significant effects of balance, combined, and body weight-supported exercise programs." This statement seems to conflict with lines 246 - 248. Aren't balance, combined, and body weight supported exercises are all "complex" and are all a type of "sensorimotor training"?
Authors
Thank you for the comment. We have included the definition of complex intervention and added some explanation for the lack of evidence. Additionally, we have rewritten the sentence for better understanding.
"Dance, alternative exercise, resistance, endurance training, sensorimotor training not including endurance, and sensorimotor training including endurance, could be included in this classification."
"…although we did not find significant effects of balance, combined, and body weight-supported exercise programs, which seems not to adequately foster all the UPDRS III dimensions."
Specific comment
Lines 258 259: "In addition, the scarcity of studies in some exercise categories makes difficult to conclude the characteristics of the best intervention." This statement seems to conflict with lines 243-245, where the effectiveness of exercise programs were ranked.
Authors
We would like to thank the reviewer's comment. We have modified the sentence to accurately write.
"In addition, the scarcity of studies reporting the above-mentioned interventions and the lack of information on their characteristics make difficult to firmly conclude about the effectiveness of these types of interventions."
Specific comment
Please make a section specific for conclusion to be consistent with the subheading in your abstract.

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	Authors We really thank the comment. As suggested this section has been included. Specific comment Please revisit lines 286-294 after addressing the conflicting statements in the discussion session. Authors Thanks for the comment. We have modified the conclusion as follows. “Among the different intervention programs, sensorimotor training including endurance, resistance, dance, sensorimotor training not including endurance, alternative exercise, and endurance training seems to be the most effective physical activity interventions.” Specific comment Thank you for the opportunity to review. Authors We appreciate the time that the reviewer has dedicated to this paper. Reviewer #2: Line 253 - I suggest adding a sentence or two regarding the effect size and confidence interval of the dance intervention. Only a few studies included dance and while the effect size was meaningful, the confidence interval was extremely wide (CI: -1.24, -0.05). Wide enough, in fact, that it may not be a useful intervention. Additionally, the dance reviewed was quite heterogeneous. Authors We would like to thank the Associated Editor’s comment. As suggested, we have included some information on dance interventions. “Additionally, because the scarcity of studies and the width of the CI, the small, but significant, effect estimated for dance should cautiously be interpreted.” Specific comment Overall, you have a very well written article with correct grammar. Authors We really thank the reviewer’s comment. Specific comment I question, to some degree, how you present the pharmacological approach. In line 17 it states, "has not been proven to be fully effective." While grammatically correct, it may not convey the message you are desiring to communicate. PD is an incurable, progressive neurodegenerative disease and while medications may help, they are clearly not the solution. You may choose to rephrase this section and the section in line 55 to better convey that medications are helpful but not the solution. As I reviewed the article, these sections distracted from your overall aims and message of the article, which was to use the best physical activity interventions. Authors We would like to thank the reviewer’s comment. As suggested, we have rephrase the introduction and abstract sections. “Background: Although the pharmacological approach may help with motor symptoms in Parkinson’s disease (PD), they are clearly not the complete solution….” “Introduction: Pharmacological and surgical treatments may help in the management of PD symptoms, but they are clearly not the solution as PD is an incurable and progressive neurodegenerative disease.3”

Dr. Dr. Kerstin Palombaro May 6, 2021

Associate Editor

Journal of Geriatric Physical Therapy

Enclosed you will find a revision of our manuscript: **"Effect of exercise on motor symptoms in patients with Parkinson's Disease: a network meta-analysis."** Manuscript ID: JGPT-D-21-00011

We would like to thank you for giving us the opportunity to revise and improve our manuscript; we also thank the reviewers for their thoughtful and constructive comments.

We have considered all of the suggestions and incorporated them into the revised manuscript. Changes to the original manuscript are marked in red, and we believe our manuscript is stronger as result of these modifications. An itemized point-by-point response to the reviewers' comments is presented below. In addition, we have updated the literature search to provide the readers the most recent evidence.

In order to ask the check list for re-submission requirements we would like to state that:

- This manuscript has not been published elsewhere and is not under consideration by another journal.
- All the authors have revised and approved the final version of the manuscript.
- The authors have no conflicts of interest to declare, and the funding sources h financial support have been properly described.

Yours sincerely,

Ivan Cavero Redondo

Reviewer Comments:

Associate Editor:

Specific comment

In your background section, I am in agreement with reviewer two regarding your presentation of pharmacology for PD. Perhaps in line 55-57 you might state something on the order of "Pharmacological interventions do not completely address motor symptoms of PD."

Authors

We would like to thank the Associate Editor's comment. We have modified the sentence as follows:

> *"Background: Although the pharmacological approach may help with motor symptoms in Parkinson's disease (PD), they are clearly not the complete solution…."*
>
> *"Introduction: Pharmacological and surgical treatments may help in the management of PD symptoms, but they do not completely address motor symptoms of PD as it is an incurable and progressive neurodegenerative disease.*[3]*"*

Specific comment

Please include a brief description of the types of exercise included in your paper.

Authors

We would like to thank the Associate Editor's comment. As suggested, we have included additional information on the types of exercises included in this paper.

> *"Data synthesis and analysis.* To perform the meta-analysis, physical exercise interventions were classified into nine categories: *endurance (aimed at increasing heart rate and energy expenditure), resistance (aimed at increasing muscle strength and muscle power), combined (including only aerobic exercise and resistance training), stretching (aimed at increasing muscle's elasticity and achieve comfortable muscle tone), dance (interventions with target balance and complex gait tasks in coordination with music), balance (aimed at improving postural reactions, by the strengthening of muscles that help keep you upright), body weight-supported (aimed at maintain the lower-limb trajectories, while increasing the motor activation*

and motor function by reducing the patient's weight) alternative exercises ([Tai-Chi, Yoga, Qui-Gong, and Ai-Chi] understood as a modality of exercise that combines body movement, mental focus, and controlled breathing for improving strength, balance, and flexibility), and sensorimotor training (aimed at improving the neuromuscular system by the emphasis on postural control and progressive challenges to the sensorimotor system, using aerobic, relaxation, postural and stretching exercises, and gait and balance training) including endurance and sensorimotor training not including endurance."

Specific comment

You discuss sensorimotor interventions. Reviewer 1 questions if all interventions are sensorimotor whereas I think of LSVT BIG. Could you operationally define this.

Authors

We really appreciate the Associate Editor's comment. As suggested, we have included the definition of "sensorimotor training" interventions in the methods section.

"sensorimotor training (aimed at improving the neuromuscular system by the emphasis on postural control and progressive challenges to the sensorimotor system, using aerobic, relaxation, postural and stretching exercises, and gait and balance training)."

Specific comment

I am in agreement of reviewer 1 re Lines 70-71: The purpose of the study was to provide evidence regarding the effectiveness of exercise programs on relieving motor symptoms of PD by comparing different types of exercise programs. Different exercise program may improve different motor symptoms in PD. How did the authors ensure fair comparisons? Also, what types of motor symptoms did the authors examined? What were the functional outcomes that the authors focus on and why?

Authors

We would like to thank the Associate Editor's comment. As suggested, we have included information regarding the motor symptoms studied and the outcomes of interest.

"Frequently, PD symptoms have been measured using the Unified Parkinson's Disease Rating Scale (UPDRS), which ensure fair comparisons among studies and

include a specific section for PD motor symptoms that consist of a combination of the following motor symptoms: speech, facial expression, rigidity, finger tapping, hand movements, pronation-supination movements of hands, toe tapping, leg agility, arising from chair, gait, freezing of gait, postural stability, posture, global spontaneity on movement, postural tremor of the hands, rest tremor amplitude and constancy of the rest tremor."

Specific comment

In the methods, please discuss please describe how the GRADE was used to ensure quality.

Authors

Thank you for the comment. We have included this information.

"Literature search, data extraction, risk of bias assessment, and grading the quality of evidence were independently performed by two researchers (CAB and ICR), and disagreements were resolved by consensus or involving a third researcher (VMV)."

Specific comment

I am in agreement with reviewer #2's comments regarding adding a sentence or two regarding the effect size and confidence interval of the dance intervention. Only a few studies included dance and while the effect size was meaningful, the confidence interval was extremely wide (CI: -1.24, -0.05). Wide enough, in fact, that it may not be a useful intervention. Additionally, the dance reviewed was quite heterogeneous.

Authors

We would like to thank the Associated Editor's comment. As suggested, we have included some information on dance interventions.

"Additionally, because the scarcity of studies and the width of the CI, the small, but significant, effect estimated for dance should cautiously be interpreted."

Specific comment

Inclusion of articles-it would be nice to have a figure demonstrating the number of articles at the start and why each set of articles were excluded. To reduce 9.298 studies to 56 required extensive culling; knowing how many were eliminated due to using the same study sample, having another intervention as a control etc would improve understanding of your methodology.

Authors

We would like to thank the reviewer's comment. As suggested, we have modified the figure 1 in supplementary material to properly reflect the study selection process.

Specific comment

Page 8, line 219 it would be helpful to explain the rationale behind removing these two studies.

Authors

We would like to apologize for the misunderstanding. These two papers are part of the sensitivity analysis and are the only two which modified the pooled effect size after their exclusion. We have modified the methods and results sections for better understanding.

> *"vii) Sensitivity analyses were performed excluding studies one by one from the pooled estimates, in order to evaluate whether any particular study significantly modified the original summary estimate."*

> *"The sensitivity analysis after removing one by one the studies from the pooled estimates showed that they were substantially modified only after removing the data from…"*

Specific comment

I am in agreement of reviewer 2 re: Line 253 - I suggest adding a sentence or two regarding the effect size and confidence interval of the dance intervention. Only a few studies included dance and while the effect size was meaningful, the confidence interval was extremely wide (CI: -1.24, -0.05). Wide enough, in fact, that it may not be a useful intervention. Additionally, the dance reviewed was quite heterogeneous.

Authors

We would like to thank the Associated Editor's comment. As suggested, we have included some information on dance interventions.

> *"Additionally, the slightly effect observed for dance should cautiously interpreted."*

Specific comment

This may just be my personal preference but rather than listing the limitations as i through vii, I find it easier to read as separate sentences.

Authors

Thank you for the suggestion. We have properly modified the limitation section.

Specific comment

Please make a section specific for conclusion to be consistent with the subheading in your abstract.

Authors

Done. Thank you.

Specific comment

Please revisit lines 286-294 after addressing the conflicting statements in the discussion session.

Authors

We really thank the comment. As suggested, we have modified this section as follows.

> *"Among the different intervention programs, sensorimotor training including endurance, resistance, dance, sensorimotor training not including endurance, alternative exercise, and endurance training seems to be the most effective physical activity interventions."*

Minor comments

Please go through your manuscript and change PD patients to patients with PD as this journal uses person-first language.

Authors

Done.

Specific comment

Change the word introduction in the abstract to background.

Authors

Done.

Specific comment

I am in agreement with reviewer 1 re: Line 68: There is no consistent evidence showing which is the "most" effective one for the PD motor symptoms. Different exercises may benefit different motor symptoms. The use of the word "most" seems to be too general and too strong. I suggest revision and provide more detail background.

Authors

We really thank the Associated Editor's comment. As suggested, we have modified the sentence.

> *"Although so far, there is no consistent evidence on which type of exercise shows the greater effects for the PD motor symptoms."*

Specific comment

Page 5, line 122 add the word "The" to the beginning of the sentence.

Authors

Done.

Specific comment

Page 5 line 167 remove the comma after studies and remove the word "these" before estimates to improve readability.

Authors

Done.

Specific comment

Please reference I^2 classification.

Authors

Thank you for the comment. As suggested, we have provided a reference for I2 classification.

Specific comment

Page 5, line 200, remove the word finally. Move this paragraph to the end of the previous paragraph or the beginning of the following paragraph, whichever makes the most sense to you.

Authors

Done.

Specific comment

I am in agreement with reviewer 1 that complex physical activity needs to be operationally defined.

Authors

We really thank the Associate Editor's comment. As suggested, we have included the definition of "complex intervention".

> "From our results, complex or multi-faceted physical activity program that emphasize on fine motor tasks like holding a pencil or gross motor tasks like getting up from the bed, could improves walking, self-care and other tasks by helping people to modify and adjust how they perceive their movements "

Specific comment

Page 9, line 269, begin the sentence with Limitations.

Authors

Done.

Specific comment

References
Only the first word of an article title should be capitalized, excluding proper nouns.

Authors

Done.

Specific comment

Reference 4 needs addressing.

Authors

Done.

Specific comment

The articles used in this study should be included in the references.

Authors

Done.

Reviewer #1: This manuscript presents a systematic review and meta-analysis to provide evidence regarding the effectiveness of exercise programs on relieving motor symptoms of PD by comparing different types of exercise programs. The methodology section was well written, and the study can contribute to the field of geriatric rehabilitation. My comments are as follows:

Specific comment

Line 48: Replace "Background" to "Introduction" to be consistent with the subheadings in the abstract. In general, the introduction section was concise and easy to follow. However, I feel some important background of the study was missing. My specific concerns are listed in the following points.

Authors

We would like to thank the reviewer's comment. As suggested, we have replaced "Background" to "Introduction"

Specific comment

Lines 65 - 67: I recommend the authors to briefly describe the exercise programs included in your review (e.g., indication, contraindication, etc). The readers may not be familiar with all the exercise programs.

Authors

We would like to thank the reviewer's comment. As suggested, we have included additional information on the indications and contraindications of the exercise programs included.

> *"Several types of exercise have been included in these PD-adapted programs, such as body weight support exercises, adapted dance, tai chi, yoga, endurance, and strength physical activity programs.[7-9] Specific PD-adapted programs have shown benefits in physical functioning, HRQOL, strength, balance and gait speed, although there is insufficient evidence on their efficacy on reducing falls or depression in people with PD."*

Specific comment

Line 68: There is no consistent evidence showing which is the "most" effective one for the PD motor symptoms. Different exercises may benefit different motor symptoms. The use of the word "most" seems to be too general and too strong. I suggest revision and provide more detail background.

Authors

We really appreciate the reviewer's comment. we have modified the sentence to accurately write.

> *"…. Although so far, there is no consistent evidence on which type of exercise shows the greater effects for the PD motor symptoms"*

Specific comment

Lines 70-71: The purpose of the study was to provide evidence regarding the effectiveness of exercise programs on relieving motor symptoms of PD by comparing different types of exercise programs. Different exercise program may improve different motor symptoms in PD. How did the authors ensure fair comparisons? Also, what types of motor symptoms did the authors examined? What were the functional outcomes that the authors focus on and why?

Authors

We would like to thank the reviewer's comment. As suggested, we have included information regarding the motor symptoms studied and the outcomes of interest.

> *"Frequently, PD symptoms have been measured using the Unified Parkinson's Disease Rating Scale (UPDRS), which ensure fair comparisons among studies and include a specific section for PD motor symptoms that consist of a combination of the following motor symptoms: speech, facial expression, rigidity, finger tapping, hand movements, pronation-supination movements of hands, toe tapping, leg agility, arising from chair, gait, freezing of gait, postural stability, posture, global spontaneity on movement, postural tremor of the hands, rest tremor amplitude and constancy of the rest tremor."*

Specific comment

Line 73: Methods was generally well written, but I have some clarifications. How many researchers involved in the study selection process? If multiple, how was the agreement reached? Similarly, how many researchers evaluate the quality of the study using GRADE? If multiple, was the grading results consistent?

Authors

We thank the reviewer's comment. we have included some information on the researchers involved in the process.

"Literature search, data extraction, risk of bias assessment, and grading the quality of evidence were independently performed by two researchers (CAB and ICR), and disagreements were resolved by consensus or involving a third researcher (VMV)."

Specific comment

Lines 154-155: Could the authors provide references for I^2 classification?

Authors

Thank you for the comment. As suggested, we have provided a reference for I2 classification.

Specific comment

Line 180: Results section was nicely written. I have no comments.

Authors

We really appreciate the reviewer's comment.

Specific comment

Lines 234-235: Please check these sentences - they are a bit confusing, especially the "including endurance" and "not including endurance" part.

Authors

We appreciate the reviewer's comment. We have modified the sentence to properly write the publication bias section.

"Publication bias was found for the direct comparison of sensorimotor training not including endurance versus resistance ($p = 0.066$)"

Specific comment

Line 246-248: Please define "complex physical activity." Is resistance training or endurance training considered complex or not complexed? Also, I am confused the relationship between life style interventions and exercise programs.

Authors

We really thank the reviewer's comment. As suggested, we have included the definition of "complex intervention".

"From our results, complex or multi-faceted physical activity program that emphasize on fine motor tasks like holding a pencil or gross motor tasks like getting up from the bed, could improves walking, self-care and other tasks by helping people to modify and adjust how they perceive their movements "

Specific comment

Lines 250-252: I am not sure if I am convinced by this sentence "The absence of described side effects of physical activity programs makes them a potentially useful adjunct to medication." The absence of described side effects could simply because they were not reported in the study.

Authors

Thank you for the comment. We have modified the mentioned sentence.

"The absence of reported side effects of physical activity programs makes them a potentially useful adjunct to medication,[22] although patients might be closely followed as side effects could occur based on patient's stage or severity of the health condition."

Specific comment

Lines 253 -255: "In our study, most types of exercise confirmed these previous findings, although we did not find significant effects of balance, combined, and body weight-supported exercise programs." This statement seems to conflict with lines 246 - 248. Aren't balance, combined, and body weight supported exercises are all "complex" and are all a type of "sensorimotor training"?

Authors

Thank you for the comment. We have included the definition of complex intervention and added some explanation for the lack of evidence. Additionally, we have rewritten the sentence for better understanding.

"Dance, alternative exercise, resistance, endurance training, sensorimotor training not including endurance, and sensorimotor training including endurance, could be included in this classification."

"...although we did not find significant effects of balance, combined, and body weight-supported exercise programs, which seems not to adequately foster all the UPDRS III dimensions."

Specific comment

Lines 258 259: "In addition, the scarcity of studies in some exercise categories makes difficult to conclude the characteristics of the best intervention." This statement seems to conflict with lines 243-245, where the effectiveness of exercise programs were ranked.

Authors

We would like to thank the reviewer's comment. We have modified the sentence to accurately write.

> *"In addition, the scarcity of studies reporting the above-mentioned interventions and the lack of information on their characteristics make difficult to firmly conclude about the effectiveness of these types of interventions."*

Specific comment

Please make a section specific for conclusion to be consistent with the subheading in your abstract.

Authors

We really thank the comment. As suggested this section has been included.

Specific comment

Please revisit lines 286-294 after addressing the conflicting statements in the discussion session.

Authors

Thanks for the comment. We have modified the conclusion as follows.

> *"Among the different intervention programs, sensorimotor training including endurance, resistance, dance, sensorimotor training not including endurance, alternative exercise, and endurance training seems to be the most effective physical activity interventions."*

Specific comment

Thank you for the opportunity to review**.**

Authors

We appreciate the time that the reviewer has dedicated to this paper.

Reviewer #2: Line 253 - I suggest adding a sentence or two regarding the effect size and confidence interval of the dance intervention. Only a few studies included dance and while the effect size was meaningful, the confidence interval was extremely wide (CI: -1.24, -0.05). Wide enough, in fact, that it may not be a useful intervention. Additionally, the dance reviewed was quite heterogeneous.

Authors

We would like to thank the Associated Editor's comment. As suggested, we have included some information on dance interventions.

> *"Additionally, because the scarcity of studies and the width of the CI, the small, but significant, effect estimated for dance should cautiously be interpreted."*

Specific comment

Overall, you have a very well written article with correct grammar.

Authors

We really thank the reviewer's comment.

Specific comment

I question, to some degree, how you present the pharmacological approach. In line 17 it states, "has not been proven to be fully effective." While grammatically correct, it may not convey the message you are desiring to communicate. PD is an incurable, progressive neurodegenerative disease and while medications may help, they are clearly not the solution. You may choose to rephrase this section and the section in line 55 to better convey that medications are helpful but not the solution. As I reviewed the article, these sections distracted from your overall aims and message of the article, which was to use the best physical activity interventions.

Authors

We would like to thank the reviewer's comment. As suggested, we have rephrase the introduction and abstract sections.

> *"Background: Although the pharmacological approach may help with motor symptoms in Parkinson's disease (PD), they are clearly not the complete solution…."*

"Introduction: Pharmacological and surgical treatments may help in the management of PD symptoms, but they are clearly not the solution as PD is an incurable and progressive neurodegenerative disease.[3]*"*

PRISMA-NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Section, Sub-section, Paragraph #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	**Title**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	**Page 2**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	**Page 3**
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**Page 4**
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	**Page 4**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	**Page 4**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**Page 4**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**Supplementary Table 1**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**Page 5**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**Page 5-6**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**Page 5-6**
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	**Page 6-7**
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**Page 6-7**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	**Page 6-7**

Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	**Page 6-7**
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	**Page 6-7**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**Page 6-7**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	**Page 6-7**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**Page 7** **Supplementary Figure 1**
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	**Figure 1**
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	**Page 7**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**Table 1**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	**Page 7** **Supplementary Table 2**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	**Page 7-8** **Table 1-2**
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	**Page 7-8**
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	**Page 7-8**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	**Page 8-9** **Supplementary Figure 3**
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses*, and so forth).	**Supplementary Table 5, 6, and 7**
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	**Page 9-10**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	**Page 10**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**Page 10**

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	**Page 10**

Effect of exercise on motor symptoms in patients with Parkinson's Disease: a network meta-analysis.

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All authors of this manuscript declare no conflict of interest.

What is already known on this topic

- So far, there is no substantial evidence showing the most effective exercise program for Parkinson's disease (PD) motor symptoms.
- Physical activity interventions are effective in the management of PD motor symptoms, with sensorimotor training, including endurance being the most effective one.
- This information is of use to clinicians prescribing exercise for mitigating patients' motor symptoms and promoting their independence in activities of daily living.

Effect of exercise on motor symptoms in patients with Parkinson's Disease: a network meta-analysis.

Clinical implications

- So far, there is no substantial evidence showing the most effective exercise program for Parkinson's disease (PD) motor symptoms.
- Physical activity interventions are effective in the management of PD motor symptoms, with sensorimotor training, including endurance being the most effective one.
- This information is of use to clinicians prescribing exercise for mitigating patients' motor symptoms and promoting their independence in activities of daily living.

This manuscript has been proof-read and copy-edited by a native US English speaker with scientific writing experience by the service "editage by cactus", job code: VIEZV_3.

ABSTRACT:

Background: Although the pharmacological approach may help with motor symptoms in Parkinson's disease (PD), they are clearly not the complete solution. Thus, for the treatment of PD motor symptoms, physical activity has been proposed as an effective intervention.

Methods: A systematic search in MEDLINE, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials databases was conducted to identify randomized controlled trials testing the effectiveness of exercise interventions on motor symptoms of PD. Physical exercise interventions were divided into nine categories: endurance, resistance, combined, balance, dance, alternative exercises, body weight supported, sensorimotor interventions including endurance exercise, and sensorimotor interventions not including endurance exercise. A pairwise meta-analysis for direct and indirect comparisons between intervention and control/non-intervention groups was carried out.

Results: Fifty-six studies met the inclusion criteria, including 2,740 participants, aged between 57.6 and 77.7 years. Results of our analyses showed that sensorimotor training including endurance (effect size [ES]: -1.09; 95% CI: -1.68, -0.50), resistance (ES: -0.82; 95% CI:-1.23, -0.41), and dance (ES: -0.64; 95% CI: -1.24, -0.05) were the most effective physical activity interventions for mitigating PD motor symptoms.

Conclusion: Physical activity interventions are an effective strategy for the management of motor symptoms in patients with PD. Among the different exercise intervention programs, those including more complex and demanding activities, (sensorimotor training including endurance, resistance, and dance) seem to be the most effective physical activity interventions.

Abbreviations:
CI: Confidence Interval
ES: Effect Size
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation.
H&Y: Hoehn and Yahr stage
PD: Parkinson Disease
QoL: Quality of Life
SUCRA: Surface under the cumulative ranking
UPDRS: Unified Parkinson's Disease Rating Scale

INTRODUCTION

Parkinson's disease (PD) is a common, chronic, and progressive neurological disorder with a universal age-adjusted incidence rate ranging from 9.7 to 13.8 per 100,000 cases per year.[1] It is characterized by the predominant presence of motor symptoms, such as bradykinesia, rigidity, tremor, and postural instability, which are frequently associated with non-motor symptoms.[1]

The diagnosis of PD implies a progressive motor impairment and disability affecting patients' everyday activities and quality of life.[2] Pharmacological and surgical treatments may help in the management of PD symptoms, but they do not completely address motor symptoms of PD as it is an incurable and progressive neurodegenerative disease.[3] Furthermore, regular leisure-time physical activity and exercise program engagement can reduce the risk of developing PD because of their neuroprotective effect through upregulation of brain-derived nerve growth factors.[4]

Apart from their preventive effect, rehabilitation protocols that include exercise interventions adapted to patients with PD are considered a new approach to cope with the remaining motor disabilities.[5,6] The common aim of these physical activity programs is to deal with long-lasting motor symptoms through the preservation and improvement of motor functions, thereby improving global health. Several types of exercise have been included in these PD-adapted programs, such as body weight support exercises, adapted dance, tai chi, yoga, endurance, and strength physical activity programs.[7-9] Specific PD-adapted programs have shown benefits in physical functioning, HRQOL, strength, balance and gait speed, although there is insufficient evidence on their efficacy on reducing falls or depression in people with PD.[10-15] Although so far, there is no consistent evidence on which type of exercise shows the greater effects for the PD motor symptoms.

Frequently, PD symptoms have been measured using the Unified Parkinson's Disease Rating Scale (UPDRS),[16] which ensure fair comparisons among studies and include a specific section for PD motor symptoms that consist of a combination of the following motor symptoms: speech, facial expression, rigidity, finger tapping, hand movements, pronation-supination movements of hands, toe tapping, leg agility, arising from chair, gait, freezing of gait, postural stability, posture, global spontaneity on movement, postural tremor of the hands, rest tremor amplitude and constancy of the rest tremor.

Therefore, the aim of this systematic review and meta-analysis was to provide evidence regarding the effectiveness of exercise programs on relieving motor symptoms of PD measured using the motor part of the UPDRS scale by comparing different types of exercise programs.

METHODS

This network meta-analysis was guided by the Cochrane Collaboration Handbook[17] and reported following the PRISMA statement extension for systematic reviews incorporating network meta-analysis (PRISMA-NMA) statement.[18] The protocol for this network meta-analysis has been registered on PROSPERO (CRD42018087765).

Data sources and searches We searched Medline (via PubMed), Web of Science, Scopus, and Cochrane Central Register of Controlled Trials from their inception to April 2021, aiming to identify studies on the effect of physical exercise interventions on motor

symptoms of patients with PD, measured by the motor part of UPDRS. This scale is the most widely used clinical rating scale for Parkinson's disease.[19]

The search strategy included the following terms: "Parkinson," "Parkinson Disease," "physical exercise," "exercise," "CRF," "VO2max," "fitness," "cardiorespiratory fitness," "aerobic fitness," "physical fitness," "muscular resistance," "physical endurance," "muscular endurance," and "muscular strength." Additionally, previous systematic reviews and meta-analyses in the issue and reference lists of the included studies were reviewed for any relevant study. The complete strategy search for Medline is available in Supplementary Table 1.

The study selection. This network meta-analysis includes studies on the effect of physical exercise interventions on the motor symptoms of patients with PD. Inclusion criteria were as follows: i) participants: adults; ii) exposure: physical exercise programs; iii) outcome: motor symptoms of PD measured using the motor part of the UPDRS; and iv) study design: randomized and non-randomized controlled trials. No language restrictions were applied.

Studies were excluded when: i) they focused on children or adolescents, ii) PD motor symptoms were rated using scales other than UPDRS, iii) did not include a control group and included different intervention groups developing similar exercise programs, or iv) were designed as cross-over studies and did not report results at the end of the first intervention period.

Data extraction and risk of bias. We summarized the main characteristics of the included studies in Table 1, including the following: (1) characteristics of participants (sample size, including number of females, mean age, duration of PD, type of population, and basal Hoehn and Yahr stage (H&Y) and UPDRS scores), and (2) physical exercise intervention characteristics (intervention description and dose [length of the intervention, sessions per week, and duration of sessions]).

The included studies were assessed using the Cochrane Collaboration tool for assessing risk of bias (RoB2).[20] This tool assesses the risk of bias according to six domains: bias arising from the randomization process, bias due to deviations from intended interventions, due to missing outcome data, due to measurement of the outcome, due to selection of the reported result, and overall bias. The overall bias of each study

was considered as "low risk of bias" when the study was classified as "low risk" in all domains, "some concerns" when there was at least one domain classified as "some concern," and "high risk of bias" when there was at least one domain classified as "high risk" or several domains with "some concerns."

Grading the quality of evidence. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)[21] tool was used to evaluate the quality of the evidence and make recommendations. Each outcome obtained a high, moderate, low, or very low evidence value, depending on the design of the studies, risk of bias, inconsistency, indirect evidence, imprecision, and publication bias.

Literature search, data extraction, risk of bias assessment, and grading the quality of evidence were independently performed by two researchers (CAB and ICR), and disagreements were resolved by consensus or involving a third researcher (VMV).

Data synthesis and analysis. To perform the meta-analysis, physical exercise interventions were classified into nine categories: endurance (aimed at increasing heart rate and energy expenditure), resistance (aimed at increasing muscle strength and muscle power), combined (including only aerobic exercise and resistance training), stretching (aimed at increasing muscle's elasticity and achieve comfortable muscle tone), dance (interventions with target balance and complex gait tasks in coordination with music), balance (aimed at improving postural reactions, by the strengthening of muscles that help keep you upright), body weight-supported (aimed at maintain the lower-limb trajectories, while increasing the motor activation and motor function by reducing the patient's weight) alternative exercises ([Tai-Chi, Yoga, Qui-Gong, and Ai-Chi] understood as a modality of exercise that combines body movement, mental focus, and controlled breathing for improving strength, balance, and flexibility), and sensorimotor training (aimed at improving the neuromuscular system by the emphasis on postural control and progressive challenges to the sensorimotor system, using aerobic, relaxation, postural and stretching exercises, and gait and balance training) including endurance and sensorimotor training not including endurance.

Before conducting the network meta-analysis, we examined the statistical power of the interventions to find differences between groups by using the baseline mean in the motor part of the UPDRS, the sample size, and the common standard deviation for both

groups. For studies including more than one intervention groups, estimates were calculated for each comparison included in this network meta-analysis. Additionally, these estimates were also calculated for studies reporting their procedures for sample size determination.

The included studies were summarized narratively in an ad-hoc table describing the types of direct and indirect comparisons. We conducted our network meta-analysis according to the steps outlined in the PRISMA-NMA statement: i) the strength of the evidence was assessed through a network geometry graph in which the number of participants in trials was represented by the size of the node, and the thickness of the continuous line to connect nodes is proportional to the sample size in trials that directly compared the two interventions.[22] ii) Consistency was assessed by checking whether the intervention effects estimated from direct comparisons were consistent with those estimated by indirect comparisons; consequently, the Wald test and the side-splitting assessment were used. iii) Comparative evaluation of the intervention effect was assessed by performing a standard meta-analysis for each direct comparison between two physical exercise interventions using the random effect DerSimonian-Laird method.[23] These results were displayed by creating both forest plots and a league table. Additionally, statistical heterogeneity was analyzed by calculation of the I^2 statistic. According to the values of I^2,[17] the heterogeneity was considered as not important (0% to 40%), moderate (30% to 60%), substantial (50% to 90%), or considerable (75% to 100%), and the corresponding p-values were also considered. Finally, to determine the size and clinical relevance of heterogeneity, the τ^2 statistic was calculated and interpreted as low (lower than 0.04), moderate (0.04 to 0.14), and as substantial (0.14 to 0.40).[24] iv) The probability of each physical activity intervention being the most effective was presented graphically using cumulative rankograms.[25] Additionally, the surface under the cumulative ranking (SUCRA) was estimated for each intervention, which involves the assigning of a numerical value between 0 and 1, in such a way that the best intervention obtained a value for SUCRA closest to 1 and the worst intervention obtained a value closest to 0.[22] vi) Small study effect and publication bias was estimated using Egger´s test.[26] vii) Sensitivity analyses were performed excluding studies one by one from the pooled estimates, in order to evaluate whether any particular study significantly modified the original summary estimate. Finally, viii) meta-regression analyses were conducted to examine the influence of the duration of the intervention (weeks) and the weekly (min) time spent on sessions.

Meta-regressions were performed to estimate the effect of intervention group versus control groups, including at least six studies.

We used the frequentist random effects multivariate network meta-analysis to synthesize the evidence for exercise interventions and to achieve a ranking of treatments. All analyses were conducted in Stata 15.0 (Stata, College Station, Texas, USA). The following methodological issues were pointed out: i) when studies involved data on ON (when there is a successful control of motor symptoms) and OFF (when medication is not optimally effective)[27] PD motor symptoms, only data on ON motor symptoms were included in the pooled estimates; ii) when studies provided two or more endpoint measurements over time, the closest one to the most frequently reported was considered in this meta-analysis, and iii) when studies included follow-up without intervention measurements, these were not included in this meta-analysis.

RESULTS

The search retrieved 12,496 studies, of which 56 were included in this network meta-analysis.[28-83] They included 125 intervention groups with 2,038 participants, and 49 control groups with 702 participants. Their mean age was between 57.6 and 77.7 years and duration of PD from the diagnosis ranged from 2.5 to 15.7 years. Physical exercise program duration varied from 2 weeks to 3 years (involved 1 to 5 sessions per week, lasting between 120 and 180 minutes). (Table 1)

The number of intervention groups classified within each category was as follows: endurance, 31; resistance, 21; combined exercise, 3; balance, 3; dance, 7; alternative exercises, 19; body weight-supported interventions, 11; sensorimotor interventions including endurance, 8; and sensorimotor interventions not including endurance, 20.

Risk of bias and grade of evidence. The overall risk of bias was high for all included studies. Regarding each domain, the studies recorded: for randomization process 72.7% for some concerns and 9.1% for high risk of bias; for deviations from intended interventions, 95.5% as high risk of bias; for missing outcome data, all studies as low risk; for selection of the reported results, all studies as some concerns; finally, for the measurement of the outcome domain, 97.7% were at low risk (Supplementary Table 2).

The quality of evidence, as assessed by the GRADE system, was moderate in 68% of the pairwise comparison studies, and low in 32% (Supplemental Table 3).

Statistical power The calculated statistical power of the interventions to find differences ranged from 3% to 100% (Supplementary Table 4).

Exercise and motor symptoms of PD In pairwise analyses (Table 2), the highest mean difference was shown for alternative and endurance exercises versus control comparisons (-0.48; 95% CI: -0.82, -0.13 and –0.36; 95% CI: -0.54, -0.19, respectively). Moreover, dance interventions and sensorimotor interventions, not including endurance, showed better results than sensorimotor interventions, including endurance (0.87; 95% CI: 0.04, 1.70 and 0.67; 95% CI: -0.06, 1.27, respectively).

Finally, as shown in Table 2, the indirect effects of the network meta-analysis showed positive results for alternative (-0.52; 95% CI: -0.92, -0.13), dance (-0.64; 95% CI: -1.24, -0.05), endurance (-0.49; 95% CI: -0.82, -0.15), resistance (-0.82; 95% CI:-1.23, -0.41), sensorimotor interventions, including endurance (-1.09; 95% CI: -1.68, -0.50), and sensorimotor interventions, not including endurance (-0.55; 95% CI:-0.90,-0.21) versus control comparisons (Table 2).

Best treatment probabilities. The probability of being one of the two best treatments was 55% for sensorimotor interventions, including endurance and 22% for balance programs. Furthermore, the highest SUCRA was for sensorimotor interventions, including endurance (90%) and resistance programs (76%) (Figures 2, Supplementary Figures 2, and Supplementary Table 5).

Sensitivity analysis, heterogeneity, and publication bias The sensitivity analysis after removing one by one the studies form the pooled estimates showed that they were substantially modified only after removing the data from: i) Fisher et *al.*, 2008, from the body weight-support interventions versus control groups and ii) Duncan & Earhart, 2012 from the dance interventions versus control groups (Supplementary Table 6).

Three direct comparisons showed moderate heterogeneity, which ranged from I^2 = 45.5 - 57.8; τ^2 = 0.1297 - 1627 alternative exercises versus control; sensorimotor training, including endurance versus body weight support and sensorimotor training, not including endurance versus control. Six direct comparisons showed substantial

heterogeneity (body weight support versus control, body weight support versus endurance; dance versus control; resistance versus control; sensorimotor training not including endurance versus endurance; sensorimotor training not including endurance vs. sensorimotor training, including endurance), which ranged from I^2 = 72.2 - 91.6, τ^2 = 0.2145 - 1.0538 (Supplementary Table 7).

Publication bias was found for the direct comparison of sensorimotor training not including endurance versus resistance (p = 0.066) (Supplementary Figure 3 and Table 8).

Meta-regressions. Meta-regressions showed that only the duration of interventions influenced the relationship between dance interventions and UPDRS-III scores (Supplementary Table 9).

DISCUSION

This network meta-analysis aimed at providing evidence regarding the comparative effectiveness of exercise programs on motor symptoms of patients with PD as assessed using the motor part of the UPDRS. The results of this network meta-analysis show that physical activity interventions are effective in the management of PD motor symptoms. The most effective physical activity interventions (in a decreasing order) were sensorimotor training including endurance, resistance, dance, sensorimotor training not including endurance, alternative exercise, and endurance training.

From our results, complex or multi-faceted physical[9-84] activity program that emphasize on fine motor tasks like holding a pencil or gross motor tasks like getting up from the bed, could improves walking, self-care and other tasks by helping people to modify and adjust how they perceive their movements. These aims could be achieved by those physical exercise programs including postural control and progressive challenges to the sensorimotor system, using aerobic, relaxation, postural and stretching exercises, and gait and balance training. Dance, alternative exercise, resistance, endurance training, sensorimotor training not including endurance and sensorimotor training including endurance, could be included in this classification.-The pharmacological treatment of PD motor symptoms is well defined from the early stages of the disease, but gait and balance impairments persist, and adverse effects of medication usually appear.[85] The absence of reported side effects of physical activity programs makes them a potentially useful

adjunct to medication,[86] although patients might be closely followed as side effects could occur based on patient's stage or severity of the health condition.

Previous research has reported positive effects of exercise on movement. In our study, most types of exercise confirmed these previous findings, although we did not find significant effects of balance, combined, and body weight-supported exercise programs, which seems not to adequately foster all the UPDRS-III dimensions. Additionally, because the scarcity of studies and the width of the CI, the small, but significant, effect estimated for dance should cautiously be interpreted. These types of exercise are the less reported in the included studies, which could influence our data. Additionally, owing to the increasing evidence of physical activity interventions in the treatment of PD motor symptoms, there is considerable heterogeneity among the intervention characteristics (intensity, frequency, and duration).[87] In addition, the scarcity of studies reporting the above-mentioned interventions and the lack of information on their characteristics make difficult to firmly conclude about the effectiveness of these types of interventions.

Several mechanisms have been proposed to explain the benefits of exercise on PD motor symptoms. These exercises require the patient to respond to both cognitive and physical demands, incorporating specific movements involving multitask exigencies and motor skill learning.[87] Most physical activities include a visual or auditory cue, facilitating attention, balance, and rhythm on gait[88] and reinforcing the neuronal circuits that contribute to lower limb movements.[89] Additionally, some studies have hypothesized that exercise enhances the release of brain-derived neurotrophic factors and promotes neural repair and neuroplasticity.[90] The underlying mechanisms behind these are the increase in cerebral blood flow arising from these types of exercise.

Limitations Some limitations encountered in this study were as follows. First, some studies did not report whether the patients were assessed in the ON- or OFF-medication state. Second, most studies included patients with PD in II to III H&Y stages, and this could limit the effect of the interventions. Third, although we have distinguished eight exercise intervention types, it cannot be denied that there are some differences between each type of exercise classified into the same category, as well as their levels of intensity, frequency of delivery, and duration of programs. Fourth, the presence of a publication bias in the direct comparison of sensorimotor training, not including endurance versus resistance. Thus, these data should be cautiously interpreted. Fifth, only

studies reporting PD motor symptoms using the UPDRS scale have been included in this network meta-analysis and therefore, some bias could not be avoided. Sixth, although data showed no influence of some intervention characteristics (duration of the intervention in weeks and weekly session time in minutes) on the effect size of intervention versus control groups in motor symptoms assessed by UPDRS-III, the meta-regression analyses were conducted only in those comparison subgroups, including six or more studies. Finally, the calculated statistical power of the studies was small in most, which could cause difficulties to find differences between groups. The use of meta-analysis reinforces the statistical power of individual studies.

CONCLUSION

Due to the high burden of disease attributable to PD, providing patients with effective approaches that could mitigate their motor symptoms and promote their independence in activities of daily living has become a priority. The results of this network meta-analysis allow us to conclude that physical activity interventions are an effective approach in the management of PD motor symptoms. Among the different intervention programs, sensorimotor training including endurance, resistance, dance, sensorimotor training not including endurance, alternative exercise, and endurance training seems to be the most effective physical activity interventions. This information is of use to clinicians prescribing exercise for mitigating motor symptoms in patients with PD, as well as to policy makers when designing new strategies to cope with the devastating consequences of PD.

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Figure legends

Figure 1. Network of available comparisons between physical activity interventions on PD motor symptoms measured by UPDRS. Size of node is proportional to number of trial participants, and thickness of continuous line connecting nodes is proportional to number of participants randomised in trials directly comparing the two treatments. /CN: Control; BWS: Body Weight Support; BL: Balance; A: Alternative; MTnoEN: Sensorimotor Training without Endurance; SMT-EN: Sensorimotor Training with Endurance; RT: Resistance; EN: Endurance; DN: Dance; COM: Combined exercise.

Figure 2. Surface under the cumulative ranking (SUCRA)

Table 1. Characteristics of the included studies.

Study (year)	Country	Population characteristics					Intervention characteristics		
		Sample size (n# women)	Age years (mean ± SD)	Duration of PD (y) (mean ± SD)	Basal H&Y (mean ± SD)	Basal UPDRS (mean ± SD or CI)	PA intervention	PA characteristics	Dose
Abraham et al, 2018	USA	IG: 10 (1) CG: 10 (3)	IG: 66.4 (12.5) CG: 65.1 (7.5)	IG: 6.1 (3.8) CG: 8.5 (4.5)	IG: 2.0 (1.8-2.5)* CG: 2.0 (2.0-2.5)*	IG: 38.4 (13.8) CG: 32.1 (12.2)	IG: Dynamic Neuro-Cognitive Imagery (DNI) CG: health education	IG: 15min warm-up+45min DNI concept introduction and practice part A and B+20min DNI movement session+5min DNI cool-down/wrap-up CG: 90min read one lesson+30min exercises on video	2w-5sxw (120 min)
Acarer et al, 2015	Turkey	IG: 29 (12) CG: 11 (3)	IG: 67 (51-81) CG: 60 (40-71)	IG: 4.5 (1-24) CG: 8 (1-18)	IG: 22 in stage II CG: 6 in stage II	IG: 19.5 (10-54)* CG: 25 (8-41)*	IG: customized vestibular rehabilitation CG: control group	IG: adaptation exercises+substitution exercise+habitutation exercises+balance exercises+home-based exercises Control: usual care	8w-1sxw (30-45min) +2sxd of home-based exercise (30-40min)
Almeida & Bhatt, 2012	Canada	IG1. 14 (6) IG2: 14 (2) CG: 14 (3)	IG1: 63.86 (8.41) IG2: 73.93 (6.53) CG: 67.43 (9.26)	NA	NA	IG1: 23.68 (10.1) IG2: 22.07 (8.0) CG: 24.21 (9.5)	IG1: treadmill group IG2: overground group CG: control group	IG1: treadmill gaiting on equally distributed spaced cues IG2: overground gait on equal spaced cues on carpet	6w-3sxw (30min)
Amano et al, 2013	USA	IG1: 12 (5) IG2: 15 (8) IG3: 9 (2) CG: 9 (2)	IG1: 64 (13) IG2: 66 (11) IG3: 68 (7) CG: 66 (7)	IG1: 7 (7) IG2: 8 (5) IG3: 12 (7) CG: 5 (3)	IG1: 2.3 (0.4) IG2: 2.4 (0.6) IG3: 2.2 (0.4) CG: 2.4 (0.4)	IG1: 21.1 (6.8) IG2: 23.1 (6.0) IG3: 24.1 (5.7) CG: 23.1 (4.8)	IG1 and IG2: Tai Chi exercise IG3: Qi-Gong meditation CG: usual care	IG1 and IG2: Yang-style short forms IG3: Qi-Gong meditation	IG1:16w-2sxw (60min) IG2:16w-3sxw (60 min) IG3:16w-2sxw (60min)
Ayán & Cancela, 2012	Spain	IG1: 10 (6) IG2: 10 (5)	IG1: 68.9 (9.6) IG2: 71.9 (5.1)	IG1: 6.1 (3.1) IG2: 7.5 (5.5)	IG1: 2.4 (0.7) IG2: 2.0 (0.7)	IG1: 13.7 (6.9) IG2: 16.2 (6.6)	IG1: low-intensity water-based exercise IG2: muscular resistance water-based exercise	IG1: 10min warm-up+20min balance exercises+15min dynamic exercises+10min cool-down IG2: 15min warm up+30min muscular resistance+15min cool-down	12w-2sxw (60min)
Beck et al, 2017	Canada	IG1: 19 (4) IG2: 20 (4) CG: 11 (1)	IG1: 68.63 (9.91) IG2: 73.05 (7.84) CG: 71.27 (6.57)	IG1: 7.0 (5.01) IG2: 6.70 (4.16) CG: 8.36 (5.87)	NA	IG1: 20.08 (11.41) IG2: 22.89 (8.15) CG: 16.91 (9.20)	IG1: external focus of attention exercise IG2: internal focus on attention exercise CG: usual care	IG1: walking, balance, stretching, and coordination exercises with attention focused on movement of labels IG2: walking, balance, stretching, and coordination exercises with attention focused exercise on movement of limbs	11w-3sxw (60min)
Busini et al, 2006	Italy	IG1: 13 (8) IG2: 13 (9)	IG1: 65.7 (7) IG2: 62.7 (4)	IG1: 11.2 (5.4) IG2: 10.6 (4.8)	IG1: 3 in stage II IG2: 4 in stage II	IG1: 11 (2-16)* IG2: 12 (5-20)*	IG1: aerobic training IG2: Gi-gong group	IG1:10min warm-up+30min cycle ergometer at 50-60% HR+10min cool-down IG2: Gi-gong as Chinese physiotherapy approach	IG1: 7w-3sxw (45min) IG2: 7w-3sxw (50min)
Canning et al, 2012	Australia	IG:10 (5) CG: 10 (4)	IG: 60.7 (5.9) CG: 62.9 (9.9)	IG: 6.1 (4.0) CG: 5.2 (4.1)	NA	IG: 20.9 (10.2) CG: 17.9 (7.1)	IG: semi supervised home-based exercise program of treadmill walking CG: usual care	IG: warm-up+treadmill walking at 60-80% of average speed+cold-down	6w-4sxw (30-40min)
Carda et al, 2012	Italy	IG1: 15 (NA) IG2: 15 (NA)	IG1: 67.87 (7.05) IG2: 66.93 (5.13)	IG1: 3.73 (2.49) IG2: 3.73 (1.91)	IG1: 2.17 (0.24) IG2: 2.23 (0.26)	IG1: 10.33 (8.89-11.78) IG2: 10.73 (9.32-12.14)	IG1: robot treadmill walking IG2: treadmill walking	IG1: 15min at 50% BWS+15min at 30% BWS, at 1.5-3.0km/h IG2: 30min treadmill at 80-100% maximum speed	4w-3sxw (30min)

IG: intervention group; CG: control group; NA: not available; w: week; sxw: sessions per week; HR: heart rate; BWS: HRR: heart rate reserve; AAMHR: age-appropriate maximal heart rate; BWS: body weight support; min: minutes; OT: occupational therapy; PD: Parkinson Disease; * Median +IR; ^: Mean +SE

Table 1. Characteristics of the included studies. (continue)

Study (year)	Country	Population characteristics					Intervention characteristics		
		Sample size (n# women)	Age years (mean ± SD)	Duration of PD (y) (mean ± SD)	Basal H&Y (mean ± SD)	Basal UPDRS (mean ± SD)	PA intervention	PA characteristics	Dose
Carrol et al, 2017	Ireland	IG: 10 (3) CG: 8 (3)	IG: 69.5 (57.75-71.75)* CG: 74 (67-77)*	IG: 7 (3.25-12.25)* CG: 10.5 (4.25-13.5)*	IG: 2.0 (1.5-2.25)* CG: 2.0 (1.63-2.88)*	IG: 17.5 (8.75-21.25)* CG: 16.5 (10.25-21.25)*	IG: aquatic gait training CG: usual care	IG: 10min warm-up+25min gait training+10min cool-down	6w-2sxw (45min)
Cheng et al, 2017	Taiwan	IG: 12 (3) CG: 12 (4)	IG: 65.8 (11.5) CG: 67.3 (6.4)	IG: 6.1 (4.1) CG: 8.1 (4.6)	IG: 1.8 (0.6) CG: 2.0 (0.8)	IG: 19.7 (4.2) CG: 19.5 (6.3)	IG: curved-treadmill walking CG: trunk exercise	IG: 15min turning-based treadmill each direction starting on 80% of comfortable speed+10min walking on ground CG: 30min trunk-arm exercises in a sitting position+10min walking on ground	4-6w-12s (40min)
Choi et al, 2013	Korea	IG1: 7 (7) IG2: 9 (9) CG: 7 (7)	IG1: 62.3 (6.5) IG2: 65.6 (7.9) CG: 64.9 (7.2)	IG1: 5.8 (3.4) IG2: 6.1 (2.9) CG: 4.7 (4.2)	IG1: 2.5 (2-3)* IG2: 2.5 (2-3)* CG: 2.5 (2-3)*	IG1: 33.9 (15.3) IG2: 19.8 (9.0) CG: 32.8 (6.2)	IG1: combined exercise program IG2: Tai Chi exercise CG: no intervention	IG1: 5-10min warm-up+40-50min combined exercise+5min cool-down IG2: 5-10min warm-up+40-50min Sun style Tai Chi+5min cool-down	8w-3sxw
Choi et al, 2013	Korea	IG:11 (NA) CG: 9 (NA)	IG: 60.81 (7.6) CG: 65.54 (6.8)	IG: 5.2 (2.7) CG: 5.2 (2.7)	IG: 1.6 (0.6) CG: 1.8 (0.3)	IG: 22.36 (7.44) CG:17.67 (8.21)	IG: Tai Chi intervention CG: no-exercise intervention	IG: 10min warm-up+30min Tai Chi exercises+10min meditation+10min cool-down	12w-2sxw (50min) +1sxw home-based exercise
Collet et al, 2017	UK	IG: 54 (23) CG: 51 (21)	IG: 66 (9) CG: 67 (7)	IG: 4.8 (4.1) CG: 5.3 (4.1)	NA	IG: 16.7 (10.1) CG: 19.9 (9.9)	IG: aerobic exercise CG: handwriting	IG: 30min of aerobic training at 55-85% HR+30min resistance training CG: 'warm-up' hand exercises+writing exercises+hand exercises	24w-2sxw (60min)
Combos et al, 2013 (a los 6m)	USA	IG1: 24 (10) IG2: 24 (10)	IG1: 58.6 (5.6) IG2: 59.0 (4.6)	IG1: 6.5 (4.7) IG2: 6.5 (4.1)	IG1: 2.3 (0.53) IG2: 2.2 (0.41)	IG1: 20.9 (8.0) IG2: 21.6 (10.1)	IG1: modified Fitness Counts IG2: progressive resistance training	IG1: stretches+balance+breathing+non-progressive strengthening IG2: strengthening exercises	24w-2sxw (60-90min)
Cugusi et al, 2015	Italy	IG: 10 (2) CG: 10 (2)	IG: 68.1 (8.7) CG: 66.6 (7.3)	IG: 7 (2) CG: 7 (4)	IG: 2.4 (0.8) CG: 2.3 (0.5)	IG: 25.3 (11.1) CG: 25.0 (11.8)	IG: Nordic walking program CG: usual care	IG: warm up+practicing nordic walking at 60-80% of HRR+cold down	12w-2sxw (60min)
Dipascuale et al, 2016	Italy	IG: 20 (7) CG: 20 (7)	IG: 69.9 (6.42) CG: 66.4 (9.32)	IG: 27m (7) CG: 28m (8)	IG: 16 in stage II CG: 15 in stage II	IG: 11(5)* CG: 8.5 (7.5)*	IG: physiotherapy program CG: usual exercise	IG: transfers+body posture+reaching and grasping+balance+ gait CG: exercise of upper limbs+lower limbs+spine+balance+ breathing	16w-2sxw (60min)
Duncan and Earhart, 2012	USA	IG: 26 (11) CG: 26 (11)	IG: 69.3 (1.9)^ CG: 69.0 (1.5)^	IG: 5.8 (1.1)^ CG: 7.0 (1.0)^	IG: 2.6 (0.1)^ CG: 2.5 (0.1)^	IG: 44.5 (2.3)^ CG: 48.0 (1.8)^	IG: Argentine tango CG: usual care	IG: 5min greeting and practice+10min warm up+10min new steps+15min music/rhythmic training+17min amalgamation and encapsulation+3min close	48sesions-2sxw (60min)
Ebersbach et al, 2010	Germany	IG1: 20 (13) IG2: 19 (12) CG: 19 (11)	IG1: 67.1 (3.6) IG2: 65.5 (9.0) CG: 69.3 (8.4)	IG1: 6.1 (3) IG2: 7.8 (4.4) CG: 7.4 (5.9)	IG1: 2.8 (0.37) IG2: 2.6 (0.4) CG: 2.5 (0.7)	IG1: 21.1 (6.3) IG2: 18.5 (5.8) CG: 19.1 (9.7)	IG1: Lee Silverman voice treatment IG2: Nordic walking CG: home-based exercise	IG1: whole-body movements+stretching+goal-directed activities of daily living IG2: warm-up+practicing nordic walking+cool-down CG: stretching+high amplitude movements+active work for muscular power and posture	IG1: 4w-4sxw (60min) IG2: 8w-2sxw (60min) CG: 1s (60min)
Fisher et al, 2008	USA	IG1: 10 (4) IG2: 10 (5) CG: 10 (2)	IG1: 64.0 (14.5) IG2: 61.5 (9.8) CG: 63.1 (11.5)	IG1: 14.7m (9.9) IG2: 8.8m (7.9) CG: 17.7m (13.3)	IG1: 1.9 (0.5) IG2: 1.9 (0.3) CG: 1.9 (0.3)	IG1: 27.6 (10.3) IG2: 30.5 (8.7) CG: 27.6 (7.3)	IG1: treadmill walking IG2: physical therapy CG: zero-intensity group	IG1: treadmill at 10% BWS and 3.0METS-75%AAMHR IG2: passive range of motion and stretching+active range of motion+balance+gait+resistance+functional activities and transitional movement CG: education class	8w-3sxw (45min) 8w-6s (60min)

IG: intervention group; CG: control group; NA: not available; w: week; sxw: sessions per week; HR: heart rate; BWS: HRR: heart rate reserve; AAMHR: age-appropriate maximal heart rate; BWS: body weight support; min: minutes; OT: occupational therapy; PD: Parkinson Disease; * Median +IR; ^: Mean +SE

Table 1. Characteristics of the included studies. (continue)

Study (year)	Country	Population characteristics					Intervention characteristics		
		Sample size (n# women)	Age years (mean ± SD)	Duration of PD (y) (mean ± SD)	Basal H&Y (mean ± SD)	Basal UPDRS (mean ± SD)	PA intervention	PA characteristics	Dose
Lunari et al, 2017	Italy	IG1: 19 (8) IG2: 19 (9)	IG1: 71.5 (11.7) IG2: 77.7 (8.3)	NA	IG1: 3.1 (0.9) IG2: 2.2 (0.5)	IG1: 32.36 (15.46) IG2: 30.15 (12.70)	IG1: robotic-assisted gait training IG2: overground gait training	IG1: 30min robot-assisted gait training at 2.2-2.5km/h+30min conventional exercise program IG2: 30min proprioceptive neuromuscular facilitation+30min conventional exercise program	4w-6sxw (60min)
Galli et al, 2016	Italy	IG1: 25 (11) IG2: 25 (13)	IG1: 68.8 (6.9) IG2: 66.4 (9.7)	IG1: 9.9 (NA) IG2: 8.1 (NA)	IG1: 1.5-3 IG2: 2-4	IG1: 39 (34-45) IG2: 50 (43-53)	IG1: robotic-assisted gait training IG2: overground gait training	IG1: 45min robot-assisted gait training at 2.2-2.5km/h+ 135min occupational therapy for upper limbs IG2: 45min treatmill+135min occupational therapy for upper limbs	4w-5sxw (180min)
Gandesan et al, 2014	India	IG1: 20 (5) IG2: 20 (5) CT: 20 (4)	IG1: 57.7 (10.3) IG2: 57.6 (9.1) CT: 59.1 (6.8)	IG1: 4.9 (3.1) IG2: 5.7 (3.9) CT: 5.5 (3.4)	IG1: 17 in stage II IG2: 17 in stage II CT: 16 in stage II	IG1: 30.70 (5.04) IG2: 31.95 (4.26) CT: 30.15 (3.88)	IG1: walking IG2: treadmill walking CT: usual care	IG1: 5min warm-up+30min walking in straight path+turning and arm swinging strategies+5min cool-down IG2: 5min warm-up+30 min treadmill walking 20% BWS+5min cool-down	4w-4sxw (30min)
Gao et al, 2014	China	IG: 37 (14) CG: 39 (12)	IG: 69.54 (7.32) CG: 68.28 (8.53)	IG: 9.15 (8.58) CG: 8.37 (8.24)	IG: 19 in stage II CG: 12 in stage II	IG: 31.86 (11.49) CG: 30.62 (9.90)	IG: Tai Chi group CG: usual care	IG: 24-form Yang style Tai Chi exercise	12w-3sxw (60min)
Gobbi et al, 2009	Brazil	IG1: 21 (11) IG2: 13 (8)	IG1: 67 (9) IG2: 69 (8)	NA	IG1: 2 (1) IG2: 2 (1)	IG1: 21 (12) IG2: 31 (14)	IG1: multi-mode exercise IG2: adaptative program	IG1: aerobic exercise+flexibility+ strength+motor coordination+balance IG2: flexibility+strength+ motor coordination+ balance	IG1: 24w-3sxw (60min) IG2: 24w-1sxw (60min)
Hackney et al, 2007	USA	IG: 9 (3) CG: 10 (4)	IG: 72.6 (2.2)^ CG: 69.6 (2.1)^	IG: 6.2 (1.5)^ CG: 3.3 (0.5)^	IG: 2.3 (0.7)^ CG: 2.2 (0.6)^	IG: 30.6 (1.3)^ CG: 28.2 (1.2)^	IG: Argentine tango CG: exercise classes	IG: postural stretches+balance+tango-style walking+footwork patterns/experimentation with timing of steps to music CG: 40min breathing/stretching and resistance/dexterity exercises+10min stretching and strengthening exercises	13w-21s (60min)
Hackney and Earhart, 2008	USA	IG: 13 (2) CG:13 (3)	IG: 64.9 (8.3) CG: 62.6 (10.2)	IG: 8.7 (4.7) CG: 5.5 (3.3)	IG: 2.0 (1.5-2.1)* CG: 2.0 (2.0-2.0)*	IG: 25.5 (21.5-32.8)* CG: 24.0 (17.8-28.3)*	IG: Tai Chi CG: no intervention	IG: Yang Short Style of Cheng Manching	13w-2sxw (60min)
Hackney and Earhart, 2009	USA	IG1: 17 (6) IG2: 14 (3) CG: 17 (5)	IG1: 66.8 (2.4)^ IG2: 68.2 (1.4)^ CG: 65.5 (2.8)^	IG1: 9.2 (1.5)^ IG2: 6.9 (1.3)^ CG: 5.9 (1.0)^	IG1: 2.0 (0.2)^ IG2: 2.1 (0.1)^ CG: 2.2 (0.2)^	IG1: 26.9 (2.5)^ IG2: 27.6 (2.0)^ CG: 27.4 (2.4)^	IG1: waltz/foxtrot lessons IG2: tango lessons CG: no intervention	NA	13w-2sxw (60min)
Kurt et al, 2018	Turkey	IG: 20 (9) CG: 20 (7)	IG: 62.41 (6.76) CG: 63.61 (7.18)	NA	IG: 9 in stage II CG: 11 in stage II	IG: 30.09 (4.88) CG: 28.06 (5.37)	IG: water Ai Chi exercises CG: land-based exercises	IG: 15min warm-up+30min 16 different movements of Ai Chi+15min cold down CG:10min warm up+10min stretching+30min balance and gait training+10min cold down	5w-5sxw (60min)
Lee et al, 2018	Republic of Korea	IG: 25 (15) CG: 16 (9)	IG: 65.8 (7.2) CG: 65.7 (6.4)	IG: 4.5 (3.3) CG: 4.4 (3.0)	IG: 10 in stage II CG: 5 in stage II	IG: 14.8 (6.7) CG: 11.9 (3.1)	IG: Qigong and meridian therapy CG: usual care	IG: 15min relaxing the meridians+30min circulating Qi+15min stabilizing Qi	8w-2sxw (60min)
Li et al, 2012	USA	IG1: 65 (20) IG2: 65 (27) CG: 65 (26)	IG1: 68 (9) IG2: 69 (8) CG: 69 (9)	IG1: 8 (9) IG2: 8 (9) CG: 6 (5)	IG1: 34 in stage II IG2: 27 in stage II CG: 28 in stage II	IG1: 15.28 (5.59) IG2: 15.32 (6.04) CG: 15.06 (6.17)	IG1: Tai Chi IG2: resistance training CG: low-intensity exercise	IG1: 6-Tai Chi movements into 8-form routine IG2: strengthening+resistance CG: stretching+breathing	24w-2sxw (60min)

IG: intervention group; CG: control group; NA: not available; w: week; sxw: sessions per week; HR: heart rate; BWS: HRR: heart rate reserve; AAMHR: age-appropriate maximal heart rate; BWS: body weight support; min: minutes; OT: occupational therapy; PD: Parkinson Disease; * Median +IR; ^: Mean +SE

Table 1. Characteristics of the included studies. (continue)

Study (year)	Country	Population characteristics					Intervention characteristics		
		Sample size (n# women)	Age years (mean ± SD)	Duration of PD (y) (mean ± SD)	Basal H&Y (mean ± SD)	Basal UPDRS (mean ± SD)	PA intervention	PA characteristics	Dose
Meng et al, 2015	USA	IG1: 14 (5) IG2: 13 (2) CG: 10 (6)	IG1: 71.6 (6.6) IG2; 71.2 (6.5) CG: 74.9 (8.3)	IG1: 6.6 (4.4) IG2: 6.9 (6.3) CG: 5.9 (6.2)	IG1: 2.2 (0.6) IG2: 2.2 (0.7) CG: 2.1 (0.7)	IG1: 32.9 (12.0) IG2: 28.15 (11) CG: 27.6 (7.8)	IG1: power training IG2: Yoga CG: health education classes	IG1: loads on 11 pneumatic machines IG2: Vinyasa Yoga poses CG: life-style modification+medication +therapy/exercise+nutrition/long-term care	IG1: 12w-2sxw (45-60min) IG2: 12w-2sxw (60min) CG: 12w-1sxm (60min)
Miyai et al, 2002	Japan	IG1: 11 (6) IG2: 9 (4)	IG1: 69.5 (1.9)^ IG2: 69.8 (1.5)^	IG1: 4.1 (0.8)^ IG2: 4.5 (0.7)^	IG1: 2.9 (0.1)^ IG2: 2.8 (0.1)^	IG1: 18.5 (1.2)^ IG2: 18.6 (1.4)^	IG1: treadmill walking IG2: physical therapy	IG1: 45min treadmill with 0-20% BWS and 0.5-3.0km/h +45min occupational therapy and transfers IG2: 45min general conditioning+range-of-motion+ADL/gait training+ 45min occupational therapy and transfers	4w-3sxw (90min)
Modugno et al, 2010 (al on-T1)	Italy	IG: 10 (5) CG: 10 (5)	IG: 63.2 (1.13)^ CG: 62 (1.58)^	IG: 9.4 (1.1)^ CG: 10 (1.8)^	IG: 3.5 (0.17)^ CG: 3 (0.22)^	IG: 23.5 (3.01)^ CG: 26.9 (4.86)^	IG: physiotherapy CG: therapeutic theatre	IG: 10min warm-up+15min stretching+15min postural exercise+20min gait+15min balance+15min relaxation CG: 20min vocal warm-up+40min preparation of the scene+5hours staging	IG: 3y-3sxw (120-180min) CG: 3y-2-4sxm (360min)
Molinedo-Cardalda et al, 2018	Spain	IG1: 13 (8) IG2: 13 (9)	IG1: 62.85 (9.75) IG2: 66.0 (13.14)	IG1: 5.77 (3.39) IG2: 5.69 (4.4)	IG1: 2.08 (0.49) IG2: 2.00 (0.82)	IG1: 29.55 (11.26) IG2: 31.54 (11.84)	IG1: Pilates IG2: physical activity program	IG1: 10min warm-up+45min exercise with medium-resistant theraband and 0,5kg ankle/wristbans+5min cool-down IG2: 10min warm-up+45min aerobic/strength/flexibility/ articular mobility/coordination exercises+5min cool-down	12w-2sxw (60min)
Monticone et al, 2015	Italy	IG: 35 (11) CG: 35 (13)	IG: 74.1 (6.0) CG: 73.4 (7.0)	IG: 15.7 (2.6) CG: 15.3 (3.0)	IG: 20 in stage III CG: 22 in stage III	IG: 83.0 (15.3) CG: 83.0 (14.3)	IG: motor, cognitive and ergonomic training CG: resistance and velocity training	IG: task-oriented+balance+gait exercises+neuropsychological training+ADLs exercises CG: neuromotor techniques, articular mobilization, strengthening and stretching, balance and walking exercises	IG: 8w-5sxw(90min)+ 30minxw psychologist+ 30minxw OT CG: 8w-5sxw (90min)
Morris et al, 2015	Australia	IG1: 70 (28) IG2: 69 (23) CG: 71 (19)	IG1: 67.4 (10.4) IG2: 68.4 (9.9) CG: 67.9 (8.4)	IG1: 7.2 (6.2) IG2: 6 (5.5) CG: 6.9 (5.2)	IG1: 22 in stage II IG2: 17 in stage II CG: 17 in stage II	IG1: 14.6 (5,9) IG2: 14.9 (6.3) CG: 16.2 (6.5)	IG1: progressive resistance strength IG2: movement strategy training CG: life skills program	IG1: functional resistance with Theraband and BW+education to prevent falls IG2: strategies to prevent falls, improve mobility and balance during functional taks+education to prevent falls CG: social activities, practical advice, information sessions and group discussion	8w-1sxw (120min)+ 120min 1sxw of home exercise
Nadeau et al, 2013	Canada	IG1: 12 (4) IG2: 11 (1) IG3: 11 (2)	IG1: 64.0 (6.6) IG2: 60.1 (6.8) IG3: 63.4 (5.6)	NA	IG1: 1.92 (0.20) IG2: 1.92 (0.20) IG3: 1.86 (0.23)	IG1: 29.1 (11.8) IG2: 21.9 (5.5) IG3: 17.9 (6.6)	IG1: speed treadmill group IG2: mixed treadmill group IG3: low intensity routines	IG1: 5min warm-up+45 min treadmill at 80-100% preferential speed+5min cool-down IG2: 5min warm-up+45 min treadmill at +0.2km/h+5min cool-down IG3: Tai Chi+latin dance+resistance band exercise+coordination movements	24w-3sxw (60min)

IG: intervention group; CG: control group; NA: not available; w: week; sxw: sessions per week; HR: heart rate; BWS: HRR: heart rate reserve; AAMHR: age-appropriate maximal heart rate; BWS: body weight support; min: minutes; OT: occupational therapy; PD: Parkinson Disease; * Median +IR; ^: Mean +SE

Table 1. Characteristics of the included studies. (continue)

Study (year)	Country	Population characteristics					Intervention characteristics		
		Sample size (n# women)	Age years (mean ± SD)	Duration of PD (y) (mean ± SD)	Basal H&Y (mean ± SD)	Basal UPDRS (mean ± SD)	PA intervention	PA characteristics	Dose
Baccheitti et al,1999	Italy	IG1: 16 (4) IG2: 16 (5)	IG1: 62.5 (5) IG2: 63.2 (5)	IG1: 4.8 (3) IG2: 5.2 (2)	NA	IG1: 40.2 (7.7) IG2: 40.7 (7)	IG1: music therapy IG2: physical therapy	IG1: 10min entrance and interview+10min and visualization+ 15-20min choral singing and facial expression, breathing, and voice exercises+30min rhythmic movements+30-40 improvisation+20-30min free body expression+10min conversation IG2: passive stretching exercises+motor tasks+balance+ movement strategies	IG1: 13w-1sxw (120min) IG2: 8w-1sxw (90min)
Perez de la Cruz, 2017	Spain	IG1: 15 (NA) IG2: 15 (NA)	IG1: 66.80 (5.27) IG2: 67.53 (9.89)	IG1: 6.2 (2.54) IG2: 6.7 (3.22)	IG1: 2.82 (0.22) IG2: 2.66 (1.02)	IG1: 36.4 (16.53) IG2: 36.40 (15.16)	IG1: aquatic Ai Chi IG2: dry land therapy	IG1: 35min Ai Chi program+10min calm down IG2: 10min warm-up+25min strength training and aerobic exercises+10min cool-down	10w-2sxw (45min)
Picelli et al 2012	Italy	IG1. 17 (NA) IG2: 17 (NA)	68.3 (NA)	7.5 (NA)	3.45 (NA)	IG1: 46.31 (6.65) IG2: 47.20 (7.93)	IG1: robotic training IG2: physical therapy	IG1: 40min robot-assisted gait training at 1.3-1.6km/h IG2: stretching, mobilization and coordination	4w-3sxw (40min)
Picelli et al, 2013	Italy	IG1: 33 (7) IG2: 33 (11)	IG1: 68.2 (9.2) IG2: 69.7 (7.2)	IG1: 7.5 (5.6) IG2: 8.3 (4.1)	NA	IG1: 38 (32-43)* IG2: 40 (35-42)*	IG1: robotic training IG2: balance training	IG1: 40min robot-assisted gait training at 1.0-2.0km/h IG2: feedforward postural control+feedback postural control+postural adjustment	4w-3sxw (45min)
Pollakoff et al, 2013 T2	UK	IG: 12 (3) CG: 10 (2)	IG: 68.8 (48-77) CG: 66.6 (49-78)	IG: 7.90 (4.6-16.7) CG: 4.58 (0.25-16)	NA	IG: 18.5 (6.2) CG: 15.2 (4.3)	IG: exercise group CG: usual care	IG: cardiovascular activity, including treadmill, recumbent bikes, bikes, cross trainers and rowers+ gait and agility	10w-2sxw (60min)
Romenets et al, 2015	Canada	IG: 18 (6) CG: 15 (8)	IG: 63.2 (9.9) CG: 64.3 (8.1)	IG: 5.5 (4.4) CG: 7.7 (4.6)	IG: 1.7 (0.6) CG: 2.0 (0.5)	IG: 20.7 (10.1) CG: 27.5 (14.5)	IG. Argentine tango CG: control	IG: review of previous class+new step or elements+ improvisation activities+standard footwork exercises	12w-2sxw (60mn)
Sage & Almeida, 2009	Canada	IG1: 18 (6) IG2: 13 (7) CG: 15 (8)	IG1: 64.2 (10.3) IG2: 65.1 (9.3) CG: 68.6 (8.7)	IG1: 4.7 (4.9) IG2: 3.2 (2.9) CG: 2.5 (2.2)	NA	IG1: 22.47 (5.8) IG2: 22.2 (8.1) CG: 21.8 (7.2)	IG1: sensory attention focused exercise IG2: low-limb aerobic training CG: control group	IG1: 20–30min nonaerobic gait exercises + 20–30min sensory attention exercises with Thera-bands IG2: 5min warm-up+20min lower-limb aerobic training on Ellipticals at 60-75% HR+5min cool-down.	12w-3sxw (30min)
Sale et al, 2013	Italy	IG1: 10 (4) IG2: 10 (5)	IG1: 70.27 (9.81) IG2: 68.42 (9.41)	IG1: 8.41 (4.99) IG2: 8.72 (4.74)	IG1: 2.5-3.5 IG2: 2.5-3.5	IG1: 53.57 (14.74) IG2: 56.17 (13.86)	IG1: robot assisted gait IG2: treadmill rehabilitation	IG1: 45min robot-assisted gait at 1.5-2.5km/h+135min OT for upper limbs IG2: 45min treadmill+135min OT for upper limbs	4w-5sxw (180min)
Schenkman et al, 2012	USA	IG1: 41 (15) IG2: 39 (15) CG: 41 (15)	IG1: 63.4 (11.2) IG2: 64.5 (10.0) CG: 66.3 (10.1)	IG1: 3.9 (4.2) IG2: 4.9 (3.7) CG: 4.5 (3.8)	IG1: 2.2 (0.5) IG2: 2.3 (0.4) CG: 2.3 (0.4)	IG1: 24.4 (9.1) IG2: 24.3 (10.5) CG: 25.9 (8.9)	IG1: supervised aerobic exercise IG2: flexibility/balance/function exercise CG: home-based exercise	IG1: 5-10min warm-up+30min exercise at 65-80% of HRmax+5-10min cool-down. IG2: flexibility/balance/functional exercise CG: home-based exercise based on fitness Counts	IG1 and IG2: 16w-5-7sxw (45-50min) CG: 16m-1supervised-sxm (45-50min)+5-7s/w (45-50min)

IG: intervention group; CG: control group; NA: not available; w: week; sxw: sessions per week; HR: heart rate; BWS: HRR: heart rate reserve; AAMHR: age-appropriate maximal heart rate; BWS: body weight support; min: minutes; OT: occupational therapy; PD: Parkinson Disease; * Median +IR; ^: Mean +SE

Table 1. Characteristics of the included studies. (continue)

Study (year)	Country	Population characteristics					Intervention characteristics		
		Sample size (n# women)	Age years (mean ± SD)	Duration of PD (y) (mean ± SD)	Basal H&Y (mean ± SD)	Basal UPDRS (mean ± SD)	PA intervention	PA characteristics	Dose
Schenkman et al, 2017	USA	IG1: 43 (21) IG2: 45 (18) CG: 40 (16)	IG1: 64 (9) IG2: 63(10) CG: 64 (10)	IG1: 0.3 (0.1-1.3)* IG2: 0.3 (0.2-0.8)* CG: 0.4 (0.1-0.8)*	IG1: 31 in stage II IG2: 32 in stage II CG: 32 in stage II	IG1: 17 (7) IG2: 16 (7) CG: 17 (7)	IG1: high-intensity treadmill IG2: moderate-intensity treadmill CG: usual care	IG1: 5-10min warm-up+30min high- intensity treadmill exercise at 80-85% HRmax+5-10min cool down IG2: 5-10min warm-up+30min moderate-intensity treadmill exercise 60-65% HRmax+5-10min cool-down	26w-4sxw (50min)
Ahlenstedt et al, 2015	Germany	IG1: 17 (5) IG2: 15 (6)	IG1: 75.7 (5.5) IG2: 75.7 (7.2)	IG1: 10.1 (6.0) IG2: 9.3 (7.9)	IG1: 2.8 (0.26) IG2: 2.7 (0.4)	IG1: 22.6 (9.5) IG2: 20.3 (6.1)	IG1: resistance training IG2: balance training	IG1: 10min warm-up+50min strength of lower limbs IG2: 10min warm-up+50min stance- and gait tasks	7w-2sxw (60min)
Shulman et al, 2013	USA	IG1: 23 (7) IG2: 22 (6) IG3: 22 (4)	IG1: 66.1 (9.7) IG2: 65.8 (11.5) IG3: 65.3 (11.3)	IG1: 5.9 (3.9) IG2: 6.3 (3.5) IG3: 6.3 (4.0)	IG1: 19 in stage II IG2: 18 in stage II IG3: 16 in stage II	IG1: 30.3 (9.8) IG2: 31.6 (9.2) IG3: 34.5 (10.7)	IG1: higher-intensity treadmill training IG2: lower intensity treadmill training IG3: stretching and resistance training	IG1: increasing 5min, 0.2 km/h and 1% incline every week to reach 30min at 70-80% HRR IG2: 0% incline increasing 5min every 2 weeks to reach 50min at 40-50% HRR IG3: strengthening of the lower body+stretching of the upper and lower body	12w-3sxw IG1: 30min IG2: 50min IG3: NA
Silva-Batista et al, 2016	Brazil	IG1: 13 (3) IG2: 13 (3) CG: 13 (4)	IG1: 64.1 (9.1) IG2: 64.2 (10.6) CG: 64.2 (8.3)	IG1: 9.6 (3.9) IG2: 10.5 (4.1) CG: 10.7 (6.1)	IG1: 2.5 (0.5) IG2: 2.5 (0.4) CG: 2.5 (0.4)	IG1: 43.7 (13.4) IG2: 45.1 (8.2) CG: 43.4 (8.6)	IG1 and IG2: resistance training CG: educational group	IG1: 10min warm-up+resistance exercises with load/resistance progressively increased IG2: 10min warm-up+resistance exercises with load/resistance and instability progressively increased CG: bingo games and education	IG1 and IG2: 12s-2sxw (50min) CG: 12w-1sxw (60min)
Sofia et al, 2019	Italy	IG: 10 (4) CG: 10 (3)	IG: 67.8 (5.9) CG: 67.1 (6.3)	IG: 4.4 (4.5) CG: 5 (2.9)	IG: 2.1 (0.6) CG: 2.3 (0.4)	IG:13.0 (7.23) CG: 14.67 (7.02)	IG: Sardinian folk dance CG: usual care	IG: 30min warm-up+ 50min Sardinian folk dance+10min cool-down	12w-2sxw (90min)
van der Kolk et al, 2019	The Netherlands	IG: 65 (23) CG: 65 (27)	IG: 59.3 (8.3) CG: 59.4 (9.3)	IG: 3.4 (1.3-7.3) CG: 3.2 (1.6-6.8)	IG: 61 in stage II CG: 63 in stage II	IG: 19.4 (1.8) CG: 17.4 (1.8)	IG: aerobic exercise CG: no intervention	IG: 30min on stationary cycle at 50-70% of HRR+15min cold down CG: stretching+flexibility+relazation exercises	IG: 24w-3sxw (30-45min) CG: 24w-3sxw (30min)
Volpe et al, 2013	Italy	IG: 12 (5) CG: 12 (6)	IG: 61.6 (4.5) CG: 65.0 (5.3)	IG: 9.0 (3.6) CG: 8.9 (2.5)	IG: 2.2 (0.4) CG: 2.2 (0.4)	IG: 24.58 (3.87) CG: 23.92 (3.50)	IG: Irish dance CG: physiotherapy	IG: 10min warm-up+ 70 min Irish dance+10min cool-down CG: 10min warm-up+50min strength /balance/postural reeducation+20min gait training+10min cool-down	24w-1sxw (90min)
Xiao & Zhuang, 2016	China	IG1: 48 (14) IG2: 48 (15)	IG1: 66.52 (2.13)^ IG2: 68.17 (2.27)^	IG1: 6.15 (2.63)^ IG2: 5.45 (3.61)^	IG1: 2.1 (0.23)^ IG2: 2.2 (0.21)^	IG1: 26.9 (2.05)^ IG2: 27.4 (2.51)^	IG1: daily walking IG2: Baduanjin Oigong	IG1: daily walking IG2: 8 distinct movement routines of Baduanjin Qiong	IG1: 24w-7sxw (30min) IG2: 24w-4sxw (12-15min)+ 7s/w as CG
Zheng et al, 2015	China	IG1: 20 (7) IG2: 20 (9)	IG1: 66 (11.80) IG2: 64.35 (10.53)	IG1: 6.8 (5.43) IG2: 4.85 (3.72)	IG1: 7 in stage II IG2: 6 in stage II	IG1: 18.50 (6.20) IG2: 16.35 (7.38)	IG1: Tai Chi IG2: multimodal exercise training	IG1: Yang style 24-posture short form Tai Chi IG2: core muscle training+10min cross obstacle training+standing on ankle joint+10min cycle ergometer	12w-2sxw (60min)

IG: intervention group; CG: control group; NA: not available; w: week; sxw: sessions per week; HR: heart rate; BWS: HRR: heart rate reserve; AAMHR: age-appropriate maximal heart rate; BWS: body weight support; min: minutes; OT: occupational therapy; PD: Parkinson Disease; * Median +IR; ^: Mean +SE

Table 2. Pooled mean differences of physical activity on PD motor symptoms. Upper right triangle gives the pooled mean differences from pairwise comparisons (column intervention relative to row), lower left triangle pooled mean differences from the network meta-analysis (row intervention relative to column).

Control	**-0.48 (-0.82, -0.13)**	NA	-0.70 (-1.79, 0.40)	-0.06 (-0.44, 0.32)	-0.10 (-0.67, 0.48)	**-0.36 (-0.54, -0.19)**	-0.88 (-0.82, 0.06)	-0.39 (-0.87, 0.08)	-0.27 (-0.62, 0.07)
-0.52 (-0.92, -0.13)	**Alternative**	NA	NA	-0.03 (-0.50, 0.43)	NA	-0.10 (-0.46, 0.26)	0.16 (-0.16, 0.47)	-0.20 (-1.19, 0.79)	0.21 (-0.41, 0.84)
-0.71 (-1.80, 0.37)	-0.19 (-1.32, 0.94)	**Balance**	-0.24 (-0.72, 0.24)	NA	NA	NA	0.05 (-0.64, 0.75)	NA	NA
-0.35 (-0.87, 0.17)	0.18 (-0.45, 0.80)	0.37 (-0.69, 1.42)	**BWS**	NA	NA	-0.53 (-1.48, 0.43)	NA	NA	-0.13 (-0.77, 0.50)
-0.42 (-1.25, 0.41)	0.10 (-0.71, 0.92)	0.29 (-1.06, 1.65)	-0.07 (-1.04, 0.90)	**Combined**	NA	NA	NA	NA	NA
-0.64 (-1.24, -0.05)	-0.12 (-0.83, 0.59)	0.07 (-1.16, 1.30)	-0.29 (-1.08, 0.49)	-0.22 (-1.24, 0.80)	**Dance**	NA	NA	NA	**0.87 (0.04, 1.70)**
-0.49 (-0.82, -0.15)	0.04 (-0.43, 0.50)	0.23 (-0.85, 1.31)	-0.14 (-0.63, 0.36)	-0.07 (-0.95, 0.81)	0.16 (-0.52, 0.83)	**Endurance**	-0.30 (-0.72, 0.12)	NA	-0.28 (-0.80, 0.24)
-0.82 (-1.23, -0.41)	-0.29 (-0.81, 0.22)	-0.10 (-1.17, 0.96)	-0.47 (-1.07, 0.13)	-0.40 (-1.31, 0.51)	-0.17 (-0.89, 0.54)	-0.33 (-0.79, 0.12)	**Resistance**	NA	0.04 (-0.25, 0.33)
-1.09 (-1.68, -0.50)	-0.57 (-1.24, 0.10)	-0.38 (-1.58, 0.83)	-0.74 (-1.49, 0.00)	-0.67 (-1.68, 0.33)	-0.45 (-1.27, 0.38)	-0.60 (-1.24, 0.03)	-0.27 (-0.95, 0.40)	**SMT+endurance**	**0.67 (0.06, 1.27)**
-0.55 (-0.90, -0.21)	-0.03 (-0.51, 0.45)	0.16 (-0.93, 1.25)	-0.21 (-0.74, 0.33)	-0.14 (-1.02, 0.75)	0.09 (-0.58, 0.75)	-0.07 (-0.404 0.31)	0.26 (-0.18, 0.71)	0.54 (-0.04, 1.11)	**SMT not endurance**

Clinical implications

- So far, there is no substantial evidence showing the most effective exercise program for Parkinson's disease (PD) motor symptoms.
- Physical activity interventions are effective in the management of PD motor symptoms, with sensorimotor training, including endurance being the most effective one.
- This information is of use to clinicians prescribing exercise for mitigating patients' motor symptoms and promoting their independence in activities of daily living.

Figure 1

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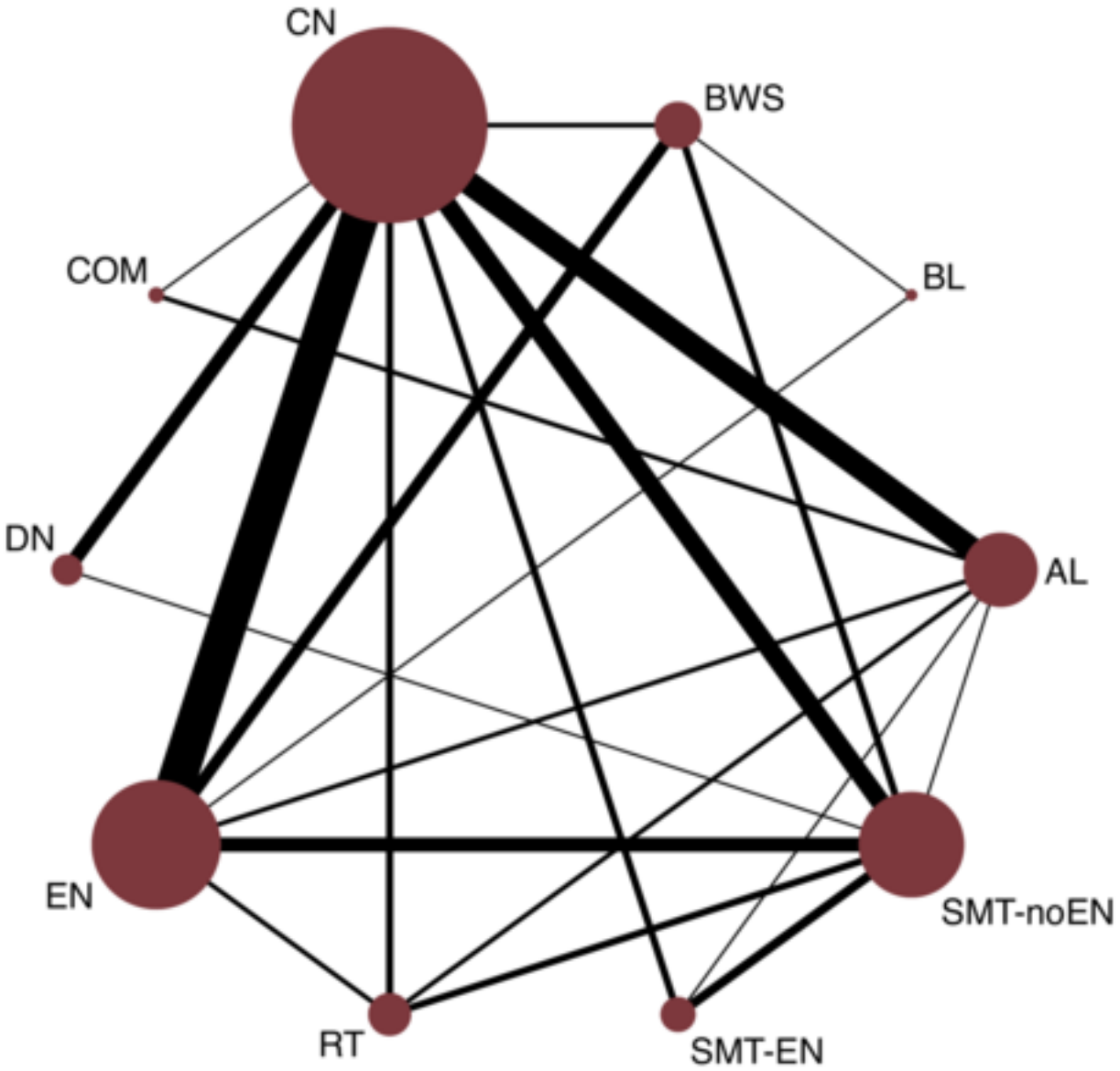

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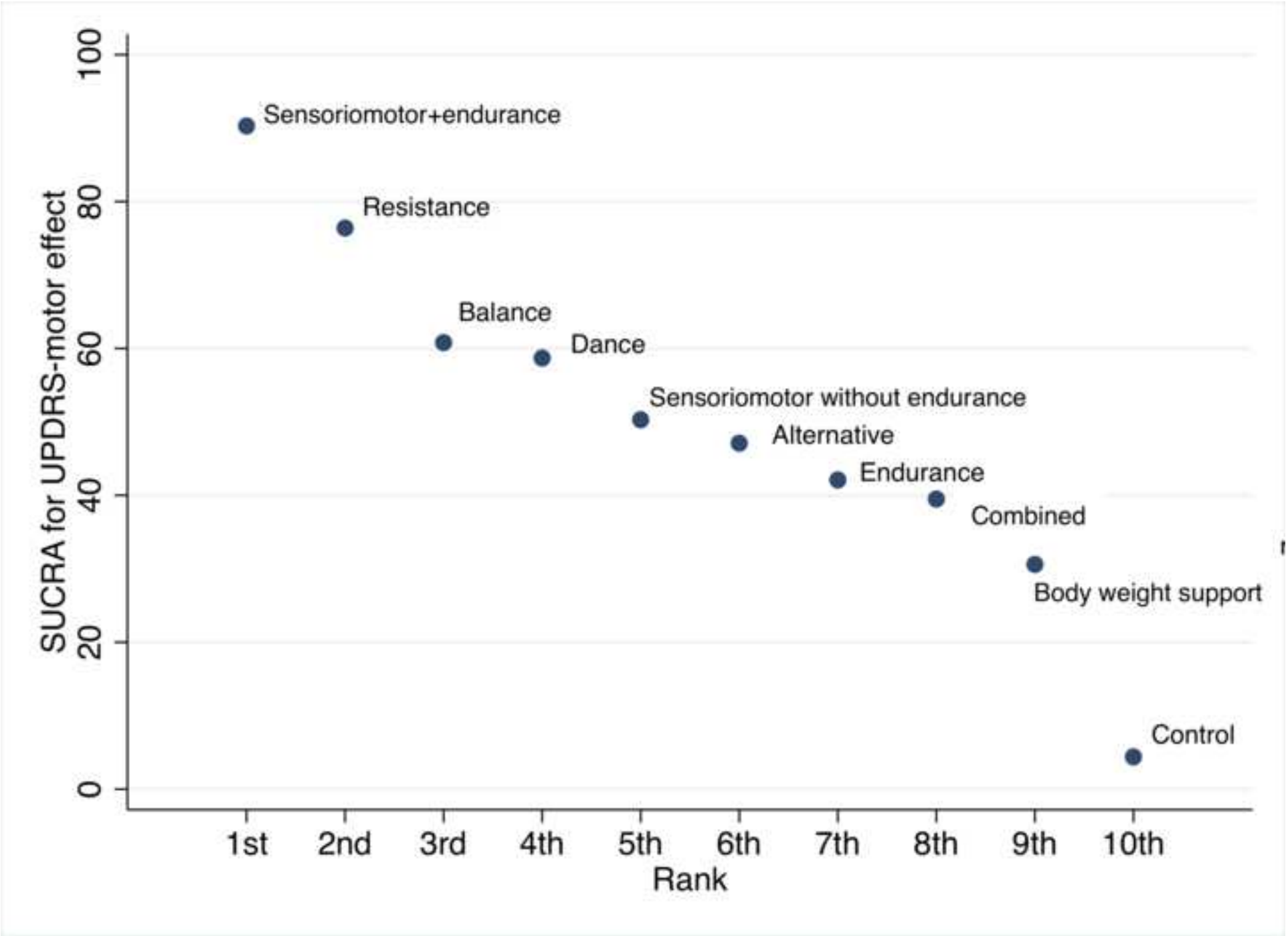

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