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Treadmill training for patients with Parkinson's disease (Review)

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[Intervention Review]

Treadmill training for patients with Parkinson's disease

Jan Mehrholz[1], Joachim Kugler[2], Alexander Storch[3], Marcus Pohl[4], Kathleen Hirsch[5], Bernhard Elsner[2]

[1]Wissenschaftliches Institut, Private Europäische Medizinische Akademie der Klinik Bavaria in Kreischa GmbH, Kreischa, Germany. [2]Department of Public Health, Dresden Medical School, Technical University Dresden, Dresden, Germany. [3]Department of Neurology, Medizinische Fakultät der TU Dresden Carl Gustav Carus, Dresden, Germany. [4]Dresden, Germany. [5]Ubiz Harzklinikum D.- C. - Erxleben GmbH, Quedlinburg, Germany

Contact address: Jan Mehrholz, Wissenschaftliches Institut, Private Europäische Medizinische Akademie der Klinik Bavaria in Kreischa GmbH, An der Wolfsschlucht 1-2, Kreischa, 01731, Germany. jan.mehrholz@klinik-bavaria.de.

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ABSTRACT

Background

Treadmill training is used in rehabilitation and is described as improving gait parameters of patients with Parkinson's disease.

Objectives

To assess the effectiveness of treadmill training in improving the gait of patients with Parkinson's disease and the acceptability and safety of this type of therapy.

Search methods

We searched the Cochrane Movement Disorders Group Specialised Register (see Review Group details for more information) (last searched September 2014), Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2014, Issue 10), MEDLINE (1950 to September 2014), and EMBASE (1980 to September 2014). We also handsearched relevant conference proceedings, searched trials and research registers, and checked reference lists (last searched September 2014). We contacted trialists, experts and researchers in the field and manufacturers of commercial devices.

Selection criteria

We included randomised controlled trials comparing treadmill training with no treadmill training in patients with Parkinson's disease.

Data collection and analysis

Two review authors independently selected trials for inclusion, assessed trial quality and extracted data. We contacted the trialists for additional information. We analysed the results as mean differences (MDs) for continuous variables and relative risk differences (RD) for dichotomous variables.

Main results

We included 18 trials (633 participants) in this update of this review. Treadmill training improved gait speed (MD = 0.09 m/s; 95% confidence interval (CI) 0.03 to 0.14; P = 0.001; I^2 = 24%; moderate quality of evidence), stride length (MD = 0.05 metres; 95% CI 0.01 to 0.09; P = 0.01; I^2 = 0%; low quality of evidence), but walking distance (MD = 48.9 metres; 95% CI -1.32 to 99.14; P = 0.06; I^2 = 91%; very low quality of evidence) and cadence did not improve (MD = 2.16 steps/minute; 95% CI -0.13 to 4.46; P = 0.07; I^2 = 28%; low quality of evidence) at the end of study. Treadmill training did not increase the risk of patients dropping out from

intervention (RD = -0.02; 95% CI -0.06 to 0.02; P = 0.32; I^2 = 13%; moderate quality of evidence). Adverse events were not reported in included studies.

Authors' conclusions

This update of our systematic review provides evidence from eighteen trials with moderate to low risk of bias that the use of treadmill training in patients with PD may improve clinically relevant gait parameters such as gait speed and stride length (moderate and low quality of evidence, respectively). This apparent benefit for patients is, however, not supported by all secondary variables (e.g. cadence and walking distance). Comparing physiotherapy and treadmill training against other alternatives in the treatment of gait hypokinesia such as physiotherapy without treadmill training this type of therapy seems to be more beneficial in practice without increased risk. The gain seems small to moderate clinically relevant. However, the results must be interpreted with caution because it is not known how long these improvements may last and some studies used no intervention in the control group and underlie some risk of bias. Additionally the results were heterogenous and we found variations between the trials in patient characteristics, the duration and amount of training, and types of treadmill training applied.

PLAIN LANGUAGE SUMMARY

Treadmill training for people with Parkinson's disease

Question: We assessed whether treadmill training and body weight support, individually or in combination, could improve walking in people with Parkinson's disease when compared with other gait training methods or no treatment.

Background:Slow walking is a common problem for people with Parkinson's disease. For people with mild to moderate Parkinsons disease it affects ability to do everyday things and their quality of life. Treadmill training uses specially designed machines to help gait rehabilitation. However, the role of treadmill training for people with Parkinson's disease in improving gait parameters is still unclear.

Study characteristics: We identified 18 relevant trials, involving 633 participants which evaluated this type of therapy, up to September 2014.

Key results and quality of the evidence: Treadmill training did improve gait speed, and stride length; but walking distance and cadence did not improve. Acceptability of treadmill training for study participants was good and adverse events were rare. It seems that such devices could be beneficial and could be applied in routine rehabilitation. However, it is still not clear when and how often they should be used and how long a benefit lasts.

The quality of this evidence for the primary outcomes was moderate to low. Adverse events were not reported in studies and drop outs did not occur more frequently in people receiving treadmill training. Also we investigated only gait parameters, improvements of activities and/or quality of life were not investigated.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Treadmill training versus no treadmill training or active control intervention or gait training for patients with Parkinson's disease

Patient or population: patients with patients with Parkinson's disease
Settings: Inpatient and outpatient setting
Intervention: Treadmill training versus no treadmill training or active control intervention or gait training

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Treadmill training versus no treadmill training or active control intervention or gait training				
Gait speed at the end of the study - Active control group (co-interventions were similar in both groups) Measures of timed gait. Scale from: 0 to inf.	The mean gait speed at the end of the study - active control group (co-interventions were similar in both groups) in the control groups was **1.17 m/s**[1]	The mean gait speed at the end of the study - active control group (co-interventions were similar in both groups) in the intervention groups was **0.07 higher** (0.03 to 0.12 higher)		434 (14 studies)	⊕⊕⊕◯ **moderate**[2]	
Gait speed at the end of the study - No interventioncontrol group (co-interventions were not similar in both groups) Measures of timed gait. Scale from: 0 to inf.	The mean gait speed at the end of the study - no intervention control group (co-interventions were not similar in both groups) in the control groups was **1.43 m/s**[1]	The mean gait speed at the end of the study - no intervention control group (co-interventions were not similar in both groups) in the intervention groups was **0.4 higher** (0.06 lower to 0.87		76 (3 studies)	⊕◯◯◯ **very low**[3,4,5]	

		higher)				
walking distance in m (at the end of study; all studies) - Active control group (co-interventions were similar in both groups) Measures of timed gait. Scale from: 0 to inf.	The mean walking distance in m (at the end of study; all studies) - active control group (co-interventions were similar in both groups) in the control groups was **441.2 m**[1]	The mean walking distance in m (at the end of study; all studies) - active control group (co-interventions were similar in both groups) in the intervention groups was **9.48 higher** (0.47 lower to 19.42 higher)		385 (9 studies)	⊕⊕◯◯ **low**[2,3,4]	
walking distance in m (at the end of study; all studies) - No intervention control group (co-interventions were not similar in both groups) Measures of timed gait. Scale from: 0 to inf.	The mean walking distance in m (at the end of study; all studies) - no intervention control group (co-interventions were not similar in both groups) in the control groups was **362 m**[1]	The mean walking distance in m (at the end of study; all studies) - no intervention control group (co-interventions were not similar in both groups) in the intervention groups was **364 higher** (294.45 to 433.55 higher)		31 (1 study)	See comment	
acceptability and safety of treadmill training - Active control group (co-interventions were similar in both groups) Number of adverse events and drop-outs	**Study population**		See comment	531 (15 studies)	⊕⊕⊕◯ **moderate**[2]	Risks were calculated from pooled risk differences
	131 per 1000	**122 per 1000** (81 to 161)				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				

acceptability and safety of treadmill training - No intervention control group (co-interventions were not similar in both groups) Number of adverse events and drop-outs	**Study population**		See comment	102 (3 studies)	⊕⊕◯◯ **low**[3,4,5,6]	Risks were calculated from pooled risk differences
	392 per 1000	**255 per 1000** (-39 to 553)				
	Moderate					
	200 per 1000	**130 per 1000** (-20 to 282)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Final values reported
[2] Downgraded due to several ratings with "High Risk of Bias"
[3] Downgraded due to 95% confidence interval includes no effect and the upper or lower confidence limit crosses the minimal clinical important difference (MCID)
[4] Downgraded due to the total population size being less than 400 (as a rule-of-thumb threshold)
[5] Downgraded due to funnel plot asymmetry (diagnosed by visual inspection)
[6] Not downgraded due to explainable statistical heterogeneity

BACKGROUND

Description of the condition

Parkinson's disease (PD) is a progressive and disabling degenerative disorder characterised clinically by bradykinesia, tremor, rigidity, and postural instability. Disability occurs at all stages of the disease and the severity of disabilities usually increases with disease duration. Patients frequently have gait impairments, difficulty in linking movements together smoothly, and episodes of freezing. These problems together with balance disturbances lead to an increased incidence of falls with the concomitant risk of fractures. In fact one study found that 27% of Parkinson's patients have had a hip fracture within 10 years of their diagnosis (Johnell 1992).

Gait hypokinesia is one of the primary movement disorders associated with PD (Morris 2000). It is an important contributor to disability and quality of life in mild to moderate Parkinson disease (Muslimovic 2008). Kinematic measures have occasionally been found to been altered in individual patients but slowness of gait is the only symptom that has been consistently reported in group comparisons between control patients and patients with idiopathic PD (Morris 2000). Cadence control remains unaffected throughout its entire range in PD and gait hypokinesia is directly attributable to an inability to internally generate sufficiently large steps. Therefore, improvements of walking speed and stride length are the primary goals of gait rehabilitation in patients with PD (Pohl 2003), and reducing gait freezing when it is present.

The current management of PD focuses on pharmacological therapy; at present levodopa is regarded as the most effective treatment. However, many patients show abnormal involuntary movements due to levodopa known as dyskinesias (Jankovic 2000). Drugs other than levodopa such as dopamine agonists may initially control symptoms for many patients but levodopa and polytherapy are often necessary in the treatment of PD, particularly in the advanced stages (Motto 2003).

Despite new pharmacological interventions, treatment becomes unsatisfactory in a large proportion of patients. After five years of levodopa treatment, many patients experience severe motor complications such as motor fluctuations and dyskinesias. Theseare difficult to manage with the available drug strategies. Complications cause functional disability and impact on the person's quality of life (Motto 2003).

In recent years, interest in functional neurosurgery of basal ganglia has increased. Patients who have developed severe motor complications that are resistant to the available pharmacological interventions could be considered surgical candidates (Motto 2003). Three major targets for functional neurosurgery are; the thalamus ventro-intermediate nucleus, internal globus pallidus, and subthalamic nucleus. Two different techniques, radiofrequency lesioning or high frequency stimulation (Limousin 1998) have been proposed. However, there is still debate concerning risks and benefits of surgery. A Cochrane review team is evaluating theses issues (Motto 2003).

Description of the intervention

Despite optimal medical and surgical therapies for PD, patients develop progressive disability (Deane 2001). However, the effectiveness of non-pharmacological options such as exercises have recently been demonstrated (Goodwin 2008). A good example for patient-tailored exercises is physiotherapy (Ashburn 2004; Comella 1994; de Goede 2001; Tomlinson 2013). The aim of physiotherapy is to enable PD patients to maintain their maximum level of mobility, activity, and independence. This outcome can be attained through monitoring of the patient's condition, implementation of appropriate physical treatments, and incorporating a range of approaches to movement rehabilitation (Tomlinson 2013). However, in spite of established pharmacological and conventional approaches there is still a need for new interventions to improve the gait of people with PD.

Recently, the use of electromechanical devices such as treadmill training has provided a promising new therapeutic approach in the rehabilitation of patients with hemiparesis and impaired gait (Mehrholz 2014). Augmenting conventional therapy with treadmill training as a supplement to conventional therapies may improve the results of other gait training therapies. With seriously afflicted hemiparetic patients who cannot walk under their own power, treadmill training with bodyweight support (BWS) might be recommended.

How the intervention might work

As described recently, treadmill training with BWS has also been used with PD patients. Results of single studies suggested better improvement in gait parameters when compared with conventional gait therapy (Miyai 2002; Pohl 2003).

Treadmill training can be used to give people with PD intensive practice (in terms of high repetitions) of complex gait cycles. Treadmill training can be used to train at higher gait speeds and to achieve greater step length compared to physiotherapy not using such devices (Cakit 2007; Pohl 2003).

However, the most effective combination of training parameters (for example, amount and timing of BWS during the gait cycle and belt speed and acceleration) is still unknown. There is, therefore, still a need for a systematic evaluation in the form of a systematic review of the available literature. The present review assesses the effectiveness and acceptability of treadmill training to augment conventional gait rehabilitation for patients with PD.

Why it is important to do this review

As the scientific evidence for the benefits of treadmill training may have changed since our Cochrane Review was first published in 2009 (Mehrholz 2010), an update of the review seems to be required in order to justify the large equipment and human resource cost needed to implement treadmill training devices as well as to confirm the safety and acceptance of this type of training. Therefore, it seems to be important that this version of our review provides an update of the best available evidence about the above-mentioned approach.

OBJECTIVES

To assess the effectiveness of treadmill training in improving the gait function of patients with Parkinson's disease and the acceptability and safety of this type of therapy. A secondary objective of this review is to find the most effective combination of training parameters (for example belt speed and acceleration).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and randomised controlled cross-over trials where only the first period was analysed as a parallel group trial.

Types of participants

We included studies with participants of both genders and all ages who were diagnosed with PD using the UK Parkinson's Disease Brain Bank Criteria (or PD diagnostic criteria as defined by the study authors) regardless of drug therapy, duration of treatment, duration of PD, or level of initial impairment.

Types of interventions

We compared treadmill training versus no treadmill training (main analysis) for improving gait. We assumed that co- interventions such as other rehabilitation interventions and medication or treatment were comparable between groups. Because this can not be assumed we compared treadmill training with a variety of other interventions in the (control group) and described these in an additional table. If co- interventions were comparable between groups e.g. active versus no-active control intervention we did a separate comparison.

No restriction was placed for the duration or characteristics of the intervention. We considered end-of-treatment assessments as provided by the studies.

Types of outcome measures

Primary outcomes

The primary outcomes were walking speed (continuous outcome) and stride length (continuous). According to Hass 2014 we defined the cut-off value representing a minimal clinical important difference (CID) for walking speed at 0.06 m/s, a moderate CID at 0.14 m/s and a large CID at 0.22 m/s

Secondary outcomes

The secondary outcomes were cadence (continuous) and walking distance (continuous).
Another secondary outcome was the acceptability and safety of treadmill training. We investigated the safety of treadmill training using the incidence of adverse events such as cardiovascular events, injuries, and pain, and any other reported adverse events. To measure the acceptance of treadmill training we used drop outs from the study due to any reason.
We provided all primary and secondary outcomes in a summary of findings table. If we had more than seven outcomes to present we prioritised them according to their relevance and presented the most important outcomes.

Search methods for identification of studies

Electronic searches

We used the search strategy developed for the Movement Disorders Group and identified relevant trials by searching the following electronic databases:

- Cochrane Movement Disorders Group Specialised Register;
- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*; last searched September 2014);
- MEDLINE (1966 to September 2014);
- EMBASE (1966 to September 2014);
- Pedro (last search September 2014).

The MeEDLINE and EMBASE searches can be found in the Appendices

Searching other resources

In addition, we also

- searched the reference lists for identified trials and review articles;
- hand-searched and screened reference lists of potentially relevant conference proceedings (1998 to September 2014**;** Appendix 5) searched ongoing trials and research registers; contacted trialists, other researchers, and manufacturers of commercial devices in our field of study to identify published, unpublished, and ongoing trials not available in the major databases; contacted trialists and other researchers to obtain additional information on trials published elsewhere and unpublished trials.

Publication status or language did not influence our decision to include.

Data collection and analysis

Selection of studies

Selection and identification of relevant trials

Two authors (JM and MP) independently read titles and, when available, abstracts of identified references and eliminated obviously irrelevant studies. Two review authors (MP and BE) independently examined potentially relevant studies using the predetermined criteria for including studies. We obtained the full text for the remaining studies. Based on our inclusion criteria (types of studies, participants, aims of interventions, outcome measures) two review authors (BE and MP) independently ranked these studies as relevant, irrelevant, or possibly relevant. We excluded all trials ranked initially as irrelevant, but included all other trials at this stage. We resolved disagreement among authors through discussion. If further information was needed to reach consensus we contacted trialists in an effort to obtain missing information

Data extraction and management

Two review authors (JM and MP) independently extracted trial and outcome data from the selected trials. If any review author was involved in any of the selected studies another member of our author group who was not involved in the study was requested to review the study information.

We established the characteristics of unpublished trials through correspondence with the trial co-ordinator or principal investigator. We used checklists to independently record details of the:

- methods of generating randomisation schedule;
- methods of concealment of allocation;
- blinding of assessors;
- use of an intention-to-treat analysis (all participants initially randomised were included in the analyses as allocated to groups);
- adverse events and drop outs for all reasons;
- important imbalance in prognostic factors;
- participants (country, number of participants, age, gender, stage of PD as assessed by Hoehn Yahr for entry to the study, inclusion and exclusion criteria);
- comparison (details of the intervention in treatment and control groups; details of co-intervention(s) in both groups; duration of treatment);
- outcomes and time points of measures (number of participants in each group and outcome, regardless of compliance).

We checked all of the extracted data for agreement among review authors, with another review author (BE or JK) arbitrating any items where consensus was not reached. If necessary, we contacted trialists to request more information, clarification, or missing data. If data was still missing we analysed the available data, but did not impute data.

The primary outcome variables of interest were continuous data, entered as means and standard deviations. We calculated a pooled estimate of the mean differences (MD) with 95% confidence intervals (CI). If studies did not use the same outcome, we use the standardised mean difference (SMD) with 95% CI.

For all binary outcomes (such as the secondary outcome 'drop out, from all causes') we calculated risk differences (RD), again with 95% CI.

If necessary we combined the results of different treadmill training groups in one (collapsed, treadmill) group and compared this with the combined results of the control group. We combined continuous data for pooled arms using the implemented RevMan Calculator. We have built a summary of findings table using the software GRADEprofiler and conducted GRADE assessments according to the GRADEprofiler help.

Assessment of risk of bias in included studies

For this update of the review two authors (BE and JM) independently assessed the risk of bias in the included trials in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We described the agreement between authors during the assessment of risk of bias, and we resolved disagreement by reaching consensus through discussion. We contacted trialists for clarification and to request missing information.

We checked all methodological quality assessments for agreement among the review authors and resolved disagreements by discussion among authors. Two review authors (MP and JM) were co-authors of one included trial (Pohl 2003); other review authors (BE and JK) did the quality assessment for this trial. We contacted study authors for clarification and to request missing information. We did test the robustness of the main results in a sensitivity analysis (Analysis 2.1).

Measures of treatment effect

For all outcomes representing continuous data, we entered means and standard deviations. We calculated a pooled estimate of the mean difference (MD) with 95%confidence interval (CI). For all binary outcomes
we calculated risk differences (RD) with 95% CI. For all analyses we used The Cochrane Collaboration's Review Manager software, RevMan 5.2 and used a random-effects model for all analyses.

Dealing with missing data

We contacted the relevant principal investigators to retrieve missing data.

Assessment of heterogeneity

We used the I^2 statistic to assess heterogeneity. We used a random effects model, regardless of the level of heterogeneity. Thus, in the case of heterogeneity we did not violate the preconditions of a fixed-effect model approach. We visually examined publication bias using funnel plots.

Subgroup analysis and investigation of heterogeneity

To quantify for heterogeneity we used the I^2 statistic for all comparisons. We always used random-effects model regardless of the level of heterogeneity. We described variability in participants, interventions, and outcomes studied (clinical diversity) in an additional table (Table 1) and in the Description of studies. The variability of studies did not influence our intention to pool trials. For all statistical analyses we used the latest version of The Cochrane Collaboration's software Review Manager (RevMan).

Sensitivity analysis

We incorporated a post hoc sensitivity analysis for methodological quality to test the robustness of our results for the primary outcome gait speed. We analysed random sequence generation, allocation concealment, blinding of outcome assessors.

RESULTS

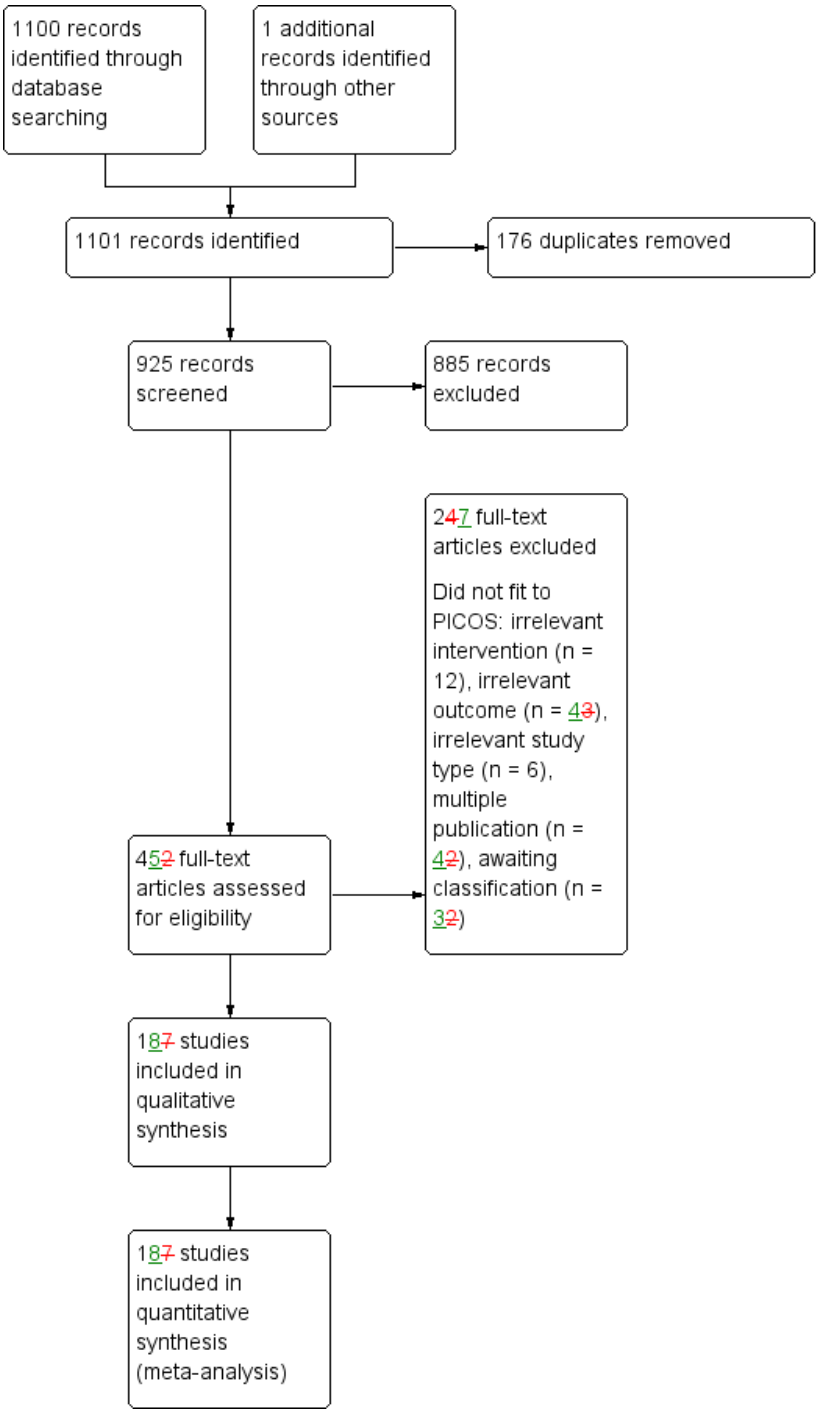
Description of studies

See:Characteristics of included studies; Characteristics of excluded studies;Characteristics of studies awaiting classification; and Characteristics of ongoing studies.
Studies that were included compared treadmill training with a variety of other active interventions and none (Characteristics of included studies; Table 2; Additional tables).
The age of participants was between 58 and 74 [BJ1] years and the disease severity was in most studies between Hoehn & Yahr stages 1 and 3.
13 out of 18 studies (72%) used UPDRS (total or subscales) at baseline for patient description but only 8 out of 18 included studies (44%) at study end (Table 3).
Only 3 out of 18 studies (17%) assessed quality of life (2 studies used the PDQ-39 and 1 study used the SF-12 PCS and MCS (Table 3).
Eight out of 18 studies (44%) described a follow-up assessment after study end (Table 3).
No adverse events were reported.
The trials were relatively comparable regarding patient's characteristics (Table 1), but experimental and control interventions varied (Table 1; Table 2). E.g. some studies used a active control group doing time and dose matched gait exercises, but some did not described what was done.

Results of the search

Figure 1 shows the flow diagram for the selection of studies. The searches of the electronic databases and trials registers generated 925 unique references for screening.

Figure 1. Study flow diagram.



After excluding non-relevant citations we obtained the full texts of 45 papers; of these, we included 18 trials in the qualitative analysis and 18 trials in the quantitative analysis of the review.

Included studies

We included 18 trials involving a total of 623 participants in the quantitative analysis of this review (Bello 2013; Cakit 2007; Canning 2012; Carda 2012; Chaiwanichsiri 2011; Fisher 2008; Frazzitta 2009; Harro 2014; Kurtais 2008; Miyai 2000; Miyai 2002; Nadeau 2013; Picelli 2013; Pohl 2003; Protas 2005; Sale 2013; Shulman 2013; Yang 2010); see the Characteristics of included studies; Table 1;).

The characteristics of participants and the characteristics of the experimental interventions in the included studies are listed and described in detail in Table 1.

The included trials compared treadmill training with a variety of other interventions. We conducted a meta-analysis of studies that measured the same treatment effect. Thus we combined treadmill training versus all other approaches as an estimate of the effect of treadmill training compared with a different treatment. However, we did not compare treadmill training type A with treadmill training type B as these are measuring different treatment effects.

Studies used a variety of primary outcomes, which are described in Characteristics of included studies.

Because only 44% of studies reported follow-up data we did not conduct a separate analysis of end-of-treatment' and follow-up' data.

Excluded studies

Six studies were excluded (Bello 2008; Fisher 2013; Ganesan 2010; Gianfrancesco 2009; Diaz de la Fe 2008; Schenkman 2012). These trials were excluded for various reasons and the details are described in Characteristics of excluded studies. If there was any doubt whether the study should be excluded or not, we retrieved the full text of the article. In cases of disagreement between the review authors, another member of the author group reviewed the information to decide on inclusion or exclusion of a study.

One ongoing study was identified. Two studies (Horak 2011; Mezzarobba 2013) are still awaiting classification and are described in Characteristics of studies awaiting classification.

Risk of bias in included studies

All details about the methodological quality are provided for each included study in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

We wrote to the authors of all the included studies requesting (if necessary) clarification of some design features or missing information in order to complete the quality ratings. The correspondence was via email and letter, and we wrote reminders every two weeks if we did not receive an answer. The risk of bias decisions are described in the (Characteristics of included studies and Figure 2).

Allocation

Nine out of 18 studies (50%) described an appropriate random sequence generation and some studies described allocation concealment appropriately (Figure 2). No included study described an inappropriate random sequence generation or allocation concealment.

Blinding

Twelve out of 18 studies (67%) used an appropriate blinding of outcome assessors and three out of 18 studies did not blind outcome assessors (17%) for two out of 18 studies (11%) this was unclear (Figure 2).

Incomplete outcome data

Fourteen studies (83%) described outcome data appropriately (Figure 2).

Effects of interventions

See: **Summary of findings for the main comparison** Treadmill training versus no treadmill training or active control intervention or gait training for patients with Parkinson's disease

See: Summary of findings for the main comparison for the main comparison 'Treadmill training versus all other interventions'.

Treadmill training versus all other interventions (no treadmill training)

Comparison 1.1 Gait speed at the end of intervention phase (primary outcome measure)

Seventeen studies with a total of 520 participants compared treadmill training versus no treadmill training on gait speed. Treadmill training improved gait speed significantly. The pooled standardised mean difference (MD, random-effect model) for gait speed was 0.09 m/s (95% CI 0.03 to 0.14; P = 0.001; level of heterogeneity I^2 = 24%; moderate quality of evidence) at the end of the study (Analysis 1.1).

Comparison 1.1.1 Active control group

Fourteen studies with a total of 434 participants used an active control group and compared treadmill training versus no treadmill training on gait speed. Treadmill training improved gait speed significantly. The pooled standardised mean difference (MD, random-effect model) for gait speed was 0.07 m/s (95% CI 0.03 to 0.12; P = 0.001; level of heterogeneity I^2 = 2%) at the end of the study (Analysis 1.1).

Comparison 1.1.2 No intervention control group

Three studies with a total of 76 participants used no intervention in the control group and compared treadmill training versus no treadmill training on gait speed. Treadmill training did not improve gait speed significantly. The pooled standardised mean difference (MD, random-effect model) for gait speed was 0.40 m/s (95% CI -0.06 to 0.87; P = 0.09; level of heterogeneity I^2 = 49%) at the end of the study (Analysis 1.1).

Comparison 1.2 Stride length at the end of intervention phase (primary outcome measure)

Overall ten studies with a total of 333 participants compared treadmill training versus no treadmill training on stride length. Treadmill training improved stride length significantly. The MD (random-effect model) for stride length was 0.05 metres (95% CI 0.01 to 0.09; P = 0.01; I^2 = 0%; low quality of evidence) at the end of the study (Analysis 1.2).

Comparison 1.2.1 Active control group (co-interventions were similar in both groups)

Nine studies with a total of 315 participants used an active control group and compared treadmill training versus no treadmill training on stride length. Treadmill training did not improve stride length significantly. The MD (random-effect model) for stride length was 0.04 metres (95% CI 0.00 to 0.09; P = 0.05; I^2 = 0%) at the end of the study (Analysis 1.2).

Comparison 1.2.2 No intervention control group (co-interventions were not similar in both groups)

One study (Protas 2005) with 18 participants used no intervention in the control group and compared treadmill training versus no treadmill training on stride length. Treadmill training did not improve stride length significantly. The MD (random-effect model) for stride length was 0.11 metres (95% CI -0.02 to 0.24; P = 0.09; I^2 = not applicable) at the end of the study (Analysis 1.2).

Comparison 1.3 Walking distance at the end of intervention phase

Overall ten studies with a total of 416 participants compared treadmill training versus no treadmill training on walking distance. Treadmill training did not improve walking distance significantly. The MD (random-effect model) for walking distance was 48.9 metres (95% CI -1.32 to 99.1; P = 0.06; I^2 = 91%; very low quality of evidence) at the end of the study (Analysis 1.3).

It should be noted however that the described effect (treadmill training on walking distance) is mainly due to one trial (Cakit 2007), additionally the results for walking distance are very heterogeneous due to this trial (Cakit 2007). After leaving out the study by (Cakit 2007) there would be no effect: The MD (random-effect model) for walking distance would be 8 metres (95% CI -3 to 20; P = 0.05; I^2 = 0%).

Comparison 1.3.1 Active control group (co-interventions were similar in both groups)

Nine studies with a total of 385 participants used an active control group and compared treadmill training versus no treadmill training on walking distance. Treadmill training did not improve walking distance significantly. The MD (random-effect model) for walking distance was 9.48 metres (95% CI -0.47 to 19.42; P = 0.06; I^2 = 0%) at the end of the study (Analysis 1.3).

Comparison 1.3.2 No intervention control group (co-interventions were not similar in both groups)

One study (Cakit 2007) with 31 participants used no intervention in the control group and compared treadmill training versus no treadmill training on walking distance. Treadmill training improve walking distance significantly. The MD (random-effect model) for walking distance was 364 metres (95% CI 294 to 434; P < 0.00001; I^2 = not applicable) at the end of the study (Analysis 1.3).

Comparison 1.4 Cadence at the end of intervention phase

Overalls, ten studies with a total of 336 participants compared treadmill training versus no treadmill training on cadence. Treadmill training did not improve cadence significantly. The MD (random-effect model) for cadence was 2.16 steps per minute (95% CI -0.13 to 4.46; P = 0.07; I^2 = 17%; low quality of evidence) at the end of the study (Analysis 1.4).

Comparison 1.4.1 Active control group (co-interventions were similar in both groups)

Nine studies with a total of 318 participants used an active control group and compared treadmill training versus no treadmill training on cadence. Treadmill training did improve cadence significantly. The MD (random-effect model) for cadence was 2.42 steps per minute (95% CI 0.07 to 4.77; P = 0.04; I^2 = 19%) at the end of the study (Analysis 1.4).

Comparison 1.4.2 No intervention control group (co-interventions were not similar in both groups)

One study (Protas 2005) with 18 participants used no intervention in the control group and compared treadmill training versus no treadmill training on cadence. Treadmill training did not improve cadence significantly. The MD (random-effect model) for cadence was -4 steps per minute (95% CI -15.11 to 7.11; P = 0.48; I^2 = not applicable) at the end of the study (Analysis 1.4).

Comparison 1.5 Acceptability and safety at the end of intervention phase

All 18 trials, with a total of 633 participants, reported drop-out rates. We pooled the reported drop outs from all causes during the trial period. The use of treadmill training in patients with PD did not increase the risk of participants dropping out (risk difference (RD) (random-effects model) -0.02; 95% CI -0.06 to 0.02; P = 0.32; I^2 = 13%; moderate quality of evidence). No adverse events were reported in included studies (Analysis 1.5).

It should be noted that the acceptability might be influenced by one trial (Cakit 2007), however this study contributes to this analysis only by 2.9% (weight) (Analysis 1.5).

Comparison 1.5.1 Active control group (co-interventions were similar in both groups)

15 trials, with a total of 531 participants used an active control group and reported drop-out rates. We pooled the reported drop outs from all causes during the trial period. The use of treadmill training in patients with PD did not increase the risk of participants dropping out (risk difference (RD) (random-effects model) -0.01; 95% CI -0.05 to 0.03; P = 0.66; I^2 = 0%). No adverse events were reported in included studies (Analysis 1.5).

Comparison 1.5.2 No intervention control group (co-interventions were not similar in both groups)

Three trials, with a total of 102 participants used no intervention in the control group and reported drop-out rates. We pooled the reported drop outs from all causes during the trial period. The use of treadmill training in patients with PD did not increase the risk of participants dropping out (risk difference (RD) (random-effects model) -0.14; 95% CI -0.43 to 0.16; P = 0.37; I^2 = 79%). No adverse events were reported in included studies (Analysis 1.5).

Comparison 2.1: Sensitivity analysis by trial methodology

To test the robustness of the main results we used for our planned sensitivity analysis subgroups of the methodological features of randomisation, concealment of allocation, and blinding of assessors (Analysis 2.1).

To examine the robustness of results, we specified variables in a sensitivity analysis that we believed could influence the size of effect observed (method of randomisation, concealed allocation and blinding of assessors; Analysis 2.1).

- *Including only studies with described method of randomisation analysis*

Eight trials with a total of 237 patients described a method of randomisation analysis. Treadmill training did improve gait speed. The pooled mean difference (MD, random-effects model) for gait speed was 0.08; 95% confidence interval (CI) 0.02 to 0.13; P = 0.006; level of heterogeneity I^2= 0%) at the end of study (Analysis 2.1).

- *Including only studies with adequate concealed allocation for the primary outcome gait speed*

Eight trials with a total of 237 patients with adequate concealment of allocation were included. Treadmill training did improve gait speed. The pooled mean difference (MD, random-effects model) for gait speed was 0.08 95% confidence interval (CI) 0.02 to 0.13; P = 0.006; level of heterogeneity I^2= 0%) at the end of study (Analysis 2.1).

- *Including only studies with blinded assessors for the primary outcome gait speed*

Twelve trials with a total of 375 patients described a blinded assessor for the primary outcome gait speed. Treadmill training did improve gait speed. The pooled mean difference (MD, random-effects model) for gait speed was 0.07; 95% confidence interval (CI) 0.00 to 0.13; P = 0.04; level of heterogeneity I^2= 31%) at the end of study (Analysis 2.1).

Comparison 2. 2: Sensitivity analysis by treadmill protocol used (gait speed increments)

To test the robustness of the main results we used for our second sensitivity analysis subgroups of the treadmill protocols used in studies (speed dependent approach, gradually increases of gait speed, constant gait speed or mixed) (Analysis 2.2).

To examine the robustness of results, we categorised variables in this second sensitivity analysis that we believed could influence the size of effect observed (treadmill protocols used in studies Analysis 2.2).

- *Including only studies with speed dependent approach*

Four trials with a total of 88 patients described a speed dependent approach. Treadmill training did not improve gait speed. The pooled mean difference (MD, random-effects model) for gait speed was 0.16; 95% confidence interval (CI) -0.08 to 0.40; P = 0.19; level of heterogeneity I^2 = 74%) at the end of study (Analysis 2.2).

It should be noted however that the described effect might be affected by one trial (Harro 2014). This trial investigated a very small contrast between groups because in the experimental as in the control group a speed dependent approach was used (see Table 1 and Table 2). After leaving out the study by (Harro 2014) the effect would be (MD (random-effect model) for gait speed would be higher (not significant) 0.27 m/s (95% CI -0.02 to 0.56; P = 0.06; and less heterogenous with I^2 = 64%).

- *Including only studies with gradual gait speed increases*

Eight trials with a total of 227 patients described a treadmill protocol with gradual increases of gait speed. Treadmill training did improve gait speed. The pooled mean difference (MD, random-effects model) for gait speed was 0.08 95% confidence interval (CI) 0.02 to 0.14; P = 0.009; level of heterogeneity I^2 = 0%) at the end of study (Analysis 2.2).

- *Including only studies with constant gait speed*

Three trials with a total of 85 patients described a treadmill protocol with constant gait speed. Treadmill training did improve gait speed. The pooled mean difference (MD, random-effects model) for gait speed was 0.12; 95% confidence interval (CI) 0.02 to 0.22; P = 0.02; level of heterogeneity I^2 = 0%) at the end of study (Analysis 2.2).

- *Including only studies with a mixed or different gait speed approaches used*

Two trials with a total of 110 patients described a treadmill protocol with mixed or different approaches. Treadmill training did not improve gait speed. The pooled mean difference (MD, random-effects model) for gait speed was 0.01; 95% confidence interval (CI) -0.19 to 0.22; P = 0.90; level of heterogeneity I^2 = 60%) at the end of study (Analysis 2.2).

Subgroup analysis

Although initially planned, we decided to do only one sensitivity analysis (Analysis 2.2) instead of a formal subgroup analysis, due to limited number of studies and limited detailed information (Differences between protocol and review).

DISCUSSION

Summary of main results

The aim of this review, which included 18 trials with a total of 623 participants, was to evaluate the effects of treadmill training on gait in patients with PD. We found evidence that the use of treadmill training may improve gait parameters, such as gait speed and stride length, of patients with PD at Hoehn Yahr stages one to three. However, walking distance and cadence did not improve [BJ1] significantly. Additionally, it is not known how long gait improvements after treadmill training may last. Adverse events and drop-outs did not occur more frequently in people receiving treadmill training than control interventions and were not judged to be clinically serious adverse events.

Overall completeness and applicability of evidence

The results of this review seem to be quite generalisable to both in and outpatient settings in industrialised countries. More specifically our results may not apply to an assumed average older patient with Parkinson's disease or patients with Hoehn & Yahr stages higher than 3. The results may therefore not be broadly generalisable to more severe or older patients. There are factors producing uncertainty for generalisations:

1. The investigated study population was quite heterogeneous (e.g. stage of disease, age, duration of illness, and walking ability).
2. The investigated experimental and control conditions were heterogeneous (e.g. type of training, frequency and duration of training; some studies had no real 'active' control group and some compared treadmill training with no active therapy).

Hence, the results may be of limited applicability for all people with PD.

One potential limitation could be that only gait parameters were considered in this update of our review. More general patient-reported scales as UPDRS, quality of life scales (e.g. PDQ-39) and health economics outcomes were not included neither in our protocol for this review (Mehrholz 2009) nor in this update of our review. The inclusion of such an analysis may be interesting, but would be beyond the scope of this update. Additionally the analysis of outcomes other than gait parameters was hardly possible because only a small amount of studies used such scales (e.g. only 4 out of 18 included studies described UPDRS total scores and

subscale scores at baseline and at study end ; see Table 3). Eventually, the results of this review are only applicable to gait parameters of people with PD. However, gait hypokinesia is one of the primary movement disorders associated with PD(Morris 2000) and an important determinant of activities and quality of life in mild to moderate Parkinson disease (Muslimovic 2008).

We were not able to find any description of adverse events of treadmill training. It is not clear whether adverse events were not reported or did not occur.

The lack of long-term follow-up in more than the half of included trials might be a crucial point, but PD is a progressive condition and therefore benefits are not expected to be longlasting (Table 3). The small but clinical benefit may well have disappeared by after 3 to 12 months. However, from the results of our review it is unclear how much of the short term benefit will lasting for how long. Studies investigating the lasting of effects of treadmill training or studies of re-intervention are therefore warranted.

Quality of the evidence

We presented the quality of evidence for our outcomes in Summary of findings for the main comparison.

We found heterogeneity between the trials in terms of trial design (two, three, or four arms; parallel group or cross-over trial; duration of follow up; selection criteria for patients), characteristics of the therapy interventions (especially frequency and duration of intervention), and participant characteristics (Hoehn Yahr severity at baseline), but it is not clear whether this limited the quality of the evidence.

Although the methodological quality of the included trials seemed generally good to moderate (Figure 2), trials investigating treadmill training are subject to potential methodological limitations; for example;

inability to blind the therapist and participants, so-called contamination (provision of the intervention to the control group) and co-intervention (when the same therapist unintentionally provides additional care to either treatment or comparison group). All these potential methodological limitations introduce the possibility of performance bias, even though not supported by our sensitivity analyses of methodological quality (Analysis 2.1).

Potential biases in the review process

A risk of publication bias is present in all systematic reviews. However, we searched extensively for relevant literature in databases and trial registers and handsearched reference lists and conference abstracts. Additionally, we contacted and asked authors, trialists and experts in the field for information on other unpublished and ongoing trials. No statistical or graphical evidence for publication bias has been found (Figure 3 and Figure 4).

Figure 3. Funnel plot of comparison: 1 Treadmill training versus no treadmill training or active control intervention or gait training, outcome: 1.1 Gait speed at the end of the study.

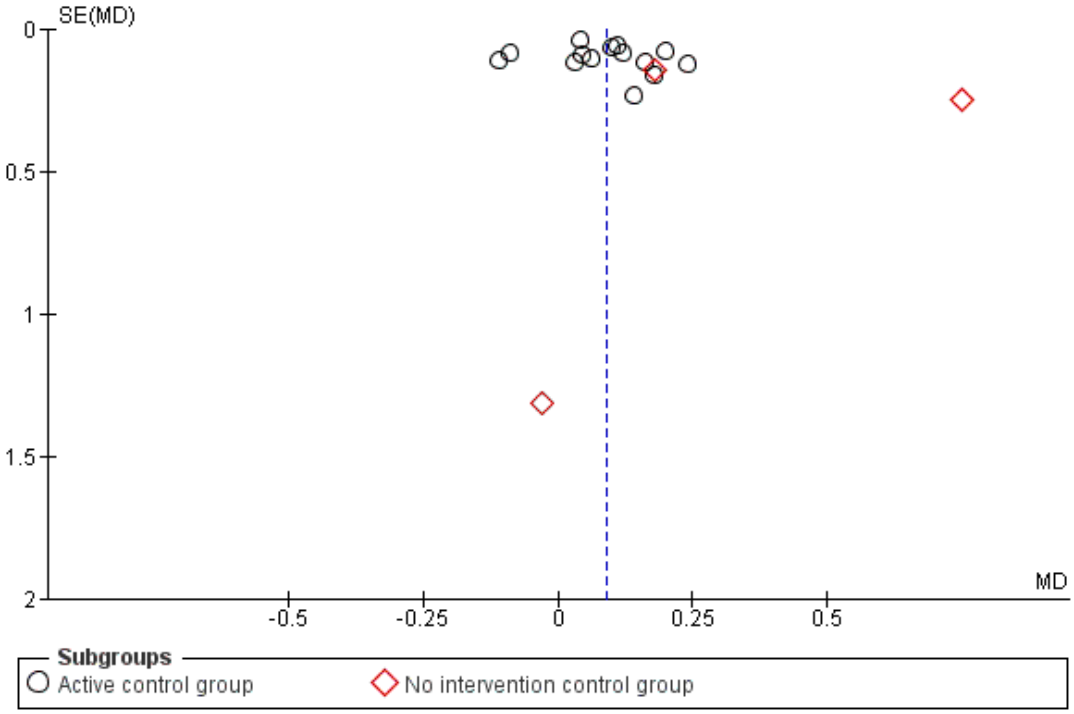
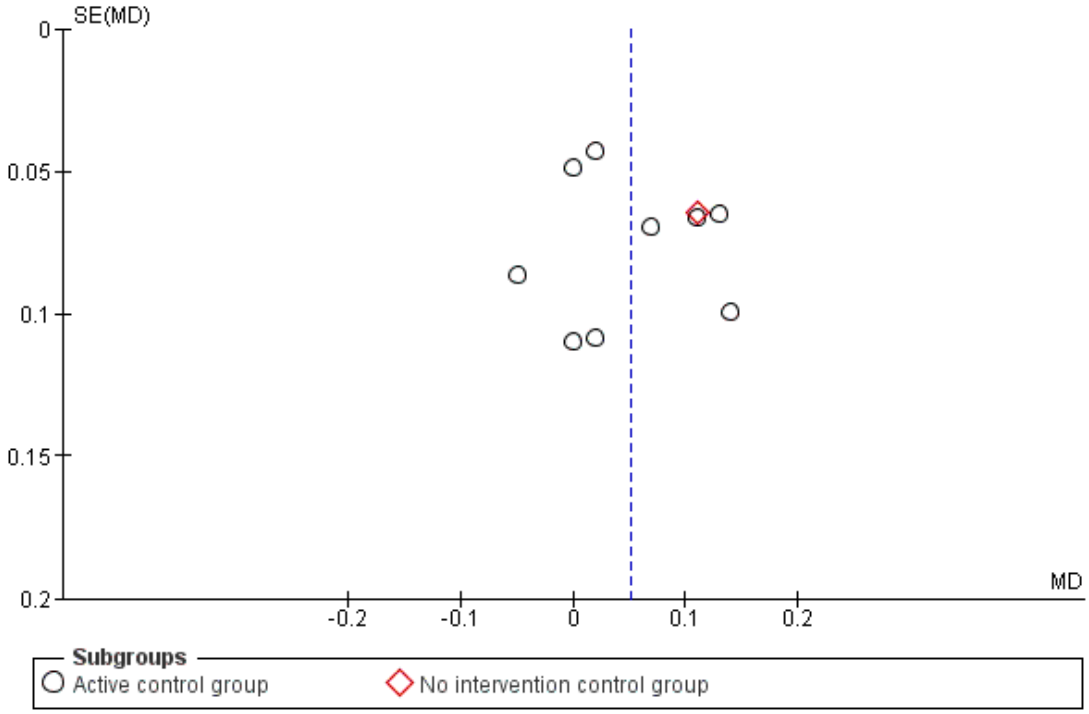


Figure 4. Funnel plot of comparison: 1 Treadmill training versus no treadmill training or active control intervention or gait training, outcome: 1.2 stride length (at the end of study; all studies).



One could argue that the clinical diversity of included trials with respect to duration and frequency of intervention and content of the control group could compromise a pooled analysis. The analyses of the primary outcome however did not reveal statistically heterogeneity (Analysis 1.1). Lastly, our aim was to provide a systematic overview about the current evidence and decided to pool the data of all available trials in a formal meta-analysis.

The exclusion of patient groups, such as those with unstable cardiovascular conditions, cognitive and communication deficits and a limited range of joint motion at the start of the intervention may limit applicability of the findings to these groups.

However, using the results from the primary outcomes it is possible to explore the apparent effectiveness of treadmill training for improving gait in patients with PD. It might be important to consider that treadmill training might be just one way to apply many repetitions of gait cycles. However, one could argue that the gait training provided by a treadmill will lead to better results because people are forced to use higher gait speeds than over ground, as recently shown in one included study. In this study of Pohl and co-workers, patients with PD were able to walk up to three times faster on a treadmill than over ground (Pohl 2003). Gait training on a treadmill could be seen as a 'forced-use-therapy, because patients are forced to use faster gait cycles and therefore higher velocities as they would self-select over ground.

The trials included explored quite different training programs and used different intensities and doses of therapy (see Table 1). For example one could argue, that the studies of Pohl 2003 and Cakit 2007 and also Harro 2014 and Protas 2005 are somewhat different from all other included trials, because a rigorous and systematic speed increments approach was used (see Table 1).

These trials were therefore somewhat different in terms of duration of training and intensity of training and effect. For instance the investigators of the Cakit 2007 trial used a speed depended treadmill approach with increments of belt speed until the highest walking speed at which the patient could walk safely (similar to the 'speed-depended walking' approach as described firstly in Pohl 2003) and trained patients for eight weeks. The study of Cakit 2007 is therefore, compared to all other studies very long and used a very intensive training paradigm. It is therefore that this at most lasting and very intensive training program results in the largest effects compared to all other studies(see Analysis 1.1; see Table 1 and Table 2)

However after excluding the studies of Pohl 2003 and Cakit 2007 from the pooled analysis (not figured), our main effects for gait speed were still present. According to our predefined inclusion

and exclusion criteria (Mehrholz 2009), and in an effort to find all randomised controlled trials on treadmill training, we decided to include these studies.

We analysed only the type of treadmill protocol used in studies as part of an analysis to explore the influence of the intensity of treadmill training. The influence of specific training parameters such duration, frequency, and intensity of treadmill training on the gait parameters of patients with PD will be the subject of further evaluation in our next update, when more studies are available.

Treadmill training has the potential to increase the number of repetitions of practice. It is important to mention however that not all of the included studies had an active control group with matched number of repetitions of practice as in the experimental group. Also the co-interventions varied greatly. In one study it was unclear what intervention the control group received (Cakit 2007). One could argue that these variations in the control interventions would lead to bias and may therefore overestimate the effect sizes, which seems clinically meaningful.

We were not aware of missing data and analysed the available data according to the Cochrane Handbook (chapter 16.1.2 General principles for dealing with missing data). We described the risk of bias due to missing data in Risk of bias in included studies (see also Figure 2). We assumed that if missing data have occurred that these data missing was at random. It is not clear how this can the results of our review biased.

Agreements and disagreements with other studies or reviews

At the time of writing the protocol for this Cochrane review we were not aware of any systematic reviews about the topic (Mehrholz 2009). However, we have found a review by Herman et al which included randomised controlled and non-controlled studies on treadmill training in PD (Herman 2008). Although Herman et al gave a comprehensive overview of all the randomised studies we found, a pooled analysis for a possible treatment effect was not done. Additionally, descriptions of patient acceptance and side effects of treadmill training in PD were not conveniently provided. According to our protocol (Mehrholz 2009), and with the intention of reducing possible sources of bias, we only included randomised controlled trials.

The authors of the review of Herman 2008 reached in the end the conclusion that 'high quality randomized controlled studies are needed before TT can be recommended with evidence based support'. Our review from 2014 includes now 18 RCTs and more than 50% of them have a low risk of bias. We might conclude based on relatively precise estimators that there is evidence that the use of treadmill training in patients with PD may improve gait parameters such as gait speed, stride length and walking distance.

Another review about physiotherapy intervention in Parkinson's disease by Tomlinson 2012 found and described the effects of eight studies compared to 18 studies in our review. The authors included in their quantitative analysis (about the effects of treadmill training) three studies with only 56 patients and estimated the treatment effect of treadmill training on gait speed with a mean difference of 0.04 m/s (Tomlinson 2012). In our review we, however, included 18 trials with 623 patients and reached a more precise effect estimation compared to (Tomlinson 2012).

The authors of the review of Tomlinson 2012 concluded that most of the observed differences between the treatments were small or for some outcomes (e.g. velocity), the differences observed were at, or approaching, what are considered minimally clinical important changes. Our conclusions are in the same line: the effect of treadmill training on gait speed might be considered as minimally clinical important. For example the benefit in walking speed of treadmill training over no or no active control intervention was a large and clinical important difference of 0.4 m/s (mainly due to Cakit 2007), while the benefit in walking speed of treadmill training over 'conventional physiotherapy' was 0.07 m/s. The latter benefit is quite lower but still a minimal clinical important difference. Eventually, this benefit is observed both with and without gait training in the control group.

Whereas benefits of gait speed can be considered to be close to the minimally clinical important difference, it should be argued that such small change in gait speed would not be automatically be seen as relevant to the general public, administrators and policy makers though.

Another up to date Cochrane review about physical therapies versus active interventions (Tomlinson 2014) should also be mentioned here. This review investigated physiotherapy interventions and rated all interventions into one of the six categories (general physiotherapy, exercise, treadmill training, cueing, dance and martial arts). On the one hand the review of Tomlinson 2014 used compared to our review a greater gamut of outcome measures e.g. UPDRS and quality of life measures and described not just gait parameters as we did. On the other, we found and included seven randomised controlled trials more (Bello 2013; Canning 2012; Carda 2012; Harro 2014; Sale 2013; Shulman 2013; Pohl 2003) than the group of Tomlinson et al. about treadmill training (six out of these seven RCTs were not found with their search). We believe therefore that our review is more specific and used a more sensitive search.

This update of our Cochrane review seems therefore to our knowledge the most up to date systematic review about treadmill training in people with PD with a pooled estimate of treatment effects and patient acceptance.

Additionally our review seems to have the most robust and strongest recommendations for treadmill training for patients with PD so far.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review provides evidence from a number of trials with moderate to good risk of bias that the use of treadmill training in patients with PD may improve clinically relevant gait parameters such as gait speed and stride length (high to moderate and moderate quality of evidence, respectively). This apparent benefit for patients is, however, not supported by all secondary variables (e.g. walking distance, cadence). In practice when treadmill training is available this technology might be used in relatively young and fit people with PD to improve gait speed as one specific parameter of gait hypokinesia.

Implications for research

There is still a need for well-designed large-scale studies to evaluate benefits of different parameters and about the frequency of treadmill training in patients with PD. Further research should address specific questions about duration of effect, frequency, training parameters and duration of treadmill training. Future research should investigate the long-term benefits of treadmill training, should investigate how often, how long and at which speed treadmill training should be done to establish a dose response relationship.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bello 2013

Methods	Randomised controlled trial Method of randomisation: not described Blinding of outcome assessors: not described Adverse events: not described Deaths: not described Drop-outs: not stated ITT: not stated
Participants	Country: Spain 22 patients (11 in treatment group, 11 in control group) Ambulatory at study onset: yes Mean age: 58 to 59 years (control and treatment group respectively) Inclusion criteria: being able to walk for 10 min without stopping, walking aids or assistance (on medication) Exclusion criteria: history of neurological conditions other than PD, orthopedic, or visual disturbances which affected walking ability and signs of cardiovascular or autonomic dysfunction
Interventions	2 arms: (1) control group used overground gait training, 3 times a week for 5 weeks (72 min a week) (2) experimental group received treadmill training without BWS, 3 times a week for 5 weeks (72 min a week)
Outcomes	Outcomes were recorded at baseline and at the end of intervention phase Unified Parkinson's Disease Ranking Scale (UPDRS) Motor Score Measures of timed gait (walking speed, cadence, stride length) at preferred and at maximal speed Timed Up-and-Go test (TUG) Posturography Knee extensor muscle strength
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	method of sequence generation not described by the authors
Allocation concealment (selection bias)	Unclear risk	method not described by the authors

Bello 2013 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	blinding not described by the authors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	no missing outcome data described

Cakit 2007

Methods	Randomised controlled trial Method of randomisation: not described
Participants	Country: Turkey Sample size: 54 participants (27 in treatment group, 27 in control group) Inclusion criteria: medically stable; able to walk a 10m distance; able to give informed consent Exclusion criteria: neurological conditions other than PD; scored greater than 3 on the Hoehn and Yahr Disability Scale; scoring less than 20 Mini-Mental State Examination; postural hypotension; cardiovascular or musculoskeletal disorder; visual or vestibular disturbance
Interventions	2 arms (1) training group: 8 weeks exercise programme including stretching, range of motion exercise and treadmill training with incrementally increasing belt speed (2) control group: 8 weeks not described further
Outcomes	Outcomes were recorded at baseline and after 8 weeks of therapy and included • walking distance on treadmill (metres) • tolerated maximum walking speed (km/h) • Falls efficacy scale • Dynamic gait index • Berg balance scale
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	method of sequence generation not described by the authors
Allocation concealment (selection bias)	Unclear risk	method not described by the authors
Blinding of outcome assessment (detection bias) All outcomes	Low risk	described as blinded to group assignment seemingly

Cakit 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	reasons for loss to follow-up apparently not related to the intervention

Canning 2012

Methods	Randomised controlled trial Method of randomisation: sealed opaque envelopes Blinding of outcome assessors: yes Adverse events: none Deaths: none Drop-outs: 3 (2 from the EXP group and 1 from the CTL group) ITT: yes
Participants	Country: Australia 20 patients (10 in treatment group, 10 in control group) Ambulatory at study onset: yes Mean age: 61 to 63years (treatment and control group respectively) Inclusion criteria: Hoehn and Yahr stages 1 or 2, age between 30 and 80 years, <2 h of leisure activity per week, stable response to levodopa, subjective gait disturbance Exclusion criteria: disabling dyskinesias or motor fluctuations; freezing while 'ON' medication; or significant balance impairment, Mini-Mental State Examination Score <24, history of falls or dizziness, other neurological/ musculoskeletal/cardiopulmonary or metabolic conditions that affected walking
Interventions	2 arms (1) experimental group: 6 weeks home based treadmill walking, 30-40 minutes a day, 4 times a week, 7 of 24 sessions supervised by physiotherapist (2) control group: 6 weeks usual care including maintaining usual physical activity levels
Outcomes	Outcomes were recorded at baseline, after 6 weeks of therapy and after 12 weeks after baseline and included Primary outcome measure: • Walking capacity (6m walk Test) Secondary outcome measures: • Exercise heart rate • Quality of life (Parkinson's Disease Questionnnaire; PDQ-39) • Walking speed • Walking speed while performing a concurrent task • Walking consistency during 6m walk Test • Unified Parkinson's Disease Ranking Scale (UPDRS) Motor Score • Fatigue Feasibility outcomes: • Exercise adherence, exercise intensity, fatigue, muscle soreness, adverse events and exercise acceptability

Canning 2012 (*Continued*)

Notes	This is the same study (now published as full text) as in our former review described as Canning 2008. The new reference is therefore Canning 2012

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After baseline assessment, a staff member who was not involved in the trial randomly allocated participants to the treadmill training or control group using opaque envelopes pre-prepared by one investigator"
Allocation concealment (selection bias)	Low risk	Quote: "After baseline assessment, a staff member who was not involved in the trial randomly allocated participants to the treadmill training or control group using opaque envelopes pre-prepared by one investigator"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:"Efficacy outcome measures were made by an assessor blinded to group allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data was balanced between groups and an intention-to-treat analysis has been performed by the authors

Carda 2012

Methods	Randomised controlled trial Method of randomisation: software-generated randomisation list Blinding of outcome assessors: yes Adverse events: none Deaths: none Drop-outs: 2 (1 in EXP and 1 in CTL) ITT: yes
Participants	Country: Italy 30 patients (15 in treatment group, 15 in control group) Ambulatory at study onset: yes Mean age: 67 to 68 years (treatment and control group respectively) Inclusion criteria: diagnosis of PD according to the UK Brain Bank Criteria, disease stage <III according to the classification of Hoehn and Yahr without motor fluctuations, being able to ambulate independently Exclusion criteria: treadmill training or other form of specific gait training for at least 6 months before the study, treadmill training or other form of specific gait training for

Carda 2012 (*Continued*)

	at least 6 months before the study, body weight more than 100 kg; respiratory disease; other neurological diseases; dementia; depression; or uncorrected visual disturbances; undergone or planned deep brain stimulation in the following 6 months
Interventions	2 arms: (1) control group used robotic gait training, 3 times a week for 4 weeks (120 min a week) (2) experimental group received treadmill training, 3 times a week for 4 weeks (120 min a week)
Outcomes	Outcomes were recorded at baseline and at the end of intervention phase Primary outcome: 6 Minute walk test Secondary outcome: 10-m walk test Timed Up-and-Go test Unified Parkinson's Disease Ranking Scale (UPDRS) Motor Score Global health status (SF-12 questionnaire)
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A software-generated randomisation list was used
Allocation concealment (selection bias)	Low risk	A researcher not involved in the experiment checked for correct patient allocation prior and after the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A physical therapist who was not involved in the treatment of the enrolled patients and who was blinded to treatment allocation performed all outcome assessments."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data was balanced between groups and an intention-to-treat analysis has been performed by the authors

Chaiwanichsiri 2011

Methods	Randomised controlled trial Method of randomisation: not described Blinding of outcome assessors: yes Adverse events: none Deaths: none Drop-outs: none ITT: yes
Participants	Country: Thailand 30 patients (10 in treatment group 1, 10 in treatment group 2, 10 in control group) Ambulatory at study onset: yes Mean age: 68 to 69 years (treatment and control group respectively) Inclusion criteria: Male sex, aged 60 to 80 years, diagnosed by neurologists as idiopathic PD, Hoehn and Yahr stage 2-3, good cognitive function on Thai Mental State Examination (TMSE) score >23, stable symptoms with unmodified anti-parkinsonian medication during the study, independent ambulation without using any gait Aids, good vision and hearing Exclusion criteria: other medical conditions that could interfere with the training program, participating in any other training program
Interventions	3 arms: (1) control group used a home walking program, 6 times a week for 4 weeks (180 min a week) (2) experimental group 1 received a home walking program 3 times a week and treadmill training with music cues 3 times a week for 4 weeks (180 min a week) (3) experimental group 2 received a home walking program 3 times a week and treadmill training 3 times a week for 4 weeks (180 min a week)
Outcomes	Outcomes were recorded at baseline and at the end of intervention phase Step length Stride length Cadence 6-m walk test Walking speed Timed Up and Go Test (TUG)
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	method of sequence generation not described by the authors
Allocation concealment (selection bias)	Unclear risk	method not described by the authors

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All participants were assessed by two physicians and one research assistant, who were blinded to group assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	no missing outcome data

Fisher 2008

Methods	Randomised controlled trial Method of randomisation: patients self selected a card with eyes closed
Participants	Country: USA Sample size: 30 participants (10 in high-intensity exercise group, 10 in low-intensity group, and 10 in zero-intensity group) Inclusion criteria: diagnosis of PD within 3 years of study participation; 18 years of age or older; medical clearance from the primary care physician to participate in an exercise program; and ability to walk Exclusion criteria: a score of less than 24 on the MMSE; physician-determined major medical problems such as cardiac dysfunction; musculoskeletal impairments or excessive pain in any joint that could limit participation in an exercise program; and insufficient endurance and stamina to participate in exercise 3 times a week for a 1-hour session
Interventions	3 arms (1) high-intensity exercise group: body weight supported treadmill walking, up to 45 minutes a day, for 24 supervised sessions in 8 weeks (2) low-intensity group: general or traditional physiotherapy, for 24 sessions in 8 weeks (3) zero-intensity (no-exercise) group: six 1 hour education class over 8 weeks
Outcomes	Outcomes were recorded at baseline, after 8 weeks of therapy and included • walking velocity (m/s) • step length (m) • stride length (m) • step width (m) • cadence • double-limb support time (% of gait cycle) • hip, knee and ankle range of motion (degree) • UPDRS • Hoehn and Yahr staging
Notes	We analysed the high intensity group (1) with low-intensity group (2) and zero-intensity group (3) (we collapsed groups 2 and 3 to one pooled control group as in our former version of this review of Mehrholz 2009).

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**

Fisher 2008 (*Continued*)

Random sequence generation (selection bias)	Low risk	patients self selected a card with eyes closed
Allocation concealment (selection bias)	Low risk	Patients were allocated to groups by self selecting a card with eyes closed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	a blinded assessor was used
Incomplete outcome data (attrition bias) All outcomes	Low risk	no missing outcome data

Frazzitta 2009

Methods	Randomised controlled trial Method of randomisation: not described Blinding of outcome assessors: unclear Adverse events: not stated Deaths: none Drop-outs: none ITT: yes
Participants	Country: Italy 40 patients (20 in treatment group, 20 in control group) Ambulatory at study onset: yes Mean age: 71 years (control and treatment group) Inclusion criteria: being able to walk without any physical assistance, sufficient vision and hearing, freezing of gait during peak medication (confirmed by clinical examination), Hoehn & Yahr stage 3, Mini Mental State Examination Score >26), constant medication Exclusion criteria: neurological conditions other than idiopathic Parkinson's disease, postural hypotension, cardiovascular, musculoskeletal, or vestibular disorders limiting locomotion or balance
Interventions	2 arms: (1) control group used traditional rehabilitation with visual and auditory cues, 7 times a week for 4 weeks (140 min a week) (2) experimental group received treadmill training with visual and auditory cues, 7 times a week for 4 weeks (140 min a week)
Outcomes	Outcomes were recorded at baseline and at the end of intervention phase Unified Parkinson's Disease Ranking Scale (UPDRS) Motor Score Freezing of Gait Questionnaire (FOGQ) 6-min walk test (distance walked) Gait speed Stride length
Notes	

Frazzitta 2009 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	method of sequence generation not described by the authors
Allocation concealment (selection bias)	Unclear risk	Not described by the authors
Blinding of outcome assessment (detection bias) All outcomes	High risk	all patients were assessed by same neurologist; no blinding described
Incomplete outcome data (attrition bias) All outcomes	Low risk	no missing outcome data

Harro 2014

Methods	Randomised controlled trial Method of randomisation: no further description in publication by the authors
Participants	Country: USA Sample size: 22 participants (11 in speed treadmill training group, and 11 in control group) Inclusion criteria: age of 18-89 years, diagnosis of idiopathic PD, stage 1-3 on the Hoehn and Yahr scale, ability to walk continuously without physical assistance for five minutes with or without an assistive device, stable PD medication schedule and dosing over past month as reported by the participant's neurologist and functional vision and hearing sufficient to perceive cues with or without aides/glasses Exclusion criteria: impaired cognitive functioning evidenced by a score of 20 or less on the Saint Louis Mental Status Examination, history of other neurologic or vestibular disorders, current orthopedic conditions that would affect the ability to walk, history of PD-related deep brain stimulation, inability to speak and read English, and unstable medical status and inability to engage in moderate exercise
Interventions	2 arms (1) treadmill training group: 6 weeks supervised speed dependent treadmill walking, 30 minutes a session, 3 times a week (2) control group: 6 weeks rhythmic auditory-cueing in small groups of five participants, 30 minutes a session, not described how often a week
Outcomes	Outcomes were recorded at baseline, after 6 weeks and after 3 months and included: • comfortable gait speed (m/s) • fast gait speed (m/s) • gait capacity (6-min walk test) • Functional Gait Assessment (score)
Notes	

Harro 2014 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	not described
Allocation concealment (selection bias)	Unclear risk	not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	described as blinded assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	not all included participants were analysed

Kurtais 2008

Methods	Randomised controlled trial Method of randomisation: no further description in publication by the authors
Participants	Country: Turkey Sample size: 30 participants (15 in treadmill training group, and 15 in control group) Inclusion criteria: stable medication, not participated in a rehabilitation programme in the previous 3 months Exclusion criteria: severe cognitive impairment; severe musculoskeletal cardiopulmonary or other systemic disorders
Interventions	2 arms (1) treadmill training group: 6 weeks supervised treadmill walking, 40 minutes a session, 3 times a week (2) control group: not further described by the authors
Outcomes	Outcomes were recorded at baseline, after 7 weeks and included: • 20m walking time (s) • timed U-turn task (s) • turning around a chair • climbing up and down a flight of stairs (s) • arising from an armless chair (s) • standing on one foot (s) • VO_{2peak} ($mL*kg^{-1}*min^{-1}$) • exercise duration (min) • Metabolic Equivalent of Task (MET)
Notes	

Risk of bias		*Risk of bias*

Kurtais 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list (personal communication)
Allocation concealment (selection bias)	Low risk	generated list was used by an independent person to allocate participants (personal communication)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	assessed and tested during "on" phase by the authors who were blind to the randomization
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data was balanced between groups and an intention-to-treat analysis has been performed by the authors

Miyai 2000

Methods	Randomised cross-over trial Method of randomisation: no further description
Participants	Country: Japan Sample size: 10 participants (5 in treadmill training group, and 5 in control group, before first cross over) Inclusion criteria: Hoehn and Yahr stage 2.5 to 3, MMSE greater than 27
Interventions	2 arms (1) treadmill training group: 4 weeks body weight supported treadmill training, 45 minutes a day, 3 days a week (2) control group: 4 weeks conventional physiotherapy, 45 minutes a day, 3 days a week
Outcomes	Outcomes were recorded at baseline, after 4 weeks and included • UPDRS • walking endurance (m/ 6 minutes) • gait speed (s/10m) • steps (steps/10m)
Notes	Raw data kindly provided by the authors were used for all analyses

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	method of sequence generation not described by the authors

Miyai 2000 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	not described by the authors
Blinding of outcome assessment (detection bias) All outcomes	High risk	no blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	no missing outcome data

Miyai 2002

Methods	Randomised controlled trial Method of randomisation: not described by the authors
Participants	Country: Japan Sample size: 24 participants (12 in treadmill training group, and 12 in control group) Inclusion criteria: diagnosis of PD, Hoehn and Yahr stage 2.5 to 3, MMSE greater than 27 Exclusion criteria: on-off phenomenon
Interventions	2 arms (1) treadmill training group: 4 weeks body weight supported treadmill training, 45 minutes a day, 3 days a week, with a total of 12 sessions (2) control group: 4 weeks conventional physiotherapy, 45 minutes a day, 3 days a week, with a total of 12 sessions
Outcomes	Outcomes were recorded at baseline, after 1, 2, 3, 4, 5 and 6 months and included • UPDRS • gait speed (s/10m) • steps (steps/10m)
Notes	Raw data kindly provided by the authors were used for all analyses Because the details of the studies of Miyai 2000 and Mixai 2002 looks similar at a first look, we contacted the lead Author Prof. Miyai. He clearly stated that these trials are dissimilar and involve different patients

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	method of sequence generation not described by the authors
Allocation concealment (selection bias)	Unclear risk	not described by the authors
Blinding of outcome assessment (detection bias) All outcomes	High risk	no blinding

Miyai 2002 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	reasons form missing outcome data unlikely to be related to true outcomes

Nadeau 2013

Methods	Randomised controlled trial Method of randomisation: computer-generated randomisation sequence Blinding of outcome assessors: yes Adverse events: none Deaths: none Drop-outs: 9 (7 in experimental groups, 2 in control group) ITT: no
Participants	Country: Canada 93 patients (29 in treatment group I, 30 in treatment group II, 34 in control group) Ambulatory at study onset: not stated Mean age: 62 to 64 years (treatment and control group respectively) Inclusion criteria: not clearly stated except idiopathic PD and living up to 45 min away from the study centre Exclusion criteria: major health problem (cancer, heart/lung problems)
Interventions	3 arms: (1) control group used low exercise intensity training in seated position, 3 times a week for 24 weeks (180 min a week) (2) experimental group I received incremental speed treadmill training, 3 times a week for 24 weeks (180 min a week) (3) experimental group II received (mixed treadmill training) incremental speed treadmill training with additional incremental treadmill inclination, 3 times a week for 24 weeks (180 min a week)
Outcomes	Outcomes were recorded at baseline, at halving interval at 3 months and at the end of intervention phase at 6 months Walking speed (GAITRite) Stride length (GAITRite) Cadence (GAITRite) Step width (GAITRite) Gait capacity (6-min walk test) Unified Parkinson's Disease Rating Scale (UPDRS) Depression Beck (Depression Inventory - II (BDI-II)) Parkinson's Disease Questionnaire (PDQ) Balance Confidence Scale Exercise intensity Exercise adherence Exercise-related adverse events
Notes	

Risk of bias	***Risk of bias***

Nadeau 2013 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence
Allocation concealment (selection bias)	Low risk	Quote: "The allocation sequence was concealed from the project director who assigned participants to groups."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants and research assistants performing the assessments were blind to group assignment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	missing outcome data imbalanced between groups but not directly attributable to the intervention; no intention-to-treat analysis performed

Picelli 2013

Methods	Randomised controlled trial Method of randomisation: randomisation list used Blinding of outcome assessors: done Adverse events: none during study period Deaths: none Drop-outs: none ITT: yes
Participants	Country: Italy 60 patients (20 in robotic gait training group, 20 in treadmill training group and 20 in Physical Therapy group) Ambulatory at study onset: yes Mean age: 68 years (control and treatment group) Inclusion criteria: confirmed diagnosis of idiopathic PD according to the UK Brain Bank Criteria; Hoehn and Yahr stage 3 determined in the "on" phase; Mini Mental State Examination >24. Exclusion criteria: severe dyskinesias or "on-off" fluctuations; change of PD medication during the study; deficits of somatic sensation involving the lower limbs; vestibular disorders or paroxysmal vertigo; other neurological or orthopedic conditions involving the lower limbs (musculoskeletal diseases, severe osteoarthritis, peripheral neuropathy, joint replacement); cardiovascular comorbidity (recent myocardial infarction, heart failure, uncontrolled hypertension, orthostatic hypotension)
Interventions	3 arms: (1) robotic gait training group, twelve, 45-min sessions, three days a week for 4 consecutive weeks

Picelli 2013 (*Continued*)

	(2) treadmill training group, twelve, 45-min sessions, three days a week for 4 consecutive weeks (3) Physical Therapy group, twelve, 45-min sessions, three days a week for 4 consecutive weeks
Outcomes	Outcomes were recorded at baseline and at the end of intervention phase Gait speed (10m walk test) 6-min walk test (distance walked) Spatiotemporal gait parameters (e.g. Stride length, cadence) Unified Parkinson's Disease Ranking Scale (UPDRS) Motor Score Berg Balance Scale Parkinson's Fatigue Scale
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	randomisation list used
Allocation concealment (selection bias)	Low risk	allocation concealment by masked investigator
Blinding of outcome assessment (detection bias) All outcomes	Low risk	blinded rater
Incomplete outcome data (attrition bias) All outcomes	Low risk	no missing outcome data

Pohl 2003

Methods	Randomised cross-over trial Method of randomisation: sealed opaque envelopes
Participants	Country: Germany Sample size: 17 participants Inclusion criteria: early PD, defined as Hoehn and Yahr stages I through III; subjective disturbances in gait; stable drug program, and in stable cardiovascular condition Exclusion criteria: paroxysmal motor fluctuations, such as on-off and wearing-off phenomena, class B, C, or D exercise risk by the ACSM criteria; cognitive deficits (defined as scores of less than 26 on the MMSE; moderate or severe depression (defined as scores of greater than 17 on the Beck Depression Inventory); and orthopedic and other gait-influencing diseases such as arthrosis or total hip joint replacement

Pohl 2003 (*Continued*)

Interventions	4 arms (1) treadmill training group with incremental speed increase: 1 session treadmill training, 30 minutes (2) treadmill training group without increases of gait speed: 1 session treadmill training, 30 minutes (3) physiotherapy group: 1 session physiotherapy including gait training, 30 minutes (4) control group: resting in a chair for 30 minutes
Outcomes	Outcomes were recorded at baseline, after 1 session of 30 minutes and included • gait speed (m/s) • steps (steps/10m)
Notes	Raw data of the authors used for all analyses, data of treadmill groups were collapsed in to one group (n=8) and data of physiotherapy and control group were also collapsed into one group (n=9)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	computer generated list
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes were used for allocation procedure. They contained one of four sequences: 'A', 'B', 'C' and 'D' An assistant blinded to group assignment and not involved in patient recruitment allocated all participants by opening one sealed envelope
Blinding of outcome assessment (detection bias) All outcomes	Low risk	blinded assessor for gait speed and steps
Incomplete outcome data (attrition bias) All outcomes	Low risk	no missing outcome data

Protas 2005

Methods	Randomised cross-over trial Method of randomisation: not stated by the authors
Participants	Country: USA Sample size: 18 participants (9 in the treadmill and 9 in the control group) Inclusion criteria: postural instability-gait difficulty predominant PD; experiences with freezing episodes, and/or a history of falls; stable regimen of antiparkinsonian medications; ability to stand and

Protas 2005 (*Continued*)

	walk without assistance; stage 2 or 3 of the Hoehn and Yahr staging; and scores of moderate or higher on all scales of the Neurobehavioral Cognitive StatusExamination (Cognistat) Exclusion criteria: not used/not described
Interventions	2 arms (1) treadmill training group: treadmill training to improve gait and standing abilities for approximately 30 minutes including forward and backward walking and side stepping, 3 times a week for 8 weeks, 24 sessions of treadmill walking and stepping training (2) control group: no training
Outcomes	Outcomes were recorded at baseline and after 8 weeks and included • gait speed (m/s) • cadence (steps/min) • stride length (cm) • step test (steps/s)
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	method of sequence generation not described by the authors
Allocation concealment (selection bias)	Unclear risk	not described by the authors
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All testing except for the fall record was conducted by a physical therapist and a technician who were blinded to the subject's group assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	no missing outcome data

Sale 2013

Methods	Randomised controlled trial Method of randomisation: custom computerized system with Lehmer's algorithm Blinding of outcome assessors: yes Adverse events: not described Deaths: none Drop-outs: none ITT: yes

Sale 2013 (*Continued*)

Participants	Country: Italy 20 patients (10 in treatment group, 10 in control group) Ambulatory at study onset: yes Mean age: 18 to 90 years (control and treatment group respectively) Inclusion criteria: aged between 18 and 90 years, diagnosis of IPD by UK Brain Bank criteria, capability to walk unassisted or with little assistance for 25 feet walk, unassisted or with little assistance, for 25 feet. Exclusion criteria: other significant neurological or orthopedic conditions, not understanding instructions, primarily wheelchair bound, substance abuse, psychiatric disorders, atypical parkinsonian syndrome, deep brain stimulation
Interventions	2 arms: (1) control group used robot-assisted gait training (device: G-EO), 5 times a week for 4 weeks (225 min a week) (2) experimental group received treadmill training, 5 times a week for 4 weeks (225 min a week)
Outcomes	Outcomes were recorded at baseline and at the end of intervention phase Primary outcome: walking speed Secondary outcomes: cadence step length stride length step width stance time swing time duration of double support
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	software based sequence generation
Allocation concealment (selection bias)	Low risk	allocation concealment done by blinded professionals as described by the authors
Blinding of outcome assessment (detection bias) All outcomes	Low risk	blinded professionals as described by the authors
Incomplete outcome data (attrition bias) All outcomes	Low risk	no missing outcome data

Shulman 2013

Methods	Randomised controlled trial Method of randomisation: random number generator Blinding of outcome assessors: yes Adverse events: none Deaths: none Drop-outs: 13 (4 from experimental group I, 3 from experimental group II and 6 from control group) ITT: no
Participants	Country: USA 80 patients (26 from experimental group I, 26 from experimental group II and 28 from control group) Ambulatory at study onset: not described Mean age: 65 to 66 years (control and treatment group respectively) Inclusion criteria: aged 40 and above, diagnosis of PD characterized by asymmetrical onset of at least 2 of 3 cardinal signs, Hoehn & Yahr stage 1 to 3, presence of gait or balance disturbances, Mini-Mental State Examination >23 Exclusion criteria: unstable medical or psychiatric conditions, aerobic training prior to study enrollment
Interventions	3 arms: (1) control group used stretching and resistance training, 3 times a week for 12 weeks (duration of sessions not described) (2) experimental group I received lower intensity treadmill exercise, 3 times a week for 12 weeks (150 min a week) (3) experimental group II received higher intensity treadmill exercise, 3 times a week for 12 weeks (90 min a week)
Outcomes	Outcomes were recorded at baseline and at the end of intervention phase Primary outcome measures: Gait speed (6-min walk test, 10m walk test) cardiovascular fitness (ergospirometry) muscle strength (1-repetition maximum strength)
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	method of sequence generation not described by the authors
Allocation concealment (selection bias)	Unclear risk	not described by the authors
Blinding of outcome assessment (detection bias) All outcomes	Low risk	physicians and staff were blinded as described by the authors

Shulman 2013 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	missing outcome data balanced between groups with similar reasons for missing data across groups

Yang 2010

Methods	Randomised controlled trial Method of randomisation: Sealed opaque envelopes Blinding of outcome assessors: no Adverse events: none Deaths: none Drop-outs: 3 (2 in the control group and 1 in the experimental group) ITT: no
Participants	Country: Taiwan 33 patients (16 in treatment group, 17 in control group) Ambulatory at study onset: yes Mean age: 66 to 68 years (control and treatment group respectively) Inclusion criteria: diagnosed with IPD by a neurologist as defined by the UK Brain Bank criteria, Hoehn & Yahr stage 1 to 3, independent ambulation, constant medication, ability to understand instructions Exclusion criteria: other conditions limiting exercise
Interventions	2 arms: (1) control group used conventional therapy, 3 times a week for 4 weeks (90 min a week) (2) experimental group received downhill treadmill training, 3 times a week for 4 weeks (90 min a week)
Outcomes	Outcomes were recorded at baseline and at the end of intervention phase Gait performance (GAITRite) Thoracic kyphosis (electronic goniometer) Muscle strength (handheld dynamometer)
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	sealed envelopes were drawn by an independent arbiter
Allocation concealment (selection bias)	Low risk	sealed envelopes were drawn by an independent arbiter

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	no blinding was done
Incomplete outcome data (attrition bias) All outcomes	Low risk	missing outcome data balanced between groups with similar reasons for missing data across groups

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bello 2008	Not a randomised controlled trial
Diaz de la Fe 2008	Not a randomised controlled trial (personal communication with the authors)
Fisher 2013	Irrelevant outcome measures
Ganesan 2010	Irrelevant outcome measures
Gianfrancesco 2009	Not a randomised controlled trial
Schenkman 2012	Experimental group received treadmill training together with training on a stationary bicycle or elliptical trainer

Characteristics of studies awaiting assessment *[ordered by study ID]*

Horak 2011

Methods	Randomised controlled trial with parallel group assignment
Participants	Estimated enrollment: 40, aged between 50 and 80 years Inclusion criteria: Diagnosis of idiopathic Parkinson's Disease Exclusion criteria: Other neurological conditions, artificial joints
Interventions	2 arms: (1) Treadmill training 4 times a week for 4 weeks with a physical therapist (2) Agility training 4 times a week for 4 weeks with a physical therapist
Outcomes	Primary Outcome Measures: Dynamic Posturography Secondary Outcome Measures: UPDRS
Notes	This study has been completed. No study results yet posted.

Mezzarobba 2013

Methods	Design: randomised controlled trial Method of randomisation: computer-generated Blinding of outcome assessors: yes Adverse events: not stated Deaths: not stated Drop-outs: not stated ITT: unclear
Participants	Country: Italy 21 patients (10 in treatment group, 11 in control group) Ambulatory at study onset: unclear Median age: 75 years Inclusion criteria: Hoehn & Yahr stage 1-3, Mini Mental State Examination Score >24 Exclusion criteria: Beck Depression Inventory score <16
Interventions	2 arms: (1) control group used motor imagery training for 20 sessions (duration not stated) (2) experimental group received treadmill training for 20 sessions (duration not stated)
Outcomes	Outcomes were recorded at baseline, at the end of intervention phase and at 4-week and at 12-week follow-up Disease stage (Hoehn and Yahr scale, Unified Parkinson's Disease Ranking Scale (UPDRS)) Freezing of Gait (Freezing of Gait Questionnaire) Quality of life (Parkinson's Disease Questionnaire (PDQ-39)) Locomotion (Timed Up and Go Test, 6-minute walk test) Balance (Berg Balance-scale) Disability (Modified Parkinson's Activity scale (MPAS))
Notes	Conference abstract

Characteristics of ongoing studies *[ordered by study ID]*

NCT01768832

Trial name or title	Exercise and Parkinson's: Comparing Interventions and Exploring Neural Mechanisms
Methods	Randomised controlled trial with parallel group assignment
Participants	Estimated enrollment: 120, aged above 30 years Inclusion criteria: Diagnosis of Parkinson's Disease, at least grade 3/5 strength and normal joint ranges of motion in both legs, good vision, independent ambulation for 10 feet with or without assistive devices, normal gross somatosensory function in the feet Exclusion criteria: Other medical condition with exercise being a contraindication, abnormal brain imaging, evidence or history of other neurological or muscular conditions, failed to pass MRI procedure
Interventions	3 arms: (1) Treadmill training 2 times a week (120 min per week) for 12 weeks (2) Tango dance training 2 times a week (120 min per week) for 12 weeks (3) Stretching 2 times a week (120 min per week) for 12 weeks

NCT01768832 (*Continued*)

Outcomes	Primary Outcome Measures: Change in Walking Velocity from Baseline to 3 Months Secondary Outcome Measures: Change in Blood oxygen level dependent signal from baseline to 3 months, Change in Mini Balance Evaluation Systems Test (Mini-BESTest) from baseline to 3 months, Change in PDQ-39 from baseline to 3 months, Change in Movement Disorder Society Unified Parkinson Disease Rating Scale (UPDRS) Subscale III from baseline to 3 months, Change in Mini Balance Evaluation Systems Test (Mini-BESTest) from 3 to 6 months, Change in UPDRS Subscale III from 3 months to 6 months, Change in PDQ-39 from 3 months to 6 months, Change in walking velocity from 3 months to 6 months
Starting date	February 2013
Contact information	Washington University School of Medicine St. Louis, Missouri, United States, 63108 Martha Hessler: hesslerm@wusm.wustl.edu Gammon M Earhart, PhD, PT: earhartg@wusm.wustl.edu
Notes	

DATA AND ANALYSES

Comparison 1. Treadmill training versus no treadmill training or active control intervention or gait training

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gait speed at the end of the study	17	510	Mean Difference (IV, Random, 95% CI)	0.09 [0.03, 0.14]
1.1 Active control group	14	434	Mean Difference (IV, Random, 95% CI)	0.07 [0.03, 0.12]
1.2 No intervention control group	3	76	Mean Difference (IV, Random, 95% CI)	0.40 [-0.06, 0.87]
2 stride length (at the end of study; all studies)	10	333	Mean Difference (IV, Random, 95% CI)	0.05 [0.01, 0.09]
2.1 Active control group	9	315	Mean Difference (IV, Random, 95% CI)	0.04 [0.00, 0.09]
2.2 No intervention control group	1	18	Mean Difference (IV, Random, 95% CI)	0.11 [-0.02, 0.24]
3 walking distance in m (at the end of study; all studies)	10	416	Mean Difference (IV, Random, 95% CI)	48.91 [-1.32, 99.14]
3.1 Active control group	9	385	Mean Difference (IV, Random, 95% CI)	9.48 [-0.47, 19.42]
3.2 No intervention control group	1	31	Mean Difference (IV, Random, 95% CI)	364.0 [294.45, 433.55]
4 cadence (at the end of study; all studies)	10	336	Mean Difference (IV, Random, 95% CI)	2.16 [-0.13, 4.46]
4.1 Active control group	9	318	Mean Difference (IV, Random, 95% CI)	2.42 [0.07, 4.77]
4.2 No intervention control group	1	18	Mean Difference (IV, Random, 95% CI)	-4.0 [-15.11, 7.11]
5 acceptability and safety of treadmill training	18	633	Risk Difference (M-H, Random, 95% CI)	-0.02 [-0.06, 0.02]
5.1 Active control group	15	531	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.05, 0.03]
5.2 No intervention control group	3	102	Risk Difference (M-H, Random, 95% CI)	-0.14 [-0.43, 0.16]

Comparison 2. Sensitivity analysis: Treadmill training versus no treadmill training

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gait speed	17		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 All studies	16	488	Mean Difference (IV, Random, 95% CI)	0.10 [0.05, 0.15]
1.2 All studies with random allocation	8	237	Mean Difference (IV, Random, 95% CI)	0.08 [0.02, 0.13]
1.3 all studies with concealed allocation	8	237	Mean Difference (IV, Random, 95% CI)	0.08 [0.02, 0.13]
1.4 All studies with blinded assessors	12	375	Mean Difference (IV, Random, 95% CI)	0.07 [0.00, 0.13]
2 Gait speed	17	510	Mean Difference (IV, Random, 95% CI)	0.09 [0.03, 0.14]

2.1 treadmill protocols using a speed dependent approach	4	88	Mean Difference (IV, Random, 95% CI)	0.16 [-0.08, 0.40]
2.2 treadmill protocols with gradual speed increases	8	227	Mean Difference (IV, Random, 95% CI)	0.08 [0.02, 0.14]
2.3 treadmill protocols with constant walking speed	3	85	Mean Difference (IV, Random, 95% CI)	0.12 [0.02, 0.22]
2.4 studies using a mixed or different approaches or did not manipulated gait speed	2	110	Mean Difference (IV, Random, 95% CI)	0.01 [-0.19, 0.22]

ADDITIONAL TABLES

Table 1. Patient characteristics in studies

Study ID	Age, mean (SD) EXP	Age, mean (SD) CON	Hoehn & Yahr stages	mean Duration of disease EXP	mean Duration of disease CON	female/ male EXP	female/ male CON	Duration of therapy	frequency of training	intensity of training in terms of minutes per session	intensity of training in terms of treadmill speed paradigm
Bello 2013	60 (11)	58 (9)	1 to 3	5 years	5 years	4/7	5/6	5 weeks	3 times a week	16' with increments of 4 ' per week	constant and as individually preferred speed
Cakit 2007	72 (6)*		1 to 2	6 years*		15/16*		8 weeks	not described	30	relatively similar to so called speed dependent treadmill approach (Pohl 2002)
Canning 2012	61 (6)	63 (10)	1 to 2	6 years	6 years	5/5	4/6	6 weeks	4 times a week	20-40	gradually increased speed

Table 1. Patient characteristics in studies (*Continued*)

Carda 2012	61 (6)	63 (10)	1 to 2	6 years	5 years	not described		6 weeks	4 times a week	30	high, (80% of max), gradually increased
Chaiwanichsiri 2011	68 (5)	69 (5)	2 to 3	6 years	4 years	0/10	0/10	4 weeks	3 times a week	20	slightly higher than preferred
Fisher 2008	64 (15)	62 (10)	1 to 2	1 year	1 year	4/6	13/7	8 weeks	3 times a week	45	progression of speed in high intensity group/ and low to moderate progression of speed in low intensity group
Frazzitta 2009	71 (8)	71 (7)	3	13 years	13 years	12/8	11/9	4 weeks	7 times a week	20	60% of max speed at start, then gradually increased
Harro 2014	65 (9)	67 (11)	1 to 3	4 years	9 years	5/5	2/8	6 weeks	3 times a week	30	both groups received speed training relatively similar to so

Table 1. Patient characteristics in studies (*Continued*)

											called speed dependent approach (Pohl 2002)
Kurtais 2008	64 (11)	66 (5)	mean 2. 2 to 2.5	5 years	5 years	7/5	5/7	6 weeks	3 times a week	40	gradually increased speed
Miyai 2000	67 (2)*		2.5 to 3	4 years*		5/5*		4 weeks	3 times a week	36-45	gradually increased speed
Miyai 2002	70 (2)	70 (2)	2.5 to 3	4 years	4.5 years	6/5	4/5	4 weeks	3 times a week	45	gradually increased speed
Nadeau 2013	62 (7)	64 (6)	1 to 2	Not reported		2/9	5/18	24 weeks	3 times a week	60	gradually increased speed
Picelli 2013	69 (8)	68 (9)	3	7 years	7 years	14/6	23/17	4 weeks	3 times a week	30	gradually increased speed
Pohl 2003	61 (9)	61 (9)	1 to 2.5	3 years	3 years	3/5	2/7	1 session	N.a.	30	similar to so called speed dependent treadmill approach (Pohl 2002)
Protas 2005	71 (7)	74 (9)	2 to 3	7 years	8 years	not described		8 weeks	3 times a week	30	relatively sim-

Table 1. Patient characteristics in studies (*Continued*)

											ilar to so called speed dependent treadmill approach (Pohl 2002)
Sale 2013	68 (9)	70 (10)	2.5 to 3.5	9 years	8 years	5/5	6/4	4 weeks	5 times a week	45	gradually increased speed
Shulman 2013	66 (10)	65 (11)	2 to 3	6 years	6 years	17/32	4/18	12 weeks	3 times a week	30-50	no clear speed increases but depending on maximal heart reserve speed was increased
Yang 2010	68 (8)	66 (11)	1 to 3	5 years	5 years	6/9	8/7	4 weeks	3 times a week	30	constant, comfortable speed

* information not available by group

Table 2. Characteristics of control group in studies

Study ID	active treatment	no interventions	gait training	control group
Bello 2013	yes		yes	overground gait training, 3 times a week for 5 weeks (72 min a week)
Cakit 2007		yes		not described further

Table 2. Characteristics of control group in studies *(Continued)*

Canning 2012	yes			usual care including advice to maintain usual physical activity levels
Carda 2012	yes		yes	robotic gait training, 3 times a week for 4 weeks (120 min a week)
Chaiwanichsiri 2011	yes		yes	home walking program, 6 times a week for 4 weeks (180 min a week)
Fisher 2008	yes		1	(2) low-intensity group: general or traditional physiotherapy, for 24 sessions in 8 weeks (3) zero-intensity (no-exercise) group: six 1 hour education class over 8 weeks
Frazzitta 2009	yes		1	traditional rehabilitation with visual and auditory cues, 7 times a week for 4 weeks (140 min a week)
Harro 2014	yes		yes	6 weeks rhythmic auditory-cueing with incremental speed increases in small groups of five participants, 30 minutes a session, not described how often a week
Kurtais 2008		yes		not further described by the authors
Miyai 2000	yes			4 weeks conventional physiotherapy, 45 minutes a day, 3 days a week
Miyai 2002	yes			4 weeks conventional physiotherapy, 45 minutes a day, 3 days a week, with a total of 12 sessions
Nadeau 2013	yes			low exercise intensity training in seated position, 3 times a week for 24 weeks (180 min a week)
Picelli 2013	yes		yes	3 arms:(1) robotic gait training group, twelve, 45-min sessions, three days a week for 4 consecutive weeks (3) Physical Therapy group, twelve, 45-min sessions, three days a week for 4 consecutive weeks
Pohl 2003	yes		yes	4 arms(3) physiotherapy group: 1 session physiotherapy including gait training, 30 minutes (4) control group: resting in a chair for 30 minutes
Protas 2005		yes		no training
Sale 2013	yes		yes	robot-assisted gait training (device: G-EO), 5 times a week for 4 weeks (225 min a week)
Shulman 2013	yes			stretching and resistance training, 3 times a week for 12 weeks (duration of sessions not described)

Table 2. Characteristics of control group in studies *(Continued)*

Yang 2010	yes			conventional therapy, 3 times a week for 4 weeks (90 min a week)

Table 3. Use of UPDRS and QoL scales and follow-up

Study ID	U PDRS at baseline	UPDRS at study end	QoL at baseline	Follow-Up
Bello 2013	UPDRS motor score	UPDRS motor score	-	no
Cakit 2007	UPDRS motor score	-	-	no
Canning 2012	UPDRS motor score	UPDRS motor score	PDQ-39	after 6 weeks
Carda 2012	UPDRS motor score	UPDRS motor score	SF-12 PCS and MCS	after 3, 6 months
Chaiwanichsiri 2011	-	-	-	after 1 months
Fisher 2008	UPDRS (total and sub-scales)	UPDRS (total and sub-scales)	-	no
Frazzitta 2009	UPDRS motor score	-	-	no
Harro 2014	-	-	-	3mo
Kurtais 2008	-	-	-	no
Miyai 2000	UPDRS (total and sub-scales)	UPDRS (total and sub-scales)	-	no
Miyai 2002	UPDRS (total and sub-scales)	UPDRS (total and sub-scales)	-	after 2,3,4,5 and 6 months
Nadeau 2013	UPDRS (total and sub-scales)	UPDRS (total and sub-scales)	PDQ-39	after 6 months
Picelli 2013	UPDRS (total)	UPDRS (total)	-	3 months
Pohl 2003	UPDRS (total and sub-scales)	-	-	no
Protas 2005	-	-	-	no
Sale 2013	UPDRS (total and sub-scales)	-	-	no
Shulman 2013	UPDRS (total and sub-scales)	-	-	no

Table 3. Use of UPDRS and QoL scales and follow-up (*Continued*)

Yang 2010	-	-	-	after 1 months

WHAT'S NEW

Last assessed as up-to-date: 16 March 2015.

Date	Event	Description
7 August 2015	New citation required and conclusions have changed	We have updated the searches to September 2014, and have revised the text as appropriate. We have included 18 trials with 633 participants in this major update compared with 8 trials with 203 participants in the last version of this review from 2009 The conclusion has been changed. Int his version we conclude that 'It seems that the use of treadmill training could be beneficial with comparable risk as conventional therapies.'

CONTRIBUTIONS OF AUTHORS

Jan Mehrholz (JM) contributed to the conception and design of the protocol and approved the final manuscript. He searched electronic databases and conference proceedings, screened titles and abstracts of references identified by the search, selected and assessed trials, extracted trial and outcome data, guided the analysis and the interpretation of the data, and contributed to and approved the final manuscript of the review.

Joachim Kugler (JK) assessed the methodological quality of selected trials, and contributed to and approved the final manuscript of the review.

Bernhard Elsner (BE) searched electronic databases and conference proceedings, screened titles and abstracts of references identified by the search, located, selected and assessed trials, extracted trial and outcome data, assessed the methodological quality of selected trials, and contributed to and approved the final manuscript of the review.

Kathleen Hirsch (KH) and Alexancer Storch (AS) contributed to and approved the final manuscript of the review.

Marcus Pohl (MP) contributed to the conception and design of the review, drafted the protocol, and assessed the methodological quality of selected trials. Together with JM, he contacted trialists about unpublished data and also entered the data, carried out statistical analysis, helped with the interpretation of the data, drafted the review and approved the final manuscript of the review.

DECLARATIONS OF INTEREST

MP and JM were co-authors of one included trial (Pohl 2003). They did not participate in the quality assessment and data extraction of this study.

SOURCES OF SUPPORT

Internal sources

- Wissenschaftliches Institut, Klinik Bavaria Kreischa, Germany.
- Department of Public Health, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden, Germany.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are some differences between the protocol and the review briefly described below. We planned to do a subgroup analysis comparing subgroups of similar interventions in terms of duration and frequency.

After introducing a sensitivity analysis with incorporating four subgroups, we decided to do not any further subgroup analysis due to the small number of studies and to avoid multiplicity.

However, since such a subgroup analyses by duration and frequency of intervention, and additionally by time of outcome assessment might be clinically relevant, these will be conducted when and if there is data available in future updates.

For primary and secondary outcomes, we did not separate analyses for data immediately after the end of the study and at follow up after the study end to look for any sustained effects. This was due to the small number of studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Exercise Therapy [instrumentation; *methods]; Gait Disorders, Neurologic [etiology; *rehabilitation]; Parkinson Disease [complications; *rehabilitation]; Randomized Controlled Trials as Topic; Walking

MeSH check words

Aged; Humans; Middle Aged