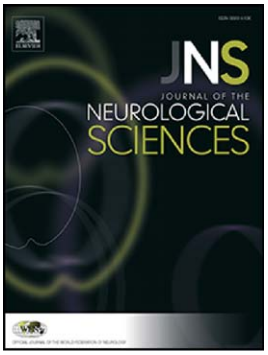


Parkinson's Disease and Intensive Exercise Therapy - a Systematic Review and Meta-analysis of Randomized Controlled Trials

Anders Uhrbrand, Egon Stenager, Martin Sloth Pedersen, Ulrik Dalgas

PII: S0022-510X(15)00201-4
DOI: doi: 10.1016/j.jns.2015.04.004
Reference: JNS 13733

To appear in: *Journal of the Neurological Sciences*

Received date: 9 February 2015
Revised date: 17 March 2015
Accepted date: 2 April 2015

Please cite this article as: Uhrbrand Anders, Stenager Egon, Pedersen Martin Sloth, Dalgas Ulrik, Parkinson's Disease and Intensive Exercise Therapy - a Systematic Review and Meta-analysis of Randomized Controlled Trials, *Journal of the Neurological Sciences* (2015), doi: 10.1016/j.jns.2015.04.004

Parkinson's Disease and Intensive Exercise Therapy - a Systematic Review and Meta-analysis of Randomized Controlled Trials.

Anders Uhrbrand[1], Egon Stenager[2,3], Martin Sloth Pedersen[1] & Ulrik Dalgas[1]

1. Section of Sport Science, Dep. Public Health, Aarhus University, Denmark
2. Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark.
3. Department of Neurology & MS-Clinic of Southern Jutland (Sønderborg, Esbjerg, Vejle), Sønderborg Hospital, Denmark.

Corresponding author:

Anders Uhrbrand (Cand. Scient)

Author Key words: Pakinson's disease, exercise physiology, sports medicin, exercise therapy

uhrbrand999@hotmail.com

0045 28875142

Steen Billes Gade 9, st. th., 8200 Århus N, Denmark

Abstract

Objective: To evaluate and compare the effect of 3 intensive exercise therapy modalities - Resistance Training (RT), Endurance Training (ET) and Other Intensive Training Modalities (OITM) - in Parkinson's Disease (PD).

Design: A systematic review and meta-analysis of randomized controlled trials.

Methods: A systematic literature search was conducted (Embase, Pubmed, Cinahl, SPORTDiscus, Cochrane, PEDro), which identified 15 studies that were categorized as RT, ET or OITM. The different exercise modalities were reviewed and a meta-analysis evaluating the effect of RT on muscle strength was made.

Results: In PD intensive exercise therapy (RT, ET and OITM) is feasible and safe. There is strong evidence that RT can improve muscle strength in PD, which is underlined by the meta-analysis (g'=0.54 [95%CI 0.22;0.86]). There is moderate evidence that ET can improve cardio-respiratory fitness in PD. RT, ET and OITM may have beneficial effects on balance, walking performance, Unified Parkinson's Disease Rating Scale-III (UPDRS-III) score and quality of life in PD, but findings are inconsistent. No studies find deterioration in any outcomes following exercise therapy.

Conclusion: RT, ET and OITM all represent feasible, safe and beneficial adjunct rehabilitation therapies in PD.

Keywords: Parkinsonism, Physiotherapy, Aerobic Training, Strength Training, Neurological, Physical Therapy.

1. Introduction

Parkinson's disease (PD) is a growing chronic and progressive neurodegenerative condition, affecting approximately 7 million, primarily elderly, people worldwide [1-3]. People with PD have more motor and non-motor complications, than healthy age-matched subjects[4,5]. The motor complications include tremor, rigidity, bradykineasia and deterioration of muscle strength, cardio-respiratory fitness, balance and walking performance[4-8], while the non-motor complications include sensory complaints, autonomic dysfunction, fatigue, apathy, sleep disturbances, depression, cognitive dysfunction and ultimately decreased quality of life (QOL)[6]. These impairments combined with fear of falling, often cause individuals to adopt a sedentary lifestyle[9], creating a viscous circle, as physical inactivity can negatively affect the clinical domains of PD[4]. Thus people with PD, in many cases, struggle with the disease *per se*, ageing and the consequences of physical inactivity. These factors can independently affect the disease, but they are also interrelated[9], enforcing the potential viscous circle.

Medical surgery is expensive and with risks while dopaminergic medication is with side-effects and inadequate in the preservation of body functions, daily activities and mobility, as the disease progresses[10-12]. Consequently, much attention has been paid towards structured multidisciplinary rehabilitation strategies, in recent years[13-15]. A subset of these multidisciplinary interventions is exercise therapy. Exercise therapy is defined as "an individualized exercise prescription (or plan) designed to restore health and prevent further disease or impairment, where the prescription, written by a doctor or rehabilitation specialist, takes into account the current medical condition and provides advice regarding exercise type, intensity, duration and frequency"[16]. Exercise therapy poses the potential to improve many clinical domains of PD[4]. Indeed studies on PD have shown improvements of muscle strength, cardio-respiratory fitness, balance, walking performance, and QOL, following exercise therapy[10,13,17-27]. Furthermore, animal studies suggest, that exercise has a neuroprotective effect in PD, but this remains to be confirmed in human studies[28-30]. Nevertheless, reviews have concluded, that there is insufficient evidence to choose one type of exercise over another[13,31].

Despite a number of previous reviews[13,32-37] being published on exercise therapy, a high number of relevant studies have been published in recent years[10,18-22,25,27,38,39], calling for an update of the literature. Furthermore, previous reviews on exercise therapy and PD have not applied strict definitions and/or subsequent division of different exercise modalities, resulting in inclusion of heterogeneous and poorly reported exercise interventions. Very different exercise modalities (eg. stretching and resistance training) have been put into the same category, leading to lack of or compromised conclusions regarding specific exercise modalities. Consequently the purpose of this review was to evaluate and compare the effect of 3 exercise therapy modalities - Resistance Training (RT), Endurance Training (ET) and Other Intensive Training Modalities (OITM) - in PD.

2. Methods

2.1. Search strategy

The present review follows the PRISMA guidelines on systematic reviews of RCT´s[40]. No predefined review protocol was published. The review is based on a systematic literature search (PubMed, Embase, Cochrane library, PEDro, Sport Discus, Cinahl) performed on August 12th 2013, using various exercise-related words and MeSH terms in combination with PD (Table 1). The search was updated on September 13th 2014, identifying further three relevant papers[41-43]. However, close reading revealed that none of these fulfilled the inclusion criteria.

2.2. Inclusion/exclusion criteria

Included studies had to:

1) investigate people with definite PD according to established criteria[44,45]

2) be a peer-reviewed, longitudinal RCT.

3) apply a RT, ET or OITM exercise intervention (according to the definitions below).

4) include a precise description of the applied exercise intervention in terms of training regime, frequency, intensity, duration and progression.

5) compare exercise to any comparator, including other forms of exercise.

6) be written in English, Danish or German.

Papers were excluded if the exercise intervention:

1) lasted less than 2 weeks.

2) was multimodal with non-includable components that were expected to interact on relevant outcomes.

3) was not standardized.

2.3. Exercise definition

RT was defined as few dynamic muscle contractions against external loads, with sufficient progression (in accordance with the 2009 ACSM guidelines[46]). ET was defined as many dynamic muscle contractions against low loads, for extended periods of time, with sufficient progression and an intensity of minimum 60% of maximal heart rate (%HRmax) or equivalent on the Borg scale, maximal oxygen uptake-scale (%VO_2peak) or percentage of heart rate reserve-scale (%HRR). To allow comparison of intensities across studies, the reported intensities of the ET trials were converted to %HRmax using equations by Panton et al[12] or the Karvonen formula[47], when appropriate. OITM was

defined as non-isolated ET or RT, but with intensity, frequency, duration and progression being so well-described that it could be determined to be closely related to RT and/or ET.

2.4. PEDro Scale

The methodological quality of the studies was assessed using the original PEDro scale[48] (Table 2). Scores on all included studies were obtained from the PEDro database. The PEDro scale has sufficient reliability for use in systematic reviews on physical therapy[48] and is a valid measure of the methodological quality of clinical trials[49].

2.5. Data analysis

This review included all outcome measures in the selected studies, but a special focus was put on the following outcomes: muscle strength, cardio-respiratory fitness, balance, walking performance, Unified Parkinson's Disease Rating Scale-III (UPDRS-III) and quality of life. Whenever sufficient data or information was lacking in any part of the review process, the relevant corresponding author was contacted.

2.6. Statistical analysis

Meta-analytical procedures were applied to further evaluate possible effects of RT on muscle strength. Insufficient data was identified to make valid meta-analyses on other outcomes. The meta-analysis was conducted in accordance with the Meta-Analysis of Observational Studies in Epidemiology framework[50].

Six studies[10,19,20,22,26,51] were included in the meta-analysis. Five studies applied isolated RT, while DiFrancisco et al[20] used a combined (resistance and endurance) training intervention group. Three studies[20,26,51] included a non-exercising control group, while the last 3 studies[10,19,22] included a sham/low intensity exercise control group. However the exercise interventions of the active control groups, was expected to have no effect on muscle strength.

Three studies[10,20,22] evaluated strength using more than one measure (e.g. leg press, knee extension, knee flexion). In these cases data was pooled into one overall measure. All data in the meta-analysis were based on patients who were "on" medication.

Effect sizes (ES) were computed as the mean change from before to after the intervention of the exercise group subtracted the mean change of the control group, divided by the pre-intervention pooled standard deviation and adjusted for sample size. A positive ES indicates a beneficial improvement of muscle strength in the intervention group, compared to the control group. The aggregated or mean ES was computed, using a random effects model and was reported as Hedges' g[52].

3. Results

3.1. Included studies

A flowchart describing literature selection is presented in Figure 1. A total of 15 RCTs were included, where two studies[10,23] had several relevant interventions, generating a total of 8 RT interventions, 6 ET interventions and 4 OITM interventions.

3.2. Study characteristics

No studies reported any serious symptom exacerbations or deterioration in any outcome measures (Table 3-7). Nine studies[10,17,19,21,22,25,27,38,51] reported on adverse events, without observing any serious adverse events. Non-serious adverse events included incidents of transient pain/soreness, joint inflammation and worsening of preexisting injuries, but these did not differ from control[18,21,24,51]. Falls were investigated in 3 studies[22,27,38] showing no significant difference between the intervention and the control group. Four studies[10,19,23,27] reported on the levodopa use of the patients. Two of these studies[10,27] reported, that the levodopa use of the patient had not changed during the course of the study (4 and 12 weeks), but they only reported the baseline values. Corcos et al[19] reported values on levodopa at baseline, 6 months, 12 months, 18 months and 24 months. There were no significant differences between the changes in levodopa use in the RT and the active control group at any time point. The RT group increased levodopa use by 21,2±49,2 mg/day after 6 months and 155,8±193,3 mg/day after 24 months. It was not reported whether these increases were statistically significant or not.

The RT training regime primarily involved the lower extremities (mainly quadriceps femoris, the hamstrings and triceps surae) using RT machines (Table 4), while some studies also included the upper extremities[19,21,38]. The intensity range was 5-20 repetitions for 1-3 sets at 40-80% of 1 repetition maximum. The ET training regime predominantly involved the lower extremities using a treadmill, stationary bike or elliptical trainer, while two studies[24,25] involved the arms as well (see Table 6). The intensity range was ≈ 60-90% of HRmax. The OITM training regime included boxing, forced exercise, and combined RT and ET and the intensity range was ≈ 61-90% of HRmax and 8-15 reps for 2 sets at 50-80% of 1RM.

3.3. Resistance Training

3.3.1. RT: Muscle strength

Strength was measured in 6 RT studies[10,19,21,22,26,51] (Table 4). All studies found significant increases in strength measures, ranging from 7-77% after 8-104 weeks of RT. Corcos et al[19] found significant

increases in strength after 6 months, 12 months, 18 months and 24 months of RT, when patients were tested both on and off medication.

The meta-analysis included data from 6 studies reflecting a total of 137 subjects (Table 5) and Figure 2). All 6 effect sizes (ES) were positive and 1 was statistically significant ($p<0.05$). The mean effect across studies was g'=0.54 [95%CI 0.22;0.86]. The null hypothesis of homogeneity could not be rejected (Q=1.844, d.f=5, p=0.870) indicating that the weighted mean ES of the sample distribution, is likely to correctly describe the average effect in the population.

In summary there is strong evidence that RT can improve strength in PD, seemingly both on and off PD medication.

3.3.2. RT: Cardio-respiratory fitness, Balance and Walking performance

Cardio-respiratory fitness was measured only in 1 RT study showing no significant improvement[10].

Balance was assessed in 2 RT studies[22,26] reporting either no effect[25] or improved subjective, but not objective balance[21].

Walking performance was measured in 5 RT studies[10,21,22,26,27] reporting significantly improved self-selected walking velocity (6%)[27], significantly improved six minute walk test (8%)[10], significantly improved stride velocity (11%)[21], significantly improved cadence (4%)[27] and significantly improved gait initiation (29%)[21] or no effect on maximal walking speed[10,22], no effect on the timed up and go test[10,22,26], no effect on walking distance[26], following RT.

In summary RT may improve balance and walking performance in PD, but findings are inconsistent.

3.3.3. RT: UPDRS-III and Quality of life

UPDRS-III was measured in 3 RT studies[10,19,27]. Following RT Shulman et al[10] found a significant decrease (improvement) of 10% in UPDRS-III, while Corcos et al[19] found a significant decrease at 6 months, 12 months, 18 months and 24 months, when patients were tested off, but not on medication.

Quality of life was measured in 2 RT studies[10,19]. Corcos et al[19] reported a significant decrease (improvement) in the parkinson's disease questionnaire (PDQ-39) after 6 months of RT, but not after 12, 18 and 24 months, while Shulman et al[10] found no significant change in the PDQ-39.

In summary, the few existing studies show that RT may positively impact UPDRS-III and quality of life, primarily when tested off medication.

3.4. Endurance Training

3.4.1. ET: Cardio-respiratory fitness

Cardio-respiratory fitness was measured or estimated in 4 ET studies[10,17,23,25] evaluating 5 ET interventions. The existing studies showed significant improvements of VO_2peak ranging between 6-22%[10,23] (Table 6). In addition Schenkman et al[25] found a significantly decreased (improvement) VO_2/kg at the same absolute submaximal intensity indicating better cardio-respiratory fitness, while Bridgewater et al[17] found significant improvements in the Bruce protocol test duration.

In summary there is moderate evidence that ET can improve cardio-respiratory fitness in PD.

3.4.2. ET: Strength, Balance and Walking performance

Strength was measured in 2 ET studies, which found no significant changes in strength[10].

Balance was reported to improve significantly in 1 ET study, in terms of the functional reach test[25].

Walking performance was measured in 2 ET studies[10,24] evaluating 3 ET interventions. Shulman et al[10] found significant improvements in the six minute walk test (11%) and maximal walking speed (7%), but not in the timed up and go test after low intensity training, while high intensity training only improved maximal walking speed (5%). Sage et al[24] found significantly increased step length (8%), but reported no change for the timed up and go test (p = 0,095), stride velocity (p = 0,07) and stride cadence.

In summary the few existing studies show, that ET may improve walking performance in PD, but findings are few and inconsistent.

3.4.3. ET: UPDRS-III and Quality of life

UPDRS-III score was measured in 4 ET studies[10,23-25] evaluating 5 ET interventions. None of the studies found any significant changes. Quality of life was measured in 2 ET studies[10,25] evaluating 3 ET interventions showing no significant changes in the PDQ-39.

In summary, ET does not seem to influence UPDRS-III and quality of life.

3.5. Other Intensive Training Modalities

3.5.1 OITM: Strength, Cardio-respiratory fitness, Balance and Walking performance

Strength was measured in 1 OITM study[20] reporting significant increases in leg press (22%), knee extension (43%) and knee flexion (28%), after combined RT and ET (Table 7). Cardio-respiratory fitness was measured in 2 OITM studies[20,23]. Ridgel et al[23] reported a significantly increased VO_2peak (11%)[23] following forced exercise, but the control group, who performed ET, also improved significantly. DiFrancisco et al[20] found a 13% significant decrease (improvement) in VO_2 at a given absolute submaximal intensity, after combined RT and ET.

Balance was measured in 2 OITM studies[18,39]. Combs et al[18] found significantly improved performance on the berg balance scale (8%), after boxing training, while Qutubuddin et al[39] found no significant change. In the study by Combs et al. the control group, who did balance training, also improved significantly on the berg balance scale.

Walking performance was measured in 1 OITM study[18] showing significant improvements in 4 gait parameters: six minute walk test (13%), timed up and go test (12%), dual-task timed up and go test (28%) and gait velocity (4%) after boxing training. The timed up and go test and dual-task timed up and go test also improved significantly in the control group, who did related training.

In summary, the few existing studies show that OITM may improve muscle strength, oxygen uptake, balance and walking performance in PD.

3.5.2 OITM: UPDRS-III and Quality of life

UPDRS-III was measured in 2 OITM studies[23,39], both evaluating forced exercise. Ridgel et al[23] found a 35% significant decrease (improvement), while Qutubuddin et al[39] found no significant change from pre to post. Quality of life was measured in 2 OITM studies[18,39], showing improvement[18] or no effect[39]. The study by Combs et al[18] also found a significant improvement in quality of life in the control group, who did related training.

In summary, OITM may improve UPDRS-III and quality of life, but findings are inconsistent.

4. Discussion

This is – to our knowledge - the first review to categorize the effects of intensive exercise therapy from 3 strictly defined training modalities. Our novel findings suggest that intensive exercise therapy (RT, ET and OITM) is feasible, safe and beneficial in PD, representing an important intervention in PD rehabilitation. There is strong evidence that RT can improve muscle strength in PD, which is underlined by findings from the meta-analysis (g'=0.54 [95%CI 0.22;0.86]). There is moderate evidence that ET can improve cardio-respiratory fitness in PD. RT, ET and OITM may have beneficial effects on balance, walking performance, UPDRS-III score and quality of life in PD, but findings are generally few, based on secondary outcomes and inconsistent. Importantly, no studies find serious adverse events or deterioration in any of the applied outcomes.

4.1. Muscle strength

This review identified strong evidence supporting that intensive exercise therapy in the form of RT can improve muscle strength in PD. Moreover, RT is an important rehabilitation strategy to improve strength or prevent strength deterioration, as the disease progresses[5,7,19], which is in line with

previous research[33,34]. Clinically this is important, since lower extremity strength is correlated to walking performance[5,33,53] and to the ability to perform activities of daily living[54,55]. The correlation seems to be non-linear, and when the muscle strength is below a certain threshold, walking performance is substantially decreased[53]. Therefore, RT may potentially benefit patients in the more advanced stages of the disease relatively more, although it could be argued that increasing the safety factor through RT at an early stage of the disease might postpone the timepoint when the threshold is reached. The patients included in this review had a mean Hoehn and Yahr score of 2,1±0,22, with no identified studies evaluating solely patients with a higher Hoehn and Yahr score or comparing effects across disability levels, calling for future studies on this aspect.

The existing studies further underline, that long term RT can improve or maintain muscle strength, while the control group experienced a decrease in muscle strength during the course of the study[19]. Also, combined RT and ET training improved muscle strength, suggesting that concurrent exercise interventions do not eliminate strength improvements[20]. This is important given the multimodal character of optimal rehabilitation[13]. The mechanisms underlying the improvements seen in strength still remains to be elucidated in PD, but would be expected to be of both neural and morphological origin[56].

4.2. Cardio-respiratory fitness

This review presents moderate evidence that intensive exercise therapy with incorporated ET can improve cardio-respiratory fitness. Two studies[17,23] measured cardio-respiratory fitness indirectly and should be interpreted with caution. The remaining two studies[10,25] used direct methods, constituting the gold standard measurements[57,58]. All 4 studies found increases in cardio-respiratory fitness, which indicates that ET effectively can improve (or prevent deterioration of) cardio-respiratory fitness, which is in line with previous research[37,59,60]. Clinically, this is important, since cardio-respiratory fitness is correlated to cardiovascular disease and all-cause mortality[61,62]. The correlation seems to be non-linear, and when below a certain threshold of cardio-respiratory fitness, the risk of cardiovascular disease and all-cause mortality is substantially increased[61]. ET targeting cardio-respiratory fitness may, therefore, be of particular importance in the later stages of the disease, though expanding the safety factor to the threshold at an early stage would seem important as well. However the patients of this review had a mean Hoehn and Yahr score of 2,1±0,22 and were generally without comorbidities, suggesting that future studies should include PD patients at more advanced stages of the disease and/or with certain co-morbidities. Also, combined RT and ET training decreased VO_2sub at a given workload, suggesting that concurrent exercise interventions do not eliminate cardio-respiratory fitness improvements[20].

4.3. Walking performance

All 3 exercise modalities (RT, ET and OITM) may increase walking performance, but findings are inconsistent. However, the increases in strength and cardio-respiratory fitness, did not consistently translate into walking performance improvements in all studies, wherefore other factors may also explain the improvements. A clinically important difference in gait speed in persons with PD on medication, has recently been suggested[63] (small: 0,06 m/s, moderate: 0,14 m/s and large 0,22 m/s) The included studies of this review showed small to moderate improvements in walking performance (0.13m/s[10], 0,09m/s[10] and 0,14m/s[18]), suggesting a possible clinical relevance. However many studies only found improvements in part of the walking performance outcomes, complicating the interpretation.

4.4. UPDRS-III

The few existing exercise studies evaluating the effects on UPDRS-III indicate that RT and a certain type of OITM (forced exercise) may improve UPDRS-III, whereas ET does not, but findings are inconsistent. The relatively larger muscle forces applied during RT and forced exercise compared to ET, may explain the discrepancy. It is not clear why RT (and forced exercise), but not ET, positively affects UPDRS-III, but this may be of potential interest given the fundamental importance of this patient reported outcome. On the other hand some caution also needs to be taken since most studies in the present review only evaluated the effects on UPDRS as a secondary outcome, and therefore may be underpowered to detect changes in this outcome. Future studies needs to address this further. None of the included studies found deterioration in the UPDRS-III score. This is of importance, given the observed natural deterioration, due to the disease[3].

While the findings of this review suggest that ET does not influence UPDRS-III and quality of life, a study by Uc et al[43] - which was excluded because of lack of proper randomization - found improvements in UPDRS-III and quality of life after 6 months of ET. The discrepancy may be explained by differences in design, intensity, frequency and duration.

The mechanisms underlying the effects of exercise on UPDRS-III remains to be elucidated, but animal studies have suggested one candidate, since large forces during exercise increase neuronal activation and dopamine sparring in the basal ganglia[19,23,28-30,64,65]. To our knowledge only one human study[41] has included a direct measure on this, and found an increase in brain-derived neurotrophic factor after high-volume physiotherapy.

Only 1 study[19] reported on the patients levodopa use as an outcome measure. Anti-parkisonian drugs deserve greater attention in future studies, since the dose reduction (or the maintenance of the

same dosage) of the anti-parkinsonian drugs is a relevant and valid outcome measure. Moreover, patients who are medically undertreated may experience difficulty engaging in intensive exercise therapy. Ideally, RCT´s should include only patients that are "optimally medically-treated", which is probably not the case for most of the trials included in of this review, based on the sparse reports on medications and doses.

4.5. Meta-Analysis

The meta-analysis is limited by relatively few studies and differences in intensity and duration across the intervention and control groups. One study used a combined (resistance and endurance) training intervention group[20], while three studies[20,26,51] used a non-exercising control group, and the last 3 studies[10,19,22] included a sham/low intensity exercise control group. However it was decided to include the studies, since the exercise interventions of the combined training and the active control groups, was expected to have no/insignificant effect on muscle strength. The studies of the meta-analysis – being RCTs and all evaluating RT – are more homogeneous than those reported in previous meta-analyses[32,33].

4.6. Excluded trials

The aim of this review was to cover all forms of intensive exercise therapy modalities. Therefore we also included the OITM category. We acknowledge that this category may seem heterogeneous compared to the RT and ET category, but all included interventions are in fact defined as non-isolated ET or RT, and having a proper description of intensity, frequency, duration and progression, making these studies interpretable and possible to relate to RT and/or ET. Especially in the OITM category a lot of trials were considered carefully, but finally not included [77-79,81-92]. In this category intensity, frequency, duration and progression of training was poorly described, and many studies were excluded due to this. Strict inclusion criteria were applied, which meant that a lot of otherwise very informative and relevant trials were excluded in the other categories as well[66-80]. It was not the intention of the present review to cover all forms of physiotherapy, since this has been done recently[13]. Also, this could potentially shade the purpose of the review, because it is unsuitable to determine cause and effect from studies that poorly describe intensity, frequency, duration and progression of training. Future studies in the field of physiotherapy are recommended, if possible, to describe these parameters comprehensively.

4.7. Clinical implications

PD is a complex disease making optimal rehabilitation complicated and multidimensional. Theoretically, optimal rehabilitation often covers numerous disciplines of which intensive exercise therapy is only one, that, depending on the exercise modality, will target specific impairments. In the included study by Sage et al[24] the control group - performing sensory attention-focused exercise – showed superior improvements compared to the ET intervention. A finding later confirmed in a larger study[73] by the same group, which was excluded from this review because of lack of proper randomization. This supports the notion, that isolated intensive exercise therapy, including only RT, ET or OITM, may not be optimal. However, before prescribing a combination of exercise modalities we need to understand the independent effects of the basic exercise modalities. The existing studies of this review suggest, that an exercise program should optimally contain elements of all the three evaluated exercise modalities. However, exercise therapy always need to be individually prescribed and designed to target specific impairments, which obviously will influence the relative contend of each exercise modality.

4.8. Limitations and future perspectives

The major limitations of the existing studies include:

1. Small sample sizes
2. Short term interventions (≤12 weeks)
3. Lack of blinding of subjects and therapists (difficult in exercise interventions)
4. No application of intention-to-treat analysis
5. Not all patients may show impairments in the evaluated symptoms at baseline which may dilute actual positive effects
6. Limited generalizability due to exclusion of patients having co-morbidities and inclusion of predominantly patients at a mild to moderate disease stage.
7. Limited understanding of underlying mechanisms explaining potential exercise gains.

5. Conclusion

RT, ET and OITM all represent feasible, safe and beneficial adjunct rehabilitation therapies in PD. There is strong evidence that RT can improve muscle strength in PD, which is underlined by meta-analytical findings. There is moderate evidence that ET can improve cardio-respiratory fitness in PD. RT, ET and OITM may have beneficial effects on balance, walking performance, UPDRS-III score and quality of life in PD, but findings are inconsistent. No studies report deterioration in any outcomes.

References

1. Parkinson's disease foundation. statistics on parkinson's. http://www.pdf.org/en/parkinson_statistics. Accessed June/19, 2014.

2. Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with parkinson disease in the most populous nations, 2005 through 2030. *Neurology*. 2007;68(5):384-386.

3. de Lau LM, Breteler MM. Epidemiology of parkinson's disease. *Lancet Neurol*. 2006;5(6):525-535.

4. Speelman AD, Van De Warrenburg BP, Van Nimwegen M, Petzinger GM, Munneke M, Bloem BR. How might physical activity benefit patients with parkinson disease? *Nat Rev Neurol*. 2011;7(9):528-534.

5. Schilling BK, Karlage RE, LeDoux MS, Pfeiffer RF, Weiss LW, Falvo MJ. Impaired leg extensor strength in individuals with parkinson disease and relatedness to functional mobility. *Parkinsonism Relat Disord*. 2009;15(10):776-780.

6. Muller B, Assmus J, Herlofson K, Larsen JP, Tysnes OB. Importance of motor vs. non-motor symptoms for health-related quality of life in early parkinson's disease. *Parkinsonism Relat Disord*. 2013;19(11):1027-1032.

7. Kakinuma S, Nogaki H, Pramanik B, Morimatsu M. Muscle weakness in parkinson's disease: Isokinetic study of the lower limbs. *Eur Neurol*. 1998;39(4):218-222.

8. Speelman AD, Groothuis JT, Van Nimwegen ML, Hopman MTE, Bloem BR, Munneke M. Physical fitness in patients with parkinson's disease. *Mov Disord*. 2010;25:S677.

9. van Nimwegen M, Speelman AD, Hofman-van Rossum EJ, et al. Physical inactivity in parkinson's disease. *J Neurol*. 2011;258(12):2214-2221.

10. Shulman LM, Katzel LI, Ivey FM, et al. Randomized clinical trial of 3 types of physical exercise for patients with parkinson disease. *JAMA Neurol*. 2013;70(2):183-190.

11. Nijkrake MJ, Keus SHJ, Kalf JG, et al. Allied health care interventions and complementary therapies in parkinson's disease. *Parkinsonism Relat Disord*. 2007;13(SUPPL. 3):S488; S494.

12. Worth PF. How to treat parkinson's disease in 2013. *Clin Med*. 2013;13(1):93-96.

13. Tomlinson CL, Patel S, Meek C, et al. Physiotherapy intervention in parkinson's disease: Systematic review and meta-analysis. *BMJ (Online)*. 2012;345(7872).

14. Momsen AM, Rasmussen JO, Nielsen CV, Iversen MD, Lund H. Multidisciplinary team care in rehabilitation: An overview of reviews. *J Rehabil Med*. 2012;44(11):901-912.

15. Post B, van der Eijk M, Munneke M, Bloem BR. Multidisciplinary care for parkinson's disease: Not if, but how! *Postgrad Med J*. 2011;87(1031):575-578.

16. Brigham and women's hospital. http://www.brighamandwomens.org. Accessed Sep/07, 2014.

17. Bridgewater KJ, Sharpe MH. Aerobic exercise and early parkinson's disease. *Neurorehabil Neural Repair*. 1996;10(4):233-241.

18. Combs S, A., Diehl M, D., Chrzastowski C, et al. Community-based group exercise for persons with parkinson disease: A randomized controlled trial. *NEUROREHABILITATION*. 2013;32(1):117-124.

19. Corcos DM, Robichaud JA, David FJ, et al. A two-year randomized controlled trial of progressive resistance exercise for parkinson's disease. *Mov Disord*. 2013;28(9):1230-1240.

20. DiFrancisco-Donoghue J, Lamberg EM, Rabin E, Elokda A, Fazzini E, Werner WG. Effects of exercise and B vitamins on homocysteine and glutathione in parkinson's disease: A randomized trial. *Neurodegenerative Dis*. 2012;10(1-4):127-134.

21. Hass CJ, Buckley TA, Pitsikoulis C, Barthelemy EJ. Progressive resistance training improves gait initiation in individuals with parkinson's disease. *Gait Posture*. 2012;35(4):669-673.

22. Paul SS, Canning CG, Song J, Fung VS, Sherrington C. Leg muscle power is enhanced by training in people with parkinson's disease: A randomized controlled trial. *Clin Rehabil*. 2014;28(3):275-288.

23. Ridgel AL, Vitek JL, Alberts JL. Forced, not voluntary, exercise improves motor function in parkinson's disease patients. *Neurorehabil Neural Repair*. 2009;23(6):600-608.

24. Sage MD, Almeida QJ. Symptom and gait changes after sensory attention focused exercise vs aerobic training in parkinson's disease. *Mov Disord*. 2009;24(8):1132-1138.

25. Schenkman M, Hall DA, Barón AE, Schwartz RS, Mettler P, Kohrt WM. Exercise for people in early- or mid-stage parkinson disease: A 16-month randomized controlled trial. *Phys Ther*. 2012;92(11):1395-1410.

26. Schilling BK, Pfeiffer RF, Ledoux MS, Karlage RE, Bloomer RJ, Falvo MJ. Effects of moderate-volume, high-load lower-body resistance training on strength and function in persons with parkinson's disease: A pilot study. *Parkinson's Dis*. 2010.

27. Shen X, Mak MK. Repetitive step training with preparatory signals improves stability limits in patients with parkinson's disease. *J Rehabil Med*. 2012;44(11):944-949.

28. Lau YS, Patki G, Das-Panja K, Le WD, Ahmad SO. Neuroprotective effects and mechanisms of exercise in a chronic mouse model of parkinson's disease with moderate neurodegeneration. *Eur J Neurosci*. 2011;33(7):1264-1274.

29. Lau Y-, Das-Panja K, Patki G, Ahmad SO. Protection against chronic parkinson's neurodegeneration and mitochondrial dysfunction by endurance exercise. *Parkinsonism Relat Disord*. 2010;16:S60.

30. Ahlskog JE. Does vigorous exercise have a neuroprotective effect in parkinson disease? *Neurology*. 2011;77(3):288-294.

31. Deane KH, Jones D, Ellis-Hill C, Clarke CE, Playford ED, Ben-Shlomo Y. A comparison of physiotherapy techniques for patients with parkinson's disease. *Cochrane Database Syst Rev*. 2001;(1)(1):CD002815.

32. Goodwin VA, Richards SH, Taylor RS, Taylor AH, Campbell JL. The effectiveness of exercise interventions for people with parkinson's disease: A systematic review and meta-analysis. *Mov Disord*. 2008;23(5):631-640.

33. Lima LO, Scianni A, Rodrigues-de-Paula F. Progressive resistance exercise improves strength and physical performance in people with mild to moderate parkinson's disease: A systematic review (provisional abstract). . 2013(4):7-13.

34. Brienesse LA, Emerson MN. Effects of resistance training for people with parkinson's disease: A systematic review (provisional abstract). . 2013(4):236-241.

35. Falvo MJ, Schilling BK, Earhart GM. Parkinson's disease and resistive exercise: Rationale, review, and recommendations. *Mov Disord*. 2008;23(1):1-11.

36. Keus SHJ, Munneke M, Nijkrake MJ, Kwakkel G, Bloem BR. Physical therapy in parkinson's disease: Evolution and future challenges. *Mov Disord*. 2009;24(1):1-14.

37. Mehrholz J, Friis R, Kugler J, Twork S, Storch A, Pohl M. Treadmill training for patients with parkinson's disease (cochrane review) [with consumer summary]. *Cochrane Database of Systematic Reviews*. 2010(1).

38. McGinley JL, Martin C, Huxham FE, et al. Feasibility, safety, and compliance in a randomized controlled trial of physical therapy for parkinson's disease. *Parkinson's Dis*. 2012.

39. Qutubuddin A, Reis T, Alramadhani R, Cifu DX, Towne A, Carne W. Parkinson's disease and forced exercise: A preliminary study. *Rehabit Res Pract*. 2013;2013.

40. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Int J Surg*. 2010;8(5):336-341.

41. Frazzitta G, Maestri R, Ghilardi MF, et al. Intensive rehabilitation increases BDNF serum levels in parkinsonian patients: A randomized study. *Neurorehabil Neural Repair*. 2014;28(2):163-168.

42. Kelly NA, Ford MP, Standaert DG, et al. Novel, high-intensity exercise prescription improves muscle mass, mitochondrial function, and physical capacity in individuals with parkinson's disease. *J Appl Physiol*. 2014;116(3):582-592.

43. Uc EY, Doerschug KC, Magnotta V, et al. Phase I/II randomized trial of aerobic exercise in parkinson disease in a community setting. *Neurology*. 2014;83(5):413-425.

44. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic parkinson's disease: A clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry*. 1992;55(3):181-184.

45. Calne DB, Snow BJ, Lee C. Criteria for diagnosing parkinson's disease. *Ann Neurol*. 1992;32 Suppl:S125-7.

46. American College of Sports Medicine. American college of sports medicine position stand. progression models in resistance training for healthy adults. *Med Sci Sports Exerc*. 2009;41(3):687-708.

47. KARVONEN MJ, KENTALA E, MUSTALA O. The effects of training on heart rate; a longitudinal study. *Ann Med Exp Biol Fenn*. 1957;35(3):307-315.

48. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther*. 2003;83(8):713-721.

49. de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: A demographic study. *Aust J Physiother*. 2009;55(2):129-133.

50. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-2012.

51. Bloomer RJ, Schilling BK, Karlage RE, Ledoux MS, Pfeiffer RF, Callegari J. Effect of resistance training on blood oxidative stress in parkinson disease. *Medicine & Science in Sports & Exercise*. 2008;40(8):1385-1389.

52. Larry V. Hegdes, Ingram Olkin. *Statistical methods for meta-analysis.* Orlando: Academic Press; 1985.

53. Buchner DM, Larson EB, Wagner EH, Koepsell TD, de Lateur BJ. Evidence for a non-linear relationship between leg strength and gait speed. *Age Ageing*. 1996;25(5):386-391.

54. Hasegawa R, Islam MM, Lee SC, Koizumi D, Rogers ME, Takeshima N. Threshold of lower body muscular strength necessary to perform ADL independently in community-dwelling older adults. *Clin Rehabil*. 2008;22(10-11):902-910.

55. Kojima N, Kim H, Saito K, et al. Association of knee-extension strength with instrumental activities of daily living in community-dwelling older adults. *Geriatr Gerontol Int*. 2013.

56. Folland JP, Williams AG. The adaptations to strength training : Morphological and neurological contributions to increased strength. *Sports Med*. 2007;37(2):145-168.

57. Katzel LI, Sorkin JD, Macko RF, Smith B, Ivey FM, Shulman LM. Repeatability of aerobic capacity measurements in parkinson disease. *Med Sci Sports Exerc*. 2011;43(12):2381-2387.

58. Stickland MK, Butcher SJ, Marciniuk DD, Bhutani M. Assessing exercise limitation using cardiopulmonary exercise testing. *Pulm Med*. 2012;2012:824091.

59. Herman T, Giladi N, Gruendlinger L, Hausdorff JM. Six weeks of intensive treadmill training improves gait and quality of life in patients with parkinson's disease: A pilot study. *Arch Phys Med Rehabil*. 2007;88(9):1154-1158.

60. Herman T, Giladi N, Hausdorff JM. Treadmill training for the treatment of gait disturbances in people with parkinson's disease: A mini-review. *J Neural Transm*. 2009;116(3):307-318.

61. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: A meta-analysis. *JAMA*. 2009;301(19):2024-2035.

62. Wermuth L, Stenager EN, Stenager E, Boldsen J. Mortality in patients with parkinson's disease. *Acta Neurol Scand*. 1995;92(1):55-58.

63. Hass CJ, Bishop M, Moscovich M, et al. Defining the clinically meaningful difference in gait speed in persons with parkinson disease. *J Neurol Phys Ther*. 2014;38(4):233-238.

64. Tillerson JL, Caudle WM, Reveron ME, Miller GW. Exercise induces behavioral recovery and attenuates neurochemical deficits in rodent models of parkinson's disease. *Neuroscience*. 2003;119(3):899-911.

65. Spraker MB, Yu H, Corcos DM, Vaillancourt DE. Role of individual basal ganglia nuclei in force amplitude generation. *J Neurophysiol*. 2007;98(2):821-834.

66. Bergen JL, Toole T, Elliott RG, Wallace B, Robinson K, Maitland CG. Aerobic exercise intervention improves aerobic capacity and movement initiation in parkinson's disease patients. *Neurorehabilitation*. 2002;17(2):161-168.

67. Cruise KE, Bucks RS, Loftus AM, Newton RU, Pegoraro R, Thomas MG. Exercise and parkinson's: Benefits for cognition and quality of life. *Acta Neurol Scand*. 2011;123(1):13-19.

68. Dibble LE, Hale TF, Marcus RL, Droge J, Gerber JP, LaStayo PC. High-intensity resistance training amplifies muscle hypertrophy and functional gains in persons with parkinson's disease. *Mov Disord*. 2006;21(9):1444-1452.

69. Dibble LE, Hale TF, Marcus RL, Gerber JP, LaStayo PC. High intensity eccentric resistance training decreases bradykinesia and improves quality of life in persons with parkinson's disease: A preliminary study. *Parkinsonism Relat Disord*. 2009;15(10):752-757.

70. Hirsch MA, Toole T, Maitland CG, Rider RA. The effects of balance training and high-intensity resistance training on persons with idiopathic parkinson's disease. *Arch Phys Med Rehabil*. 2003;84(8):1109-1117.

71. Lauhoff P, Murphy N, Doherty C, Horgan NF. A controlled clinical trial investigating the effects of cycle ergometry training on exercise tolerance, balance and quality of life in patients with parkinson's disease. *Disabil Rehabil*. 2013;35(5):382-387.

72. Park A, Zid D, Russell J, et al. Effects of a formal exercise program on parkinson's disease: A pilot study using a delayed start design. *Parkinsonism Relat Disord*. 2014;20(1):106-111.

73. Sage MD, Johnston RE, Almeida QJ. Comparison of exercise strategies for motor symptom improvement in parkinsons disease. *Neurodegenerative Dis Manage*. 2011;1(5):387-395.

74. Tanaka K, Quadros A, J., Santos RF, Stella F, Gobbi LT, Gobbi S. Benefits of physical exercise on executive functions in older people with parkinson's disease. *BRAIN COGNIT*. 2009;69(2):435-441.

75. Allen NE, Canning CG, Sherrington C, et al. The effects of an exercise program on fall risk factors in people with parkinson's disease: A randomized controlled trial. *Mov Disord*. 2010;25(9):1217-1225.

76. Hass CJ, Collins MA, Juncos JL. Resistance training with creatine monohydrate improves upper-body strength in patients with parkinson disease: A randomized trial. *Neurorehabil Neural Repair*. 2007;21(2):107-115.

77. Volpe D, Signorini M, Marchetto A, Lynch T, Morris ME. A comparison of irish set dancing and exercises for people with parkinson's disease: A phase II feasibility study. *BMC Geriatrics*. 2013;13(54):Epub.

78. Laupheimer M, Hartel S, Schmidt S, Bos K. Exercise training - effects of MOTOmed(registered trademark) exercise on typical motor dysfunction in parkinson s disease. *Neurol Rehabil*. 2011;17(5-6):239-246.

79. Pohl M, Rockstroh G, Ruckriem S, Mrass G, Mehrholz J. Immediate effects of speed-dependent treadmill training on gait parameters in early parkinson's disease. *Arch Phys Med Rehabil*. 2003;84(12):1760-1766.

80. Fisher BE, Li Q, Nacca A, et al. Treadmill exercise elevates striatal dopamine D2 receptor binding potential in patients with early parkinson's disease. *Neuroreport*. 2013;24(10):509-514.

81. Schmitz-Hubsch T, Pyfer D, Kielwein K, Fimmers R, Klockgether T, Wullner U. Qigong exercise for the symptoms of parkinson's disease: A randomized, controlled pilot study. *Mov Disord*. 2006;21(4):543-548.

82. Duncan RP, Earhart GM. Randomized controlled trial of community-based dancing to modify disease progression in parkinson disease. *Neurorehabil Neural Repair*. 2012;26(2):132-143.

83. Hackney ME, Earhart GM. Health-related quality of life and alternative forms of exercise in parkinson disease. *Parkinsonism Relat Disord*. 2009;15(9):644-648.

84. Foster E, R., Golden L, Duncan R, P., Earhart G, M. Community-based argentine tango dance program is associated with increased activity participation among individuals with parkinson's disease. *Arch Phys Med Rehabil*. 2013;94(2):240-249.

85. Amano S, Nocera JR, Vallabhajosula S, et al. The effect of tai chi exercise on gait initiation and gait performance in persons with parkinson's disease. *Parkinsonism Relat Disord*. 2013.

86. Abbott R, Lavretsky H. Tai chi and qigong for the treatment and prevention of mental disorders. *Psychiatr Clin North Am*. 2013;36(1):109-119.

87. Aggarwal A. Stay healthy through game-care therapeutics: It's time to play the game! *Value Health*. 2011;14(7):A298.

88. Mhatre PV, Vilares I, Stibb SM, et al. Wii fit balance board playing improves balance and gait in parkinson disease. *PM R*. 2013.

89. Pompeu JE, Mendes FAS, Silva KG, et al. Effect of nintendo wii-based motor and cognitive training on activities of daily living in patients with parkinson's disease: A randomised clinical trial. *Physiotherapy*. 2012;98(3):196-204.

90. Colgrove YS, Sharma N, Kluding P, et al. Effect of yoga on motor function in people with parkinson's disease: A randomized, controlled pilot study. .

91. Ebersbach G, Ebersbach A, Edler D, et al. Comparing exercise in parkinson's disease--the berlin LSVT®BIG study. *Movement disorders : official journal of the Movement Disorder Society*. 2010;25(12):1902-1908.

92. Miyai I, Fujimoto Y, Yamamoto H, et al. Long-term effect of body weight-supported treadmill training in parkinson's disease: A randomized controlled trial. *Arch Phys Med Rehabil*. 2002;83(10):1370-1373.

Table 1. Retrieved articles and search terms.

Database	Retrieved articles	Search Terms (MeSH etc.)
Embase	812	"parkinson disease" AND ("exercise" OR "kinesiotherapy") AND ("[danish]/lim" OR"[english]/lim" OR "[german]/lim") AND "[humans]/lim" AND "[embase]/lim"
PubMed	761	"Parkinson Disease" AND ("Exercise" OR "Exercise Therapy" OR "aerobic training" OR "endurance training" OR "endurance exercise" OR "cardiovascular exercise" OR "cardiovascular training" OR "aerobic exercise")
Cinahl	82	"Parkinson Disease" AND "Exercise"
SPORTDiscus	77	"PARKINSON'S disease" AND "EXERCISE"
Cochrane	63	"Parkinson Disease" AND "Exercise"
PEDro	54	Abstract & Title: "Parkinson". Therapy: "Fitness Training"

Table 2. Pedro score.

Study	Total score (0-10)	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11
Paul et al 2014	8	x	x	x			x	x	x	x	x
Corcos et al 2013	7	x	x	x			x	x		x	x
Shulman et al 2013	4	x		x			x				x
Combs et al 2013	7	x	x	x			x		x	x	x
Qutubuddin et al 2013	5	x		x			x			x	x
Hass et al 2012	6	x		x				x	x	x	x
Shen et al 2012	7	x	x	x			x	x		x	x
McGinley et al 2012	5	x					x	x		x	x
Schenkman et al 2012	8	x	x	x			x	x	x	x	x
DiFrancisco et al 2012	5	x		x				x		x	x
Schilling et al 2010	4	x		x						x	x
Ridgel et al 2009	6	x		x			x	x		x	x
Sage et al 2009	7	x		x			x	x	x	x	x
Bloomer et al 2008	4	x		x						x	x
Bridgewater et al 1996	4	x		x			x			x	
Total (0-15)	mean: 5,8	15	5	14	0	0	11	9	5	14	14

Criteria specification (for further specification, see Maher et al[93]):
Criteria #2: Randomized allocation
Criteria #3: Concealed allocation
Criteria #4: Similarity between groups at baseline
Criteria #5: Blinding of subjects
Criteria #6: Blinding of therapists
Criteria #7: Blinding of assessors
Criteria #8: Outcome measures obtained from at least 85% of initially allocated subjects
Criteria #9: All received treatment or key outcome was analyzed by "intention-to-treat"
Criteria #10: Between-group statistical comparisons
Criteria #11: Both point and variability measures provided

Table 3. Study characteristics.

Mode	Study	Pedro score (0-10)	Sample size total/IG (n)	Dropouts IG/CG (%)	Hoehn and Yahr (stage)[b]	Age (yrs)	PD duration (yrs)	Gender (m:f)	Adverse events (n)	'ON'/'OFF' medicine	Training duration (wks)	Frequency (sessions/wk)	Training adherence (%)	Supervised
RT	**Paul et al 2014**	8	40/20	10%/10%	2±0,8	66	7,8	1,7:1	None#	'ON'	12	2	84%	yes
	Corcos et al 2013	7	48/24	17%/25%	2,3±0,5	59	6,5	1,4:1	None#	'ON'+'OFF'	104	2	100%	yes
	Shulman et al 2013 RT	4	80/28	39%/27%	2,2 (2-3)	66	6,2	3:1	None	'ON'	12	3	NR	yes
	Hass et al 2012	6	18/9	0%/0%	2,3 (1-3)	66	8,8	3,5:1	None	'ON'	10	2	NR	yes
	Shen et al 2012	7	29/14	0%/7%	2,3±0,5	65	6,5	1,2:1	None	'ON'	4	3	97%	NR
	McGinley et al 2012	5	141/70	1%/17%	2,5[m] (2-3)	68	6,7	2:1	None#	NR	8	1	83%	yes
	Schilling et al 2010	4	18/9	11%/22%	2 (1,5-2,5)	59	NR	1,6:1	NR	'ON'	8	2	NR	yes
	Bloomer et al 2008	4	16/8	25%/13%	NR (1-2)	59	NR	1:1	None	'ON'	8	2	NR	yes
Group mean[a]		5,6	49/23	13%/15%	2,2±0,18	64	7,1	1,9:1	-	-	9[m]	2,1	91%	-
ET	**Shulman et al 2013 ET-86%**	4	80/26	23%/35%	2,2 (2-3)	66	6,2	3:1	None	'ON'	12	3	NR	yes
	Shulman et al 2013 ET-70%	4	80/26	31%/31%	2,2 (2-3)	66	6,2	3:1	None	'ON'	12	3	NR	yes
	Schenkman et al 2012	8	82/41	24%/22%	2,3 (1-3)	65	4,2	1,7:1	None#	'ON'	68	0,23-3	NR	yes
	Ridgel et al 2009 ET	6	10/5	0%/0%	1,7 (1-3)	61	6,2	4:1	NR	'OFF'	8	3	100%	yes
	Sage et al 2009	7	32/17	24%/0%	NR	67	2,9	0,7:1	NR	'ON'	12	3	87%	NR
	Bridgewater et al 1996	4	26/13	0%/0%	2,1 (1-3)	67	4	1,6:1	None	NR	12	2	95%	yes
Group mean[a]		5,8	46/20	15%/11%	2,1±0,23	65	4,1	1,8:1	-	-	12[m]	2,8	94%	-
OITM	**Combs et al 2013**	7	31/17	35%/21%	2[m] (1-4)	67[m]	3,9[m]	2,1:1	NR	NR	12	2-3	NR	yes
	Qutubuddin et al 2013	5	33/NR	NR/NR	NR	68	7,2	NR	NR	'ON'	8	2	NR	yes
	DiFrancisco et al 2012	5	19/10	10%/0%	2 (2)	68	8,5	1,7:1	NR	NR	6	2	NR	NR
	Ridgel et al 2009 OITM	6	10/5	0%/0%	1,7 (1-3)	61	6,2	4,0:1	NR	'OFF'	8	3	100%	yes
Group mean[a]		5,8	23/11	15%/7%	1,9±0,17	66	6,5	2,2:1	-	-	8[m]	2,4	-	-
Overall mean total[a]		5,8	42/19	13%/ 12%	2,1±0,22	65	6,1	1,9:1	-	-	10[m]	2,3	92%	-

Shulman et al had 3 relevant interventions, Ridgel et al had 2 relevant interventions.
RT = Resistance Training, ET = Endurance Training, OITM = Other Intensive Training Modalities, IG = intervention group, CG = control group, PD = Parkinson's disease, HIT = high intensity training, LIT = low intensity training, NR = not reported, m = median, # = some non-serious adverse events reported, a = studies only accounted for once, b = mean ± standard deviation / range, m:f = male:female, wks = weeks, yrs = years

Table 4. Resistance Training.

Study	Training regime (TR) Intensity (IN) Control group (CG)	Outcomes
Paul et al 2014	TR: 4 leg exercises IN: 3 sets x 8 reps at 40-60 % 1RM with emphasis on speed CG: Sham training	**Strength ↑:** HipF 40%#, HipAbd 34%#, ChestP 7%# **Balance ↑:** Visual analogue scale ↑ 1,5 out of 5# **Walking performance ↑:** Visual analogue scale ↑ 2,1 out of 5# Peak power ↑: LP 17%#, KF 21%#, HipF 46%#, HipAbd 43%# Speed at peak power ↑: KF 5%# **Strength →:** LP (p =0,07), KF (p = 0,06) **Balance →:** Choice stepping reaction, Maximal balance range, Single leg stance time **Walking performance →:** TUG, Fast walking speed
Corcos et al 2013	TR: 11 exercises, whole-body program INT: Strength: 1-3 sets x 8 reps at 30-60% 1RM. Rep: 6-9 seconds. Speed: 2 sets x 12 reps at 70-80% 1RM. Rep: As fast as possible. Alternating between Strength for 8 wks and Strength + Speed for 8 wks CG: Low intensity ex	**Strength ↑** (off): ElbowF: 16%$, 15%#, 13%#, 18%# (6 mo, 12 mo, 18 mo, 24 mo) **Strength ↑** (on): ElbowF: 12%$, 11%#, 19%#, -1%# (6 mo, 12 mo, 18 mo, 24 mo) **UPDRS-III ↓** (off): 19%$, 18%#, 17%#, 25%# (6 mo, 12 mo, 18 mo, 24 mo) **QOL ↑** (on): PDQ-39 ↓ 22%# (6 mo) ElbowF maximal movement speed ↑ (off): 19%$, 34%# (6 mo, 24 mo) Physical performance test ↑ (off) 11%$, 18%$ (6 mo, 24 mo) **UPDRS-III →** (on): (6 mo, 12 mo, 18 mo, 24 mo) **QOL →** (on): PDQ-39: (12 mo, 18 mo, 24 mo)
Shulman et al 2013 RT	TR: 3 leg exercises + stretching IN: 2 sets x 10 reps CG: Low intensity ET and high intensity ET	**Strength ↑*:** LP 16%*, KE 13%* **Walking performance ↑:** 6MWT 8%* **UPDRS-III ↓**: 10%* **Cardio-respiratory fitness →:** VO_2 peak/kg **Walking performance →:** TUG, 10 m fast pace time, 15 m fast pace time **QOL →:** PDQ-39
Hass et al 2012	TR: 6 exercises (4 leg) + multidirectional ankle theraband exercises IN: 2 sets x 12-20 reps at ≈ 70% 1RM CG: No ex. Continue usual activities	**Strength ↑:** KE 77%*, KF 57%* **Walking performance ↑:** Stride velocity 11%#, Gait initiation: Anticipatory phase posterior ↑ 29%# **Walking performance →:** Stride length (p = 0,05), Gait initiation: Anticipatory phase lateral, Transitional phase posterior, Transitional phase lateral, Locomotor phase anterior, Locomotor phase lateral (p = 0,06)
Shen et al 2012	TR: Leg exercises + functional movements (rowing, stepping) IN: 2 sets x 15 reps at 60% 1RM CG: Step training with cues	**Walking performance ↑:** Gait velocity 6%$, Gait cadence 4%# **Walking performance →:** Stride length **UPDRS-III (postural and gait) →** (p = 0,085)
McGinley et al 2012[b]	TR: 7 exercises (5 leg) IN: 1-3 sets x 8-15 reps at >5 modifiedRPE. CG: No ex. "Life skill" sessions	Safety: 1) New soreness for >48h: n = 25 CG: n = 0 2) Number of fallers: n = 10 CG: n = 24, 3) Falls during training (no sequale): n = 1 CON: n = 0 Retention: 99%, 96%, 93% CG: 83%, 76%, 79% (EOT+1 wk, EOT+3 mo, EOT+12 mo) Training adherence: 83% CG: 81%

Schilling et al 2010	TR: 3 leg exercises IN: 3 sets x 5-8 reps CG: No ex. Continue usual activities	**Strength ↑:** LP 24%#, LP/kg 29%# **Walking performance →:** 6MWT, TUG **Balance →:** Activities-specific balance confidence scale
Bloomer et al 2008	TR: 3 leg exercises IN: 3 sets x 5-8 reps CG: No ex. Continue usual activities	**Strength ↑:** LP 18%¢ H2O2 ↓ 16%£

↑ = significantly increased, → = no change, ↓ = significantly decreased (improved), level of significance ($p<0.05$)
* = significant within-group change from pre to post in intervention group, # = change in intervention group significantly larger than change in control group, $ = significant within-group change from pre to post in both intervention and control group, b = a feasibility study, none of the outcomes are statistically significant, ¢ = p value not reported, £ = only significant post vs post difference, TR = training regime, IN = intensity, CG = control group, reps = repetitions, 1RM = one repetition maximum, ex = exercise, RPE = rating of perceived exertion, LP = leg press, KE = knee extension, KF = knee flexion, HipF = hip flexion, HipAbd = hip abduction, ChestP = chest press, ElbowF = elbow flexion, TUG = timed up-and-go, UPDRS-III = Unified Parkinson's Disease Rating Scale, off = off medication, on = on medication, QOL = quality of life, PDQ-39 = parkinson's disease questionnaire-39 items, VO2 peak = peak oxygen uptake, mo = months, 6MWT = 6 minute walk test, H2O2 = hydrogen peroxide.

Table 5. Effect sizes and summary statistics of strength changes following RT.

Study	Sample size	Hedges' g	Std. error	95% CI Lower	95% CI Upper
Paul et al 2014	36	0.608	0.341	-0.060	1.276
Corcos et al 2013	38	0.373	0.328	-0.269	1.016
Shulman et al RT 2013	36	0.369	0.341	-0.299	1.037
DiFrancisco et al 2012	18	1.045	0.503	0.060	2.031
Schilling et al 2010	15	0.781	0.537	-0.272	1.833
Bloomer et al 2008	13	0.379	0.561	-0.721	1.480
Mean effect, total		**0.537**	**0.164**	**0.215**	**0.859**

All data based on patients who were "on" medication.

Table 6. Endurance Training.

Study	Training regime (TR) Intensity (IN) Control group (CG)	Outcomes
Shulman et al 2013 ET-86%	TR: Treadmill IN: 70-80 % HRR (≈84-89 % HRmax§) for 15-30 min CG: ET low intensity and RT	**Cardio-respiratory fitness ↑:** VO_2 peak /kg ↑ 7 %# **Walking performance ↑:** 10 m fast pace time ↓ 5%* **Strength →:** LP, KE **Walking performance →:** 6MWT (p = 0,07), TUG, 15 m fast pace time (p = 0,09) **UPDRS-III →** **QOL →:** PDQ-39
Shulman et al 2013 ET-70%	TR: Treadmill IN: 40-50 % HRR (≈67-73 % HRmax§) for 15-50 min CG: ET high intensity and RT	**Cardio-respiratory fitness ↑:** VO_2 peak /kg ↑ 6 %# **Walking performance ↑:** 6MWT 11%*, 10 m fast pace time ↓ 7%*, 15 m fast pace time ↓ 7%* **Strength →:** LP, KE **Walking performance →:** TUG **UPDRS-III →** **QOL →:** PDQ-39
Schenkman et al 2012	TR: Treadmill or bicycle or elliptical trainer IN: 65-80 % HRmax for 30 min CG: Home based flexibility and strengthening	**Cardio-respiratory fitness ↑:** VO_2 sub/kg ↓: chi square test difference: 4 mo: -1 vs. CG#, 16 mo: -1,3 vs. CG# UPDRS total ↓**:** chi square test difference: 4 mo -3,6 vs. CG# UPDRS ADL ↓**:** slope difference: -0,2 vs. CG# UPDRS total ↓**:** slope difference: -0,5 vs. CG# **Balance →:** Functional reach test **Cardio-respiratory fitness →:** VO_2 sub/kg: 10 mo (p = 0,079) **UPDRS-III →** **QOL →:** PDQ-39 Continuous scale - physical functional performance (primary outcome) →
Ridgel et al 2009 ET	TR: Bicycle at 60 rpm IN: 60-80% HRR (≈78-89 % HRmax§) for 40 min CG: Forced exercise at 86 rpm, same INT	**Cardio-respiratory fitness ↑:** VO_2 peak ↑ 17%$ **UPDRS-III →**
Sage et al 2009	TR: Seated semi-recumbent ellipticals (legs and arms) IN: 60-75 % HRmax, <5 RPE, 50 rpm, for 20 min CG: No ex. Continue usual activities	**Walking performance ↑:** Step length 8%# **Walking performance →:** TUG (p = 0,095), Stride velocity (p = 0,07), Stride cadence. **UPDRS-III →**
Bridgewater et al 1996	TR: walking activities with music IN: 65-85 %HRmax for 20-30 min CG: No ex. Continue usual activities. Talks on health	**Cardio-respiratory fitness ↑:** Bruce test duration ↑# %NR Habitual activity level ↑# %NR (pre vs. EOT+4wks) Depression ↓**:** Levine-Pilowsky questionnaire* %NR (pre vs. EOT+4wks)

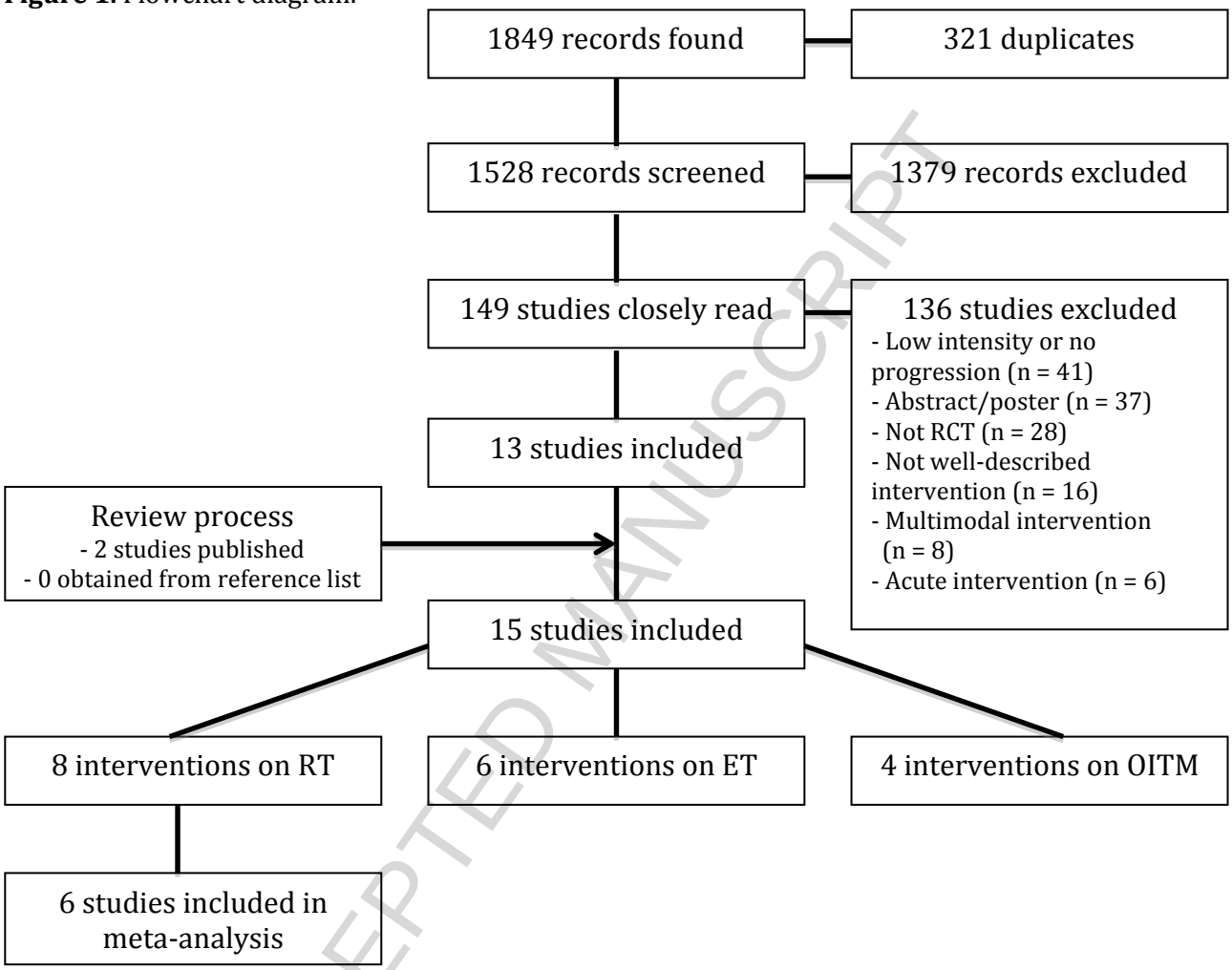
↑ = significantly increased, → = no change, ↓ = significantly decreased (improved), level of significance (p<0.05)
* = significant within-group change from pre to post in intervention group, # = change in intervention group significantly larger than change in control group (Shulman ET studies compared to Shulman RT), $ = significant within-group change from pre to post in both intervention and control group, NR = not reported, TR = training regime, IN = intensity, CG = control group, ex = exercise, HRR = heart rate reserve, HRmax = maximal heart rate, rpm = repetitions per minute, RPE = rating of perceived exertion, VO2 peak = peak oxygen uptake, 6MWT = 6 minute walk test, TUG = timed up-and-go, UPDRS-III = Unified Parkinson's Disease Rating Scale part III, QOL = quality of life, PDQ-39 = parkinson's disease questionnaire-39 items, VO2 sub = submaximal oxygen uptake, mo = months, ADL = activities of daily living, § = for information on how %HRmax was calculated from %HRR see section: "*Exercise definition".*

Table 7. Other Intensive Training Modalities.

Study	Training regime (TR) Intensity (IN) Control group (CG)	Outcomes
Combs et al 2013[c]	TR: Boxing, strengthening, endurance activities, stretching. IN: Self-paced with encouragement for 60 min. CG: Balance, strengthening, endurance activities, stretching.	**Balance ↑:** Berg balance scale ↑ 8%$ **Walking performance ↑:** 6MWT 13%*, TUG ↓ 12%$, Dual-task TUG ↓ 28%$, Gait velocity 4%* **QOL ↑:** PDQL ↑ 3%$ **Balance →:** Activities-specific balance confidence scale
Qutubuddin et al 2013	TR: Forced exercise on a theracycle (legs) IN: 61-80 % HRR (≈79-89 % HRmax[§]) for 30 min. CG: No ex.	**UPDRS-III ↓**: 34%* (pre vs. EOT+4 mo) **Balance →:** Berg balance scale **UPDRS-III →:** (pre vs. EOT) **QOL →:** PDQ-39 (p = 0,07)
DiFrancisco et al 2012	TR: ET: Treadmill or stairmaster + RT: 5 exercises (3 leg) IN: ET: 60-70% VO2 peak (≈69-76% HRmax[§]) for 20 min. RT: 2 sets x 8-15 reps at 50-80 % 1RM CG: No ex. Continue usual activities	**Strength ↑:** LP 22%#, KE 43%#, KF 28%# **Cardio-respiratory fitness ↑:** VO_2 sub ↓ 13%# Glutathione level ↑14%# Glutathione to glutathione disulfide ratio ↑21%# Homocysteine level (primary outcome) →
Ridgel et al 2009 OT	TR: Forced exercise on a stationary tandem bicycle at 86 rpm. IN: 60-80% HRR (≈78-89 % HRmax[§]) for 40 min. CG: Bicycle at 60 rpm, same INT.	**Cardio-respiratory fitness ↑:** VO_2 peak ↑ 11%$ **UPDRS-III ↓:** 35%# Bimanual dexterity task performance ↑: 1) Interlimb coordination ↑: ≈ 83%* (pre vs. EOT) and ≈ 88%* (pre vs. EOT+4wks), 2) Rate of force production, 1 hand ↑: ≈ 34%# (pre vs. EOT) and ≈32%# (pre vs. EOT+4wks), 3) Center of pressure, both hands ↓: 71%# (pre vs. EOT) and 63%# (pre vs. EOT+4wks) **UPDRS-III →:** (pre vs. EOT+ 4 wks) (p = 0,09)

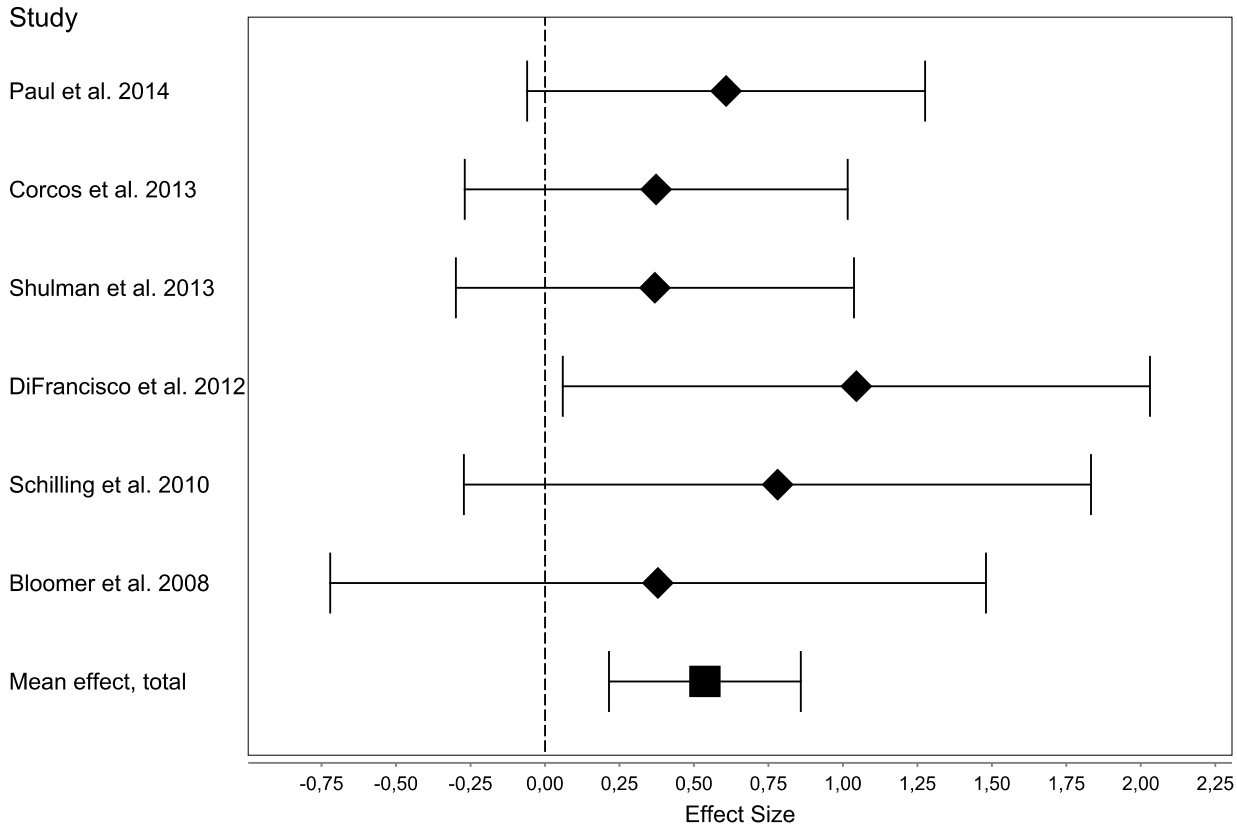
↑ = significantly increased, → = no change, ↓ = significantly decreased (improved), level of significance ($p<0.05$)
* = significant within-group change from pre to post in intervention group, # = change in intervention group significantly larger than change in control group, $ = significant within-group change from pre to post in both intervention and control group, c = % change calculated from median values, TR = training regime, IN = intensity, CG = control group, ex = exercise, HRR = heart rate reserve, HRmax = maximal heart rate, rpm = repetitions per minute, 6MWT = 6 minute walk test, TUG = timed up-and-go, QOL = quality of life, PDQL = parkinson's disease quality of life questionnaire, PDQ-39 = parkinson's disease questionnaire-39 items, LP = leg press, KE = knee extension, KF = knee flexion, VO2 sub = submaximal oxygen uptake, VO2 peak = peak oxygen uptake, UPDRS-III = Unified Parkinson's Disease Rating Scale part III, mo = months, § = for information on how %HRmax is calculated from %HRR and %VO2 peak see section: "*Exercise definition*"

Figure 1. Flowchart diagram.



RT: Resistance Training, ET: Endurance Training, OITM: Other Intensive Training Modalities, the difference between 15 studies and 18 interventions is due to some studies having more than one relevant intervention.

Figure 2. Forrest plot of the effect sizes and 95% CI's of strength changes following RT.



Highlights

- Intensive exercise therapy modalities are feasible, safe and beneficial in PD.
- Resistance training can improve muscle strength in PD
- Endurance training can improve cardio-respiratory fitness in PD
- Intensive exercise therapy may have beneficial effects on functional measures
- No studies find deterioration in any outcomes following intensive exercise therapy