Review

Exercise as medicine in Parkinson's disease

Martin Langeskov-Christensen ,[1,2] Erika Franzén,[3,4] Lars Grøndahl Hvid ,[1,5] Ulrik Dalgas[1]

[1]Exercise Biology, Department of Public Health, Aarhus University, Aarhus, Denmark
[2]Department of Neurology, Viborg Regional Hospital, Viborg, Denmark
[3]Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy, Karolinska Institutet, Stockholm, Sweden
[4]Department of Physical Therapy, Karolinska University Hospital, Stockholm, Sweden
[5]The Danish MS Hospitals, Ry and Haslev, Denmark

Correspondence to
Dr Martin Langeskov-Christensen; mach@clin.au.dk

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ABSTRACT

Parkinson's disease (PD) is an incurable and progressive neurological disorder leading to deleterious motor and non-motor consequences. Presently, no pharmacological agents can prevent PD evolution or progression, while pharmacological symptomatic treatments have limited effects in certain domains and cause side effects. Identification of interventions that prevent, slow, halt or mitigate the disease is therefore pivotal. Exercise is safe and represents a cornerstone in PD rehabilitation, but exercise may have even more fundamental benefits that could change clinical practice. In PD, the existing knowledge base supports exercise as (1) a protective lifestyle factor preventing the disease (ie, primary prevention), (2) a potential disease-modifying therapy (ie, secondary prevention) and (3) an effective symptomatic treatment (ie, tertiary prevention). Based on current evidence, a paradigm shift is proposed, stating that exercise should be individually prescribed as medicine to persons with PD at an early disease stage, alongside conventional medical treatment.

INTRODUCTION

Parkinson's disease (PD) is a chronic debilitating disorder of the central nervous system. It is the fastest growing neurodegenerative disorder and more than 10 million persons are diagnosed worldwide.[1] People with PD (pwPD) experience deleterious motor and non-motor consequences that affect their quality of life.[2] From an economic societal perspective, PD is associated with substantial healthcare costs.[3] Today there is no approved treatment that prevents the development of PD or stops or slows PD progression, and the currently available pharmacological symptomatic treatments are not effective for several symptoms, often reduce their effectiveness over time and cause side effects.[4] The identification of safe and effective symptomatic treatments (attenuating symptoms of the disease, ie, tertiary prevention[5]), disease-modifying treatments (decreasing the severity of PD or slowing/halting progression of the disease by affecting the underlying pathology/pathophysiology, ie, secondary prevention[5]) and potentially even preventive treatments (preventing disease development or stopping individuals from becoming at high risk, i.e, primary prevention[5]) is therefore highly needed in PD.

One of the most promising interventions is exercise with recent reviews[2 6] showing beneficial effects on several PD symptoms and relevant clinical severity markers. Importantly, exercise seems to have a number of effects that are overlapping, comparable or even superior to those of PD medication, which is aligned with the current international focus, where exercise is considered medicine for 26 chronic conditions.[7]

Over the past decade the number of PD exercise studies has almost tripled.[6] While early studies emphasised exercise as an interesting symptomatic treatment[8] (ie, tertiary prevention), more recent studies have also proposed exercise as being potentially disease-modifying by slowing disease progression[9] (ie, secondary prevention) and even reducing the risk of getting PD[10] (ie, primary prevention). Based on such studies, exercise should arguably have a much more pivotal role in the treatment of PD. Moreover, if exercise does indeed provide primary and secondary prevention in PD, it offers an adjunct treatment avenue that should change clinical practice. In this review, we synthesise the existing knowledge on the effects of exercise as primary, secondary and tertiary prevention against PD and discuss potential underlying mechanisms. Using this framework, we aim to provide a clear overview of current strengths and shortcomings within the literature, which will hopefully inspire researchers within the field to accelerate discovery.

FRAMEWORK AND DEFINITIONS

The present review covers the existing evidence evaluating whether exercise or physical activity offers primary, secondary or tertiary prevention in pwPD. In addition, we review potential underlying mechanisms and discuss future directions.

According to Caspersen *et al*,[11] physical activity is defined as 'any bodily movement produced by skeletal muscles that result in energy expenditure'. Physical activity in daily life can be categorised as occupational, sports, conditioning, household or other activities, whereas exercise (according to the modified definition of Gaemelke *et al*[12]) is a subset of physical activity defined as 'a voluntary activation of the skeletal muscles resulting in movement of a body part in time and space in addition to being planned, structured, repetitive and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective'.

An interesting, yet non-investigated, aspect is whether physical activity and exercise lead to comparable effects. To avoid any unfounded conclusions on the potential superiority of either, we here use the conception that moderate-to-vigorous physical activities and moderate-to-high intensity exercise elicit comparable effects.[13]

As exercise comprises many different modalities having different effects,[6] the present paper applied

the following categorisation of modalities, when summarising reviews and meta-analyses:

1. 'General exercise': reviews that use exercise interventions combining different basic exercise modalities (ie, multimodal exercise) or meta-analyses that pool findings from different exercise modalities (eg, combined effects of aerobic exercise, resistance exercise and multimodal exercise).
2. 'Resistance exercise', 'aerobic exercise', and 'balance and gait exercise': basic exercise modalities.
3. 'Other modalities': relevant modalities that have been summarised in a review or a meta-analysis (ie, dancing, martial arts, yoga, boxing, exergaming and hydrotherapy).

The categorisation was made to distinguish between potential differences across types of exercise, knowing that great methodological diversity exists in the literature covering exercise studies in PD. There is currently no consensus on how this should be done. Of note, reviews and meta-analyses were not restricted to one of the categories. If a review included data from 'General exercise' studies as well as 'Other modalities' it was included in both categories.

SEARCH STRATEGY AND SELECTION CRITERIA

References for this review were identified by searches of PubMed between 1969 and February 2023, and via references from relevant articles. PubMed was selected as the most relevant and comprehensive database in this field, although we acknowledge that relying on one database only (and the reference lists of the identified literature) may be a limitation in terms of the number of studies identified. We used combinations of the medical subject headings 'Parkinson's disease', 'exercise therapy', 'physical activity', 'exercise', and 'training'. No language restrictions were imposed. The final reference list was selected by author consensus on the basis of originality, impact and topical relevance. The search strategy was chosen to cover all aspects, including all types of study designs, of exercise as primary, secondary and tertiary prevention against PD.

EXERCISE AND PD: SAFETY AND FEASIBILITY

Two systematic reviews[6 14] found that exercise is generally considered safe based on a very limited number of reported adverse events. Across 48 located randomised controlled trials on PD and exercise, 33 reported on safety without any reports on serious adverse events. Adverse events were only reported in eight studies and included transient pain/soreness, joint inflammation, falls, dizziness, tiredness and worsening of pre-existing injuries, yet with only four events being related to an exercise intervention. In addition, the mean dropout rates were comparable between exercise intervention groups (8%) and control groups (11%), and the exercise groups completed, on average, 91% of the planned exercise sessions. Based on a very low risk of adverse events, a relatively low dropout rate that corresponds to non-exercising PD controls, and a generally high exercise adherence, exercise can therefore be considered both safe and feasible in pwPD. This is consistent with the safety profile of exercise in related diseases such as multiple sclerosis[15] and stroke,[16] whereas more adverse events (yet not serious) have been reported in Alzheimer's disease.[17]

EXERCISE (AND PHYSICAL ACTIVITY) AS PRIMARY PREVENTION IN PD: RISK REDUCTION

A combination of genetic and environmental factors, and interactions thereof, is associated with the development of PD.[4] Overall, however, the genetic contribution to PD is limited.[18] While the impact of causative genes is relatively well understood, it is more challenging to assess the sum of all environmental risk factors and their interactions with genetic features, partly because the environment is constantly changing.[4] Nevertheless, physical activity and exercise have recently gained attention as modifiable protective lifestyle factors.[10 19–22] The majority (ie, 9 out of 11) of the prospective studies investigating this were included and assessed in two recent systematic reviews.[10 19]

The first by Belvisi and colleagues[19] assessed six prospective studies and found that the five largest supported a protective role of physical activity against PD. These studies included between 43 368 and 143 325 participants (of which between 286 and 767 persons had PD) with a follow-up period of 9–12 years. The second by Fang and colleagues[10] included meta-analyses in the assessment of eight prospective studies with a total of 544 336 participants (2192 pwPD) and a median follow-up period of 12 years (range: 6–22). Categorical (ie, the highest vs the lowest category of physical activity) and quantitative (ie, metabolic equivalent of task-hours (MET-hours)) dose–response associations between physical activity and PD risk were investigated. Intriguingly, a markedly reduced risk of PD was associated with the highest levels of either total physical activity (relative risk: 0.79; 95% CI: 0.68 to 0.91) or moderate to vigorous physical activity (relative risk: 0.71; 95% CI: 0.58 to 0.87). Furthermore, the quantitative analysis revealed a dose–response association in men, showing that for each 10 MET-hours per week increase in total or moderate to vigorous physical activity, the risk of PD decreased by 10% and 17%, respectively. However, no dose–response association was observed in women. A plausible explanation for this is that only four of the eight studies included women and three of those studies enrolled fewer than 150 women with PD. Additionally, a time-lag meta-analysis with six of the identified studies excluding the first 4–10 years of follow-up showed that reverse causation, where decreased physical activity is driven by early non-diagnosed PD, is unlikely to explain the observed protective effects of moderate to vigorous physical activity.

Since these reviews[10 19] three additional cohort studies have been published.[20 21 23] Llamos-velasco and colleagues identified 47 PD/Parkinsonism cases among 2943 participants with available self-reported physical activity information after 3 years of follow-up.[20] Here, the active group (vs sedentary) showed a lower risk of Parkinsonism (HR: 0.18; 95% CI: 0.07 to 0.51), but this effect was restricted to men (HR: 0.34; 95% CI: 0.11 to 0.99) with PD. In contrast, the recent study by Portugal and colleagues, covering data from the E3N cohort (1196 cases, 23 879 controls; 1990–2018) of women affiliated with a national health insurance plan for persons working in education, showed that a higher physical activity level is associated with lower PD incidence in women without being explained by reverse causation.[23] A general limitation in cohort studies is that physical activity information is collected via questionnaires, which can lead to errors due to recall bias. In contrast, Müller and colleagues measured physical fitness objectively in a cohort of 7347 male veterans (94 pwPD, mean follow-up of 12.5 years) and expressed exercise capacity as METs, estimated from peak treadmill speed and grade.[21] Here, a strong inverse association showed that men who had high levels (>12 METs) versus low levels (<8 METs) of exercise capacity were 76% less likely to develop PD (HR: 0.24; 95% CI: 0.08 to 0.73). These findings extend earlier studies, adding evidence from objectively measured physical fitness supporting an inverse association with PD incidence. Such convincing results based on objectively measured physical fitness levels may imply that

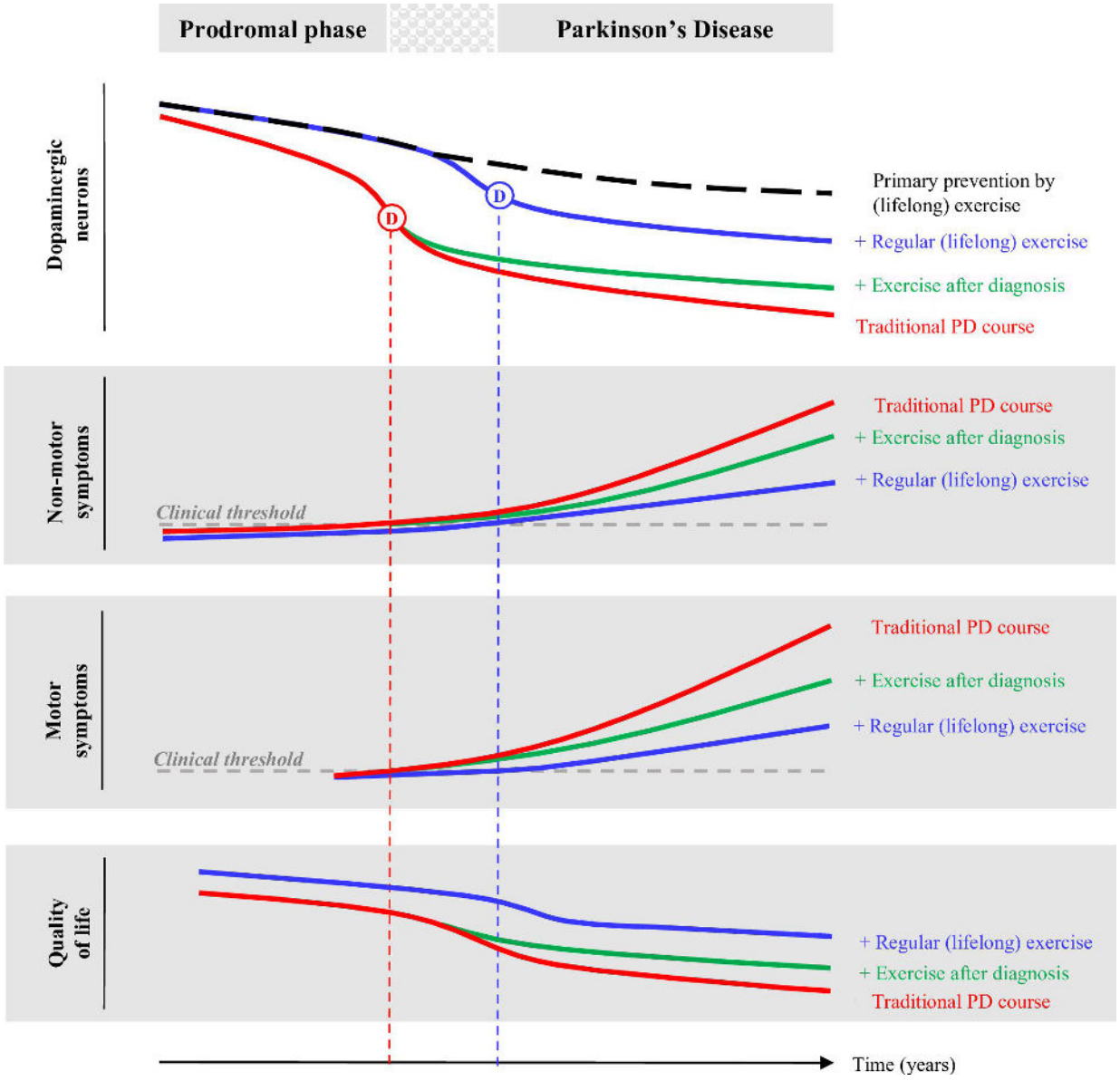

Figure 1 Conceptualisation of exercise-induced effects in PD. Conceptualisation of how exercise potentially has primary, secondary and tertiary preventive effects on PD. The shown outcomes relate to dopaminergic neurons, non-motor symptoms, motor symptoms and (health-related) quality of life. The different lines visualise the development for patients engaging in regular (lifelong) exercise (blue lines), patients engaging in exercise after diagnosis (green lines) and for patients who follow a traditional course of PD without engaging in exercise. The black dotted line visualises how primary prevention could potentially be achieved by regular (lifelong) exercise. The D's in the circles represent the time of diagnosis. PD, Parkinson's disease.

the observed beneficial effects based on self-reported data are underestimated.

To summarise, evidence support that people engaged in higher levels of moderate to vigorous physical activities in middle or later life have a lowered risk of PD. The above-mentioned findings meet several of the criteria for establishing causality including consistency of findings, strength of associations, temporality, biological gradient (demonstration of dose–response) and biological plausibility.[24] This compelling evidence is conceptualised in figure 1 showing that regular, potentially lifelong, exercise decreases the risk of PD or potentially postpones the time of diagnosis. In perspective, similar findings have been observed in multiple sclerosis[25] as well as Alzheimer's disease[26 27] suggesting a broader protective effect of exercise and physical activity on neurodegenerative diseases. A further perspective deals with the potential protective effect of drug therapy. However, while some evidence suggests that ibuprofen and other common medications (eg, calcium channel blockers) are associated with a lower risk of PD, evidence is currently contradicting.[19 28 29] Consequently, no specific drugs have yet been proven to definitively reduce the risk of developing PD.

EXERCISE (AND PHYSICAL ACTIVITY) AS SECONDARY PREVENTION IN PD: DISEASE MODIFICATION

Do exercise or physical activity elicit neuroprotective effects that ultimately impact the progression of fully manifest, prodromal and preclinical PD? Encouragingly, leading PD exercise experts advocate for exercise as a potentially disease-modifying treatment (ie, affecting the underlying pathology of the disease) and/or as an adjunct neuroprotective treatment.[6 30–41]

Most evidence supporting this notion originates from the basic sciences involving widely used rodent neurotoxicant-induced PD models (eg, 6-OHDA and MPTP).[32] These, however, have fundamental limitations including comparisons between normal behaving animals and sedentary animals (rather than exercise vs normal), prelesion exercise which is very hard to copy in humans, and the use of young animals despite ageing being the main risk factor for developing PD.[42] Such limitations must be acknowledged when translating evidence from animals to humans. Nevertheless, several studies show that aerobic exercise (no studies on other exercise modalities could be located) prevents the loss of, protect, and/or restore dopaminergic neurons and reduce toxin-induced lesions in the nigrostriatal pathway,[43 44] thus leading to a milder neurological disease course by impacting the main pathological hallmark of PD. By cautiously translating such results to human pathology, promoting engagement in exercise to pwPD may offer a non-pharmacological tool capable of counteracting disease progression.

Comprising cross-sectional,[9 45–47] retrospective and observational cohort,[48] (pilot/exploratory) interventional[9 49–53] and review studies,[6 30–41 54–56] the existing human clinical studies have primarily evaluated scores from the original or Movement Disorders Society–sponsored revision of the Unified Parkinson's Disease Rating Scale ((MDS)-UPDRS) and MRI outcomes as markers of disease activity/progression. However, all but four[49–51 53] of these studies were not designed or powered to assess these outcomes, thus limiting the strength of most existing evidence. Moreover, only one study[49] attempted to apply a double-blind, randomised controlled trial design which highlights one of the many complexities (eg, blinding, exercise science confounding variables,[57] inclusion bias, uniformity of population in a very heterogeneous disease) when designing exercise studies in PD.

In the cross-sectional studies, a higher cardiorespiratory fitness was associated with increased frontoparietal network connectivity,[9] whereas cardiorespiratory fitness was neither associated with the Hoehn and Yahr scale nor UPDRS total and motor scores.[45] The latter is supported by a recent systematic review that also did not show an association between (MDS)-UPDRS motor scores and cardiorespiratory fitness based on data from 13 studies.[54] Oppositely, an improved MDS-UPDRS total score was associated with improvements in lower extremity muscle strength ($r = -0.44$) after 3 months of supervised combined strength/endurance exercise.[47] In accordance, another study reported lower extremity muscle strength ($r = -0.67$) and activation deficits ($r = -0.65$) to be strongly associated with the UPDRS motor score.[46] These findings are supported by a recent systematic review showing that measures of lower extremity muscle strength display weak-to-strong negative associations (r range = −0.44 to −0.76) with (MDS)-UPDRS total, motor and motor experiences of daily living scores.[56] Although association does not imply causation such findings, using proxy measures of long-term exercise engagement, may serve as a useful stepping-stone to scientific advancement and as justification of further studies evaluating resistance exercise.

In a recent retrospective and observational cohort study including 237 people with early PD and 5 years follow-up, Tsukita and colleagues found that higher physical activity levels were robustly associated with slower deterioration of activities of daily living, processing speed and postural instability and gait disturbance (MDS-UPDRS motor PIGD subscore); symptoms that are refractory to medication.[48] Moreover, no association was observed between baseline physical activity levels and the clinical progression of PD suggesting that it is never too late to start exercising to obtain long-term effects.[58] The findings also highlight that pwPD who are challenged in performing high-intensity exercise due to severe motor and/or non-motor complications, are still able to achieve positive effects with long-term moderate to vigorous physical activity (eg, housecleaning, longer daily walks). Despite limitations (eg, observational instead of interventional, self-report physical activity questionnaires) such findings signify the importance of maintaining a high regular physical activity level and persistent exercise habits in pwPD, and they provide preliminary cautious evidence for a disease-modifying potential of high-volume physical activity/exercise.

Intriguingly, early but converging interventional evidence show that exercise may exert disease-modifying effects in pwPD. Three phase I/II trials found that 6 months of moderate to high-intensity aerobic exercise, performed 3–4 days/week, stabilised or improved PD motor symptoms in early PD (ie, de novo[50] and mean disease duration since diagnosis of approximately 3.5[49] or 5.5 years[52]), with exercise performed at a higher intensity (ie, 80%–85% maximum heart rate) being more effective than moderate intensity (ie, 60%–65% maximum heart rate).[50] Interestingly, one of these trials used a subgroup comprising 56 pwPD to explore disease-related functional and structural changes in the corticostriatal sensorimotor network.[9] The preliminary neuroimaging evidence together with clinical and behavioural results from this study suggest that high-intensity aerobic exercise may stabilise disease progression in the corticostriatal sensorimotor network, while simultaneously reducing global brain atrophy. Such findings imply that exercise-induced neural plasticity is possible despite PD being a chronic central nervous system disease. In another trial applying moderate-intensity aerobic exercise as part of two 28-day multidisciplinary intensive rehabilitation treatments, with a 1-year interval and a 2-year follow-up, UPDRS-II and UPDRS-III scores improved when compared with the control group receiving pharmacological treatment only.[51] Although it is difficult to decipher if the applied intervention had one or more 'active ingredients', these results add further support to the beneficial effects of aerobic exercise in PD. Lastly, the long-lasting PRET-PD trial by Corcos and colleagues,[53] showed that 2 years of progressive resistance exercise led to a clinically relevant reduction in UPDRS-III scores and improved strength, mobility and cognition, when compared with an active control group performing stretches, balance exercises, breathing and non-progressive strengthening. This suggests that resistance exercise may be neuroprotective and a useful adjunct therapy to improve PD motor signs.[59–61]

Providing further encouraging support—although study designs vary considerably and there are several methodological limitations— previous literature reviews and meta-analyses have identified potential improvements in the (MDS)-UPDRS total, UPDRS-II and/or UPDRS-III following general exercise therapy,[62] resistance exercise,[63 64] aerobic exercise,[6] Tango[64] and Tai Chi.[65] Of the different parts of the (MDS)-UPDRS, part III has increasingly become the motor outcome measure of choice in clinical trials.[66] Figure 2 shows effect sizes (ie, 0.15–0.47) in favour of different exercise modalities on the (MDS)-UPDRS III. An interesting question is how these effects compare to the effects of dopaminergic medication, although no studies have so far explored this. Hence, rough comparisons across medication and exercise studies should therefore be done cautiously. As an example, the effect size on aerobic exercise (6–26 weeks) corresponds to a mean difference favouring exercise of 2.62 (95% CI: 0.41 to 5.64) points in the off-medication state,[6] which is comparable to the estimated difference of 2.25 points per year (95% CI: 1.11 to 3.39, assessed off-medication) in the

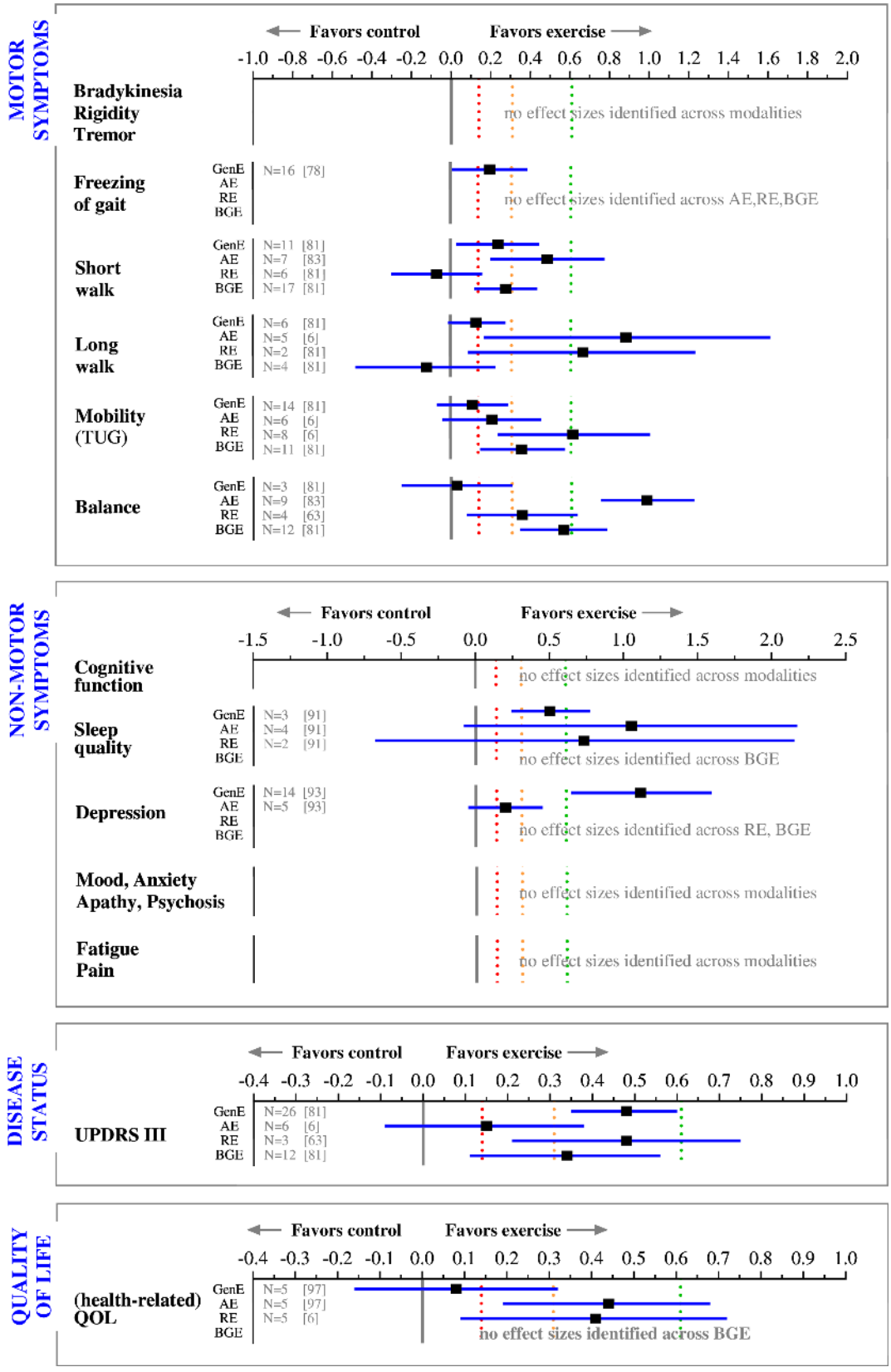

Figure 2 Summary of selected meta-analyses showing secondary and tertiary preventive effects of exercise on Parkinson's disease. Summary of reported effect sizes (derived from meta-analyses/studies selected by the authors) across different outcomes related to motor symptoms, non-motor symptoms and QoL. The meta-analyses included passive control groups. The number of studies used to calculate the effect sizes and references to the studies are displayed in grey text. Dotted vertical lines represent effect sizes that are determined as small (0.14), medium (0.31) and large (0.61). 'Short walk' refers to the 10-Metre Walk Test whereas 'Long walk' refers to the 6-Minute Walk Test. Independent effect sizes for bradykinesia, rigidity and tremor do not exist, but the UPDRS-III provides an effect size on these symptoms along with other symptoms collectively. AE, aerobic exercise; BGE, balance and gait exercise; GenE, general exercise; QOL, quality of life; RE, resistance exercise; TUG, timed-up-and-go test; UPDRS, Unified Parkinson's Disease Rating Scale.

MDS-UPDRS III progression in pwPD who are unmedicated compared with those who are medicated.[66] Another important question arises regarding the cost-effectiveness of exercise versus medication. With PD being one of the brain disorders with the highest attributable direct costs per person,[67] any adjuvant treatments to pharmaceutics that are safe, effective and cost-effective should be highly prioritised. Estimated mean primary PD-related pharmaceutical 12 month costs in 2013 have been reported to range between €757 and 2787 (US$1006–US$3701), depending on PD stage.[68] Given the scarce literature on cost-effectiveness of exercise a direct comparison to this is not possible. However, analyses on effectiveness and costs of specialised physiotherapy indicate better quality of care, lower annual costs (both physiotherapy: €395 difference, and total healthcare costs: €530 difference) and better outcomes (fewer hospital visits for PD-related complications) than usual care physiotherapy.[69] While acknowledging many unknown factors, such findings cautiously indicate that individually tailored exercise programmes may also be considered cost-effective for secondary prevention in PD.

Additional reviews[30–32 34–36 38 40 41 70 71] provide further support of a disease-modifying effect of exercise in their summary of tentative modes of action, describing a functional or anatomical change, as well as the molecular mechanisms of action (see Potential exercise-induced pathophysiological effects in PD below for details). While encouraging, detailed and more convincing insights into the underlying mechanisms are still lacking. Nonetheless, the combination of consistent findings in animal models of PD and the overall effect of exercise on (MDS)-UPDRS scores in pwPD suggests that exercise has a prophylactic effect on factors mediating disease progression. Consequently, the current knowledge base supports exercise as a potential safe, inexpensive and accessible disease-modifying therapy in PD. This is conceptualised in figure 1 depicting diminished progression with exercise as compared with a traditional PD course. Lastly, to put these findings in perspective, the notion that exercise and physical activity may be neuroprotective has also been voiced by experts within the fields of multiple sclerosis,[25] and Alzheimer's disease.[27] While encouraging evidence points towards beneficial effects of exerkines (eg, interleukin-6, cathepsin B, 3-hydroxybutyrate and lactate) leading to increased expression of brain-derived neurotrophic factor (BDNF) in the central nervous system, solid human findings are nevertheless warranted to support this.[72] This is partly evidenced by the sparse and inconclusive effects of physical exercise on whole/regional grey matter brain volume in populations at risk of neurodegeneration.[73] However, both clinical and preclinical evidence do show the effectiveness of exercise in treating cognitive function and memory in Alzheimer's disease,[27] as well as factors mediating disease activity in multiple sclerosis,[25] emphasising the potential benefits of exercise in neurological diseases.

EXERCISE AS TERTIARY PREVENTION IN PD: SYMPTOMATIC TREATMENT

The combination and severity of symptoms vary and depend on the PD subtype[74] along with the disease duration adding complexity when tailoring exercise to pwPD. Also, the physical activity level of pwPD is of importance,[75] as this is markedly lower than in matched healthy controls.[76] Hence, several PD symptoms could arise due to the disease processes per se, the reduced physical activity levels per se or a combination of the two. The latter seem most plausible, based on the preliminary but converging evidence suggesting that exercise may exert disease-modifying effects in pwPD. This is supported by numerous beneficial effects of exercise on motor and non-motor symptoms, physiological impairments, indirect measures of disease activity/progression and participation in pwPD. Table 1 and figure 2 summarise data from reviews and/or meta-analyses on the effects of exercise in PD.

As seen in table 1 and in figure 2, general exercise, aerobic exercise and resistance exercise can positively impact several outcomes. Furthermore, other exercise modalities also show beneficial effects on various outcomes. Intriguingly, all exercise modalities lead to improvements in walking capacity, postural stability/balance and the (MDS)-UPDRS-III score. Interestingly, the effect sizes in figure 2 on balance (0.03–0.99) and mobility (0.11–0.62) range from similar to superior, depending on exercise modality, when compared with the reported improvements of Levodopa on balance (0.22–0.30) and mobility (0.35) outcomes.[77] Of note, cost-effectiveness analyses of balance training for elderly with PD show a high probability of cost-effectiveness in the short-term perspective when considering the willingness-to-pay thresholds used in Europe,[78] and generally Tai Chi and multidisciplinary interventions seem to be more cost-effective for early PD management.[79] Furthermore, all exercise modalities except for balance and gait exercise improved cognition, sleep dysfunction and quality of life (table 1). Of note, cognition may deserve particular attention as it influences or is influenced by other symptoms (eg, physical inactivity negatively affects cognition[80]). Based on the information outlined above, it seems that engagement in any type of exercise entails important impacts on PD symptomatology. This is essential knowledge for both pwPD who cannot perform specific types of exercise due to impairments and/or lack of motivation (ie, other potentially more motivating options are available and effective) and for clinicians prescribing exercise. The fact that all exercise modalities can positively affect the (MDS)-UPDRS-III score, which is both regarded as an indirect measure of disease progression as well as a measure of a wide range of symptomatic motor signs, highlights exercise as an effective intervention for reducing the impact of PD as well as of associated sequelae. Of note, however, (MDS)-UPDRS change scores contain substantial error variance, emphasising the need for more reliable instruments to forward our understanding of the heterogeneity in PD progression.[81] Furthermore, due to the heterogeneity of PD, specific exercise therapy goals and task-specific interventions should be promoted, along with general exercise programmes, to best meet pwPD's challenges, which is consistent with both PD exercise guidelines,[82 83] systematic reviews[84 85] and the principle of specificity known from athletes. In this regard, basic exercise modalities such as aerobic exercise, resistance exercise and balance and gait exercise can improve the aerobic capacity, muscle strength and postural stability/balance in pwPD, respectively. While muscle weakness has critical implications as it contributes to postural instability, gait difficulties, bradykinesia and may lead to falls,[56] the aerobic capacity is a strong health and performance predictor in both healthy and clinical populations.[54] Since different exercise types (eg, resistance exercise vs aerobic exercise) induce very distinctive physiological adaptions (eg, neuromuscular vs cardiorespiratory), pwPD should be encouraged to incorporate different types of exercise into their programmes to maintain or improve these highly relevant physiological outcomes. While little evidence exists to support a dose–response relationship between volume or intensity and expected effects, current PD exercise guidelines recommend 3–5 days/week of aerobic exercise (20–60 mins at moderate intensity) and 2–3 days/week of resistance training (1–3 sets of 8–12 repetitions between 40% and 50% of 1 repetition maximum).[86] In accordance, exercise

Table 1 Summary of the secondary and tertiary preventive effects of different exercise modalities

	PD vs healthy	General exercise*	Aerobic exercise	Resistance exercise	Balance and gait exercise	Other modalities†
Motor symptoms						
Bradykinesia	↓	-	↑[34]	↑[34 35]	-	-
Rigidity	↓	-	↑[34]	-	-	-
Tremor	↓	-	↑[116]	-	-	↑[116]
Freezing of gait	↓	↑[84]	-	-	-	↑[84 88]
Walking capacity/mobility	↓	↑[114 117]	↑[34 71 117–119]	↑[34 64 71 114 117]	↑[114]	↑[34 64 88–90 114 120]
Balance	↓	↑[34 114]	↑[35 119]	↑[63]	↑[114]	↑[32 34 89 114 120–122]
Non-motor symptoms						
Cognitive function	↓	↑[32 123]	↑[30 34 35 71 123]	↑[32 71]	-	↑[123]
Sleep dysfunction	↓	↑[34 71 124 125]	↑[34]	↑[34 124]	-	↑[34]
Psychiatric disturbances (mood, depression, anxiety, apathy, psychosis)	↓	↑[126 127]	↑[34 71 121 126]	-	-	↑[34 71 126]
Fatigue	↓	-	↑[71]	-	-	-
Pain‡	↓	→↑[128 129]	↑[128]	-	-	↑[71 128]
Disease activity/ progression						
(MDS)-UPDRS						
Part I (non-motor experiences of daily living)		-	-	-	-	-
Part II (motor experiences of daily living)		↑[34]	-	↑[62]	-	-
Part III (motor examination)		↑[114]	↑[32–35 71 119]	↑[33 35 63]	↑[114]	↑[2 34 64 114 122]
Part IV (motor complications)		-	-	-	-	-
Total		↑[34 121]	-	-	-	↑[62]
Hoehn and Yahr		-	-	-	-	↑[34]
'Other'		↑[33 37 100]	-	-	-	-
Physiological impairments						
Muscle strength	↓	-	↑[118]	↑[34 63 71]	-	-
Aerobic capacity (VO_2-max)	(↓)	-	↑[32 35 71]	-	-	-
Quality of life						
(Health-related) quality of life	↓	↑[32 114]	↑[121 130]	↑[35]	-	↑[2 32 89 114 120 130]

Only findings supported by reviews and/or meta-analyses are shown.
The MDS-UPDRS III can be interpreted ambiguously, both as a measure of disease progression and as a symptomatic measure. To clarify the current literature that specifically examined the core motor symptoms of PD, the MDS-UPDRS appears here under 'Disease activity/progression'. Findings in the 'Other' category under 'Disease activity/progression' included increased serum levels of brain-derived neurotrophic factor, cortical motor excitability, elevated striatal dopamine D2 receptor binding and weakening of the overactive indirect striatal pathway DA-D2R expression. The reviews/meta-analyses included in this table describe between-group effects (except for pain which is within group effects) and include a mixture of passive and active control groups.
'→' indicates no effect of exercise on the listed parameter; '↑' indicates beneficial effect of exercise on the listed parameter; and '↓' indicates impaired in PD when compared with healthy people.
*General exercise covers reviews that use exercise interventions combining different basic exercise modalities (ie, multimodal exercise) or meta-analyses that pool findings from different exercise modalities (eg, combined effects of aerobic-, resistance and multimodal exercise).
†Other modalities include dancing, martial arts, yoga, boxing, exergaming and hydrotherapy.
‡Non-controlled trials included in addition to controlled trials.
MDS-UPDRS, Movement Disorders Society–sponsored revision of the Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease.

interventions with high compliance to the American College of Sports Medicine recommendations show better improvements on motor function, mobility and quality of life compared with exercise interventions with low or uncertain compliance[87]. Of note, 'other' exercise modalities, such as dancing, boxing and martial arts, are becoming more popular and have attracted increasing research interest. The existing literature, however, must be interpreted cautiously due to few existing studies, small study populations, poorly described intervention protocols and a large heterogeneity in the applied interventions.[88–90] Nonetheless, the overall results indicate positive effects of 'other' modalities on several outcomes, which should be further addressed in future well-designed large randomised controlled trials.

Surprisingly, specific data on the effects of general exercise on three core motor features of PD (ie, rigidity, tremor, bradykinesia) and (MDS)-UPDRS-I and (MDS)-UPDRS-IV were absent (see table 1). Although included in the MDS-UPDRS-III, future exercise studies attempting to isolate these core symptoms are needed to expand our understanding of how to best treat them individually. Additionally, the effects of exercise on fatigue and pain[91] were sparsely investigated. These knowledge gaps may serve as a useful stepping-stone

to scientific advancement. Lastly, it is important to note that based on the reviews found, several studies (1) evaluated the short-term effects of exercise on a specific symptom as a secondary outcome rather than as the primary outcome, suggesting that some studies were inappropriately powered, and (2) did not enrol participants based on their baseline symptom status, suggesting that they may not have had the symptom of interest at baseline. The latter could result in a ceiling effect, thereby diluting the potential effects of exercise. Nonetheless, the summarised effects of exercise in table 1 clearly show that exercise and physical activity have favourable effects in pwPD and may induce a postponement of clinical disability, as illustrated in figures 1 and 2. Similarly, exercise studies in other neurodegenerative diseases such as multiple sclerosis,[25] Alzheimer's disease[92] and stroke[93] highlight the positive multidomain benefits on physical, functional, as well as cognitive symptoms.

POTENTIAL EXERCISE-INDUCED PATHOPHYSIOLOGICAL EFFECTS IN PD

To optimally apply exercise as tailored medicine it is crucial to expand our current understanding of the explanatory factors and pathways believed to mediate the exercise-induced symptomatic, disease-modifying and primary preventive effects in pwPD. Recent research suggests PD to be a much more widespread disorder than previously thought, with pathology to be found in multiple organ and tissue systems.[94] Thus, one can speculate whether the diverse symptomatic and potentially disease-modifying effects induced by exercise in PD are really resulting from the broad-spectrum effects that exercise has on most tissues and organ systems across the body or on specific neuroplastic effects. Most studies investigating underlying molecular/biological effects have applied the aforementioned animal models of PD (ie, rodent neurotoxicant-induced models) instead of pwPD. The animal studies suggest that exercise can induce neuroprotection and neuroregeneration through different molecular processes. Upregulation or regulation of neurothrophic factors has a central role in these neuroplastic effects.[44 95] For example, treadmill running increases the levels of BDNF, glial-derived neurotrophic factor and other neurotrophines in the striatum in rodent PD models.[96–99] These neurotrophines are furthermore suggested to modulate or support different processes that enhance neurogenesis, angiogenesis, dopamine transportation, synapse/transmitter release, autophagy, neuronal sprouting and mitochondrial function or reduce inflammation and cell death. In summary, these processes lead to more neurons surviving and increased levels of dopamine which in turn strengthens the neural networks in the basal ganglia, cortex, thalamus, cerebellum and brainstem, ultimately leading to improved motor and/or cognitive performance. Although most of the evidence supporting a neuroprotective effect of exercise in PD involves animal research, studies in pwPD also support potential pathophysiological effects of exercise.[9 48–50] In this context, neurotrophic factors, which are easy and less expensive to analyse indirectly (ie, as a proxy for central nervous system levels) in blood plasma or serum, have been mostly investigated. However, two recent but small meta-analyses by Hirsch *et al*[100] (including two randomised controlled trials) and Johansson *et al*[38] (including four non-controlled studies) showed inconsistent results regarding BDNF. While Hirsch and colleagues showed an effect of exercise, Johansson and colleagues did not, but both reviews highlight the low to moderate methodological quality of the included studies. Another approach involves non-invasive imaging techniques of brain function (eg, functional MRI (fMRI), electroencephalogram, functional near-infrared spectrometry, positron emission tomography (PET) and transcranial magnetic stimulation) or brain structure (MRI). For instance, a small pilot study using PET imaging showed that 8 weeks of treadmill exercise increased the dopamine D2 receptor in the exercise group (n=2) but not in the controls.[101] Interestingly, these preliminary findings are in line with the results observed in mice models.[102] Furthermore, as previously mentioned, aerobic exercise increased functional connectivity within corticostriatal and frontoparietal networks, while simultaneously reducing global brain atrophy in pwPD.[9] Another recent randomised controlled trial[103 104] found no between-group functional brain changes after 10 weeks of balance and gait exercise in pwPD but the exercise group showed a subtle within-group increase in putamen volume, which was associated with increased gait speed, as well as stronger thalamic-cerebellar connectivity. Although studies show positive effects of exercise in pwPD, the overall level of evidence for exercise-induced neuroplasticity is low due to few studies with methodological limitations including small sample sizes, no control groups and heterogenous outcomes.[38] Likewise, the pathophysiological effects of exercise in pwPD remain largely unexplored and rely on animal studies. The evidence on exercise-induced neuroplastic effects and its underlying mechanisms in pwPD is therefore still in its infancy but does nonetheless point in a positive direction.[105]

FUTURE PERSPECTIVES FOR RESEARCH AND CLINICAL PRACTICE

The present review outlines the pivotal role of exercise as both prevention and treatment of PD. Nonetheless, as highlighted in figure 3, many important basic questions remain unanswered. Though solid evidence supports a lowered PD risk in persons with higher physical activity levels, future studies using objective and quantifiable physical activity measures such as accelerometry[106] as well as intervention studies promoting exercise and physical activity are needed to advance our understanding and expand the robustness of evidence. Also, the evidence of exercise as a disease-modifying treatment is currently less robust although highly plausible. Robust biomarkers for monitoring disease progression have for long been a critical need in PD research,[107] and the lack hereof influences the understanding of potential disease-modifying strategies[108] including exercise. This should be acknowledged when assessing the existing human clinical studies within the field. The limited (pharmacological) treatment options make exercise one of the most potent non-pharmacological interventions, but future high-quality, long-term, large-scale and multinational phase III trials using more refined disease progression outcomes as well as translational basic science studies need to further confirm this. Fortunately, such aspirational endeavours are already in process,[109] which will hopefully inspire and develop the field. In addition, future 'head-to-head' studies comparing different exercise interventions along with dose–response interventions are needed to establish the most efficient exercise modalities and dosing, to help guide and improve prescription. Given the current large body of literature on basic exercise modalities (ie, aerobic exercise, strength exercise, balance and gait exercise) these would provide a natural starting point in 'head-to-head' studies. To further advance our understanding of exercise as a potential disease-modifying treatment, future trials must expand the focus on

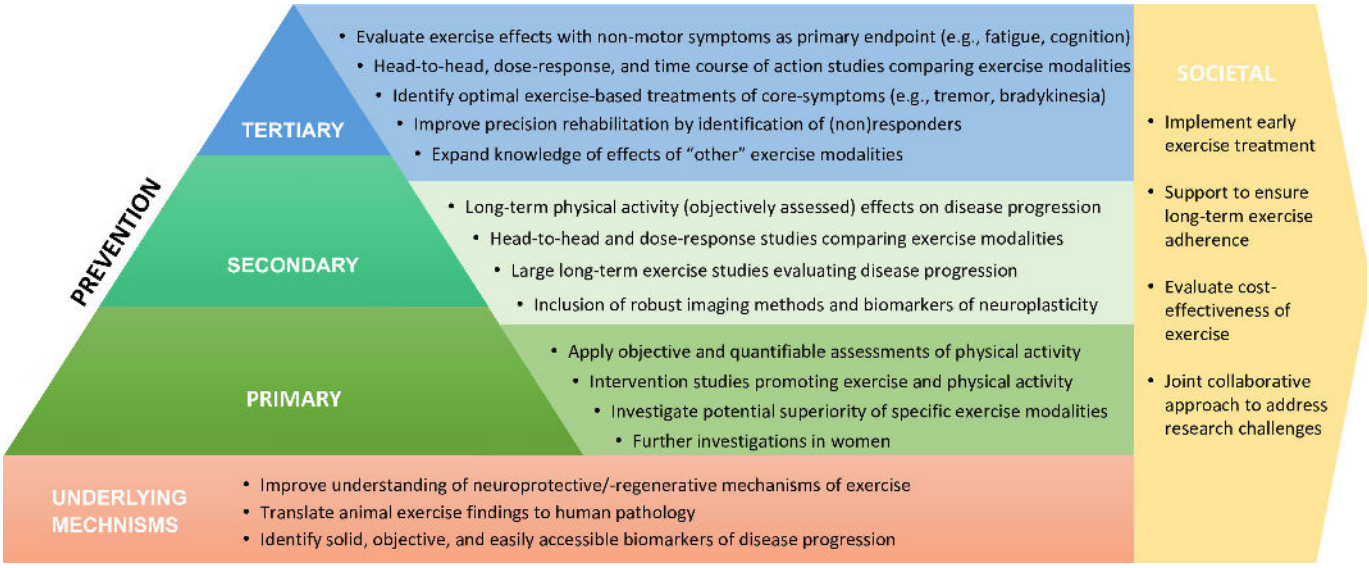

Figure 3 Future challenges and research needs in Parkinson's disease exercise studies. Summary of future challenges and research needs in Parkinson's disease Exercise studies encompassing primary, secondary and tertiary prevention. To further accelerate discovery, challenges and research needs related to the underlying mechanisms and societal implementation are also included.

underlying mechanisms. Figures 1 and 3 provide a framework that can form the backbone when designing future trials, and as mentioned above, it seems particularly relevant to include robust imaging methods (eg, PET and fMRI) and biomarkers of neuroplasticity (eg, BDNF, inflammatory markers, alpha synuclein). Furthermore, high-quality evidence on the effects of exercise on several core PD symptoms is warranted and future studies should thus target symptoms that are manifest in the included pwPD. Such studies will shed light on responders vs non-responders and demonstrate the true potential of exercise as tertiary prevention in PD. Moreover, they will expand the existing knowledge base enabling more precision rehabilitation which is highly needed given the heterogeneity of PD. Also, more focus should be placed on evaluating the cost-effectiveness of especially long-term exercise studies assessing central health outcomes and predictors (eg, comorbidities like hypertension, diabetes, obesity). These and further estimates of the relative costs of exercise (eg, in relation to drug therapy) are highly relevant when assessing the applicability of exercise as medicine in PD. Such estimates will naturally vary based on several factors, including the specific type of exercise or drug prescribed, the frequency and duration of treatment, geographical location, individual healthcare plans and disease severity. The current absence of these estimates must, of course, be acknowledged when discussing increased prescription of individualised exercise for pwPD. However, it must be emphasised that cost comparisons between drugs and exercise are not always relevant since exercise will never be a substitute for traditional anti-Parkinson medication but rather an adjunct therapy. Morover, while exercise adherence is high in PD exercise studies, pwPD are generally inactive[110] highlighting the need for future studies assessing long-term exercise adherence (eg, telerehabilitation, exercise apps, easy-to-apply exercise concepts within PD communities, where pwPD actively take part in the development and implementation of the concept). Lastly, the effect of exercise on PD subgroups such as young-onset PD are lacking and should be further examined. A final recommendation to the PD exercise field is to learn from related fields such as stroke[111] and multiple sclerosis,[112] where exercise experts have joined forces to address existing field barriers to accelerate discovery.

The existing evidence on exercise and PD suggests that exercise should be prescribed along relevant medication to pwPD as early as possible. Also, given the safety and feasibility of exercise in PD there appears to be no harm in prescribing exercise for those at risk of developing PD (ie, rapid eye movement sleep behaviour disorder, genetic predisposition) to reduce the risk of developing PD or potentially prolong the time to diagnosis. While exercise seems to alleviate numerous PD symptoms it may also pose disease-modifying potential. Consequently, the prescription of individualised training programmes with continuous follow-ups should be routine and incorporated in the standard management of PD[71] applying a multidisciplinary approach (ie, involvement and collaboration between physiotherapists, exercise physiologists, neurologists and other relevant professions). Herein lies a paradigm shift. Finally, exercise has well-known 'general' health benefits,[113] and it may therefore also reduce the risk of comorbidities in pwPD. Further recommendations on the practical prescription exist.[114 115]

CONCLUSION

Convincing evidence suggests that exercise offers primary and tertiary prevention in pwPD, whereas evidence for secondary prevention is less robust although highly plausible. Exercise should therefore be considered as medicine in pwPD and should be prescribed as an adjunct treatment as early as possible.

X Martin Langeskov-Christensen @LangeskovMartin and Lars Grøndahl Hvid @HvidLars

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ORCID iDs
Martin Langeskov-Christensen http://orcid.org/0000-0001-8397-7527
Lars Grøndahl Hvid http://orcid.org/0000-0003-3233-0429

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