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Review

# Considerations on How to Prevent Parkinson's Disease Through Exercise

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**Abstract**. The increasing prevalence of people with Parkinson's disease (PD) necessitates a high priority for finding interventions to delay or even prevent the onset of PD. There is converging evidence that exercise may exert disease-modifying effects in people with clinically manifest PD, but whether exercise also has a preventive effect or is able to modify the progression of the pathology in the prodromal phase of PD is unclear. Here we provide some considerations on the design of trials that aim to prevent PD through exercise. First, we discuss the *who* could benefit from exercise, and potential exercise-related risks. Second, we discuss *what* specific components of exercise mediate the putative disease-modifying effects. Third, we address *how* methodological challenges such as blinding, adherence and remote monitoring could be handled and *how* we can measure the efficacy of exercise as modifier of the course of prodromal PD. We hope that these considerations help in designing exercise prevention trials for persons at risk of developing PD.

Keywords: Exercise, prevention, Parkinson's disease, disease modification, considerations, non-pharmacological, treatment

## INTRODUCTION

The prevalence of Parkinson's disease (PD) increased considerably in the past decades [1], intensifying the need for development of disease-modifying treatments in a prodromal or early symptomatic disease phase. Treatments to alter disease progression when the underlying pathology is still limited hold potential to ultimately slow disease progression or, when applied during the prodromal phase, to postpone or even prevent the clinically manifest phase of PD. Trials aiming to prevent PD are scarce; only two pharmacological trials are either prepared (NCT05611372) or active (NCT04534023), while one non-pharmacological trial (NCT06193252; Slow-SPEED-NL) is currently active. We previously pointed to the merits of a complementary approach that uses non-pharmacological lifestyle interventions; among these, there is most persuasive evidence for aerobic exercise [2]. In contrast to pharmacological interventions, lifestyle interventions have limited side-effects and are widely available. On the other hand, they also pose methodological challenges with respect to, e.g., blinding or adherence. We previously provided suggestions as to whom to target, and also stressed the potential of administrating the intervention remotely, leveraging the use of digital technology to promote scalability and to overcome challenges in blinding and adherence [2].

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Through this scoping review, we aim to enrich our previous work [2] with an update on what type of exercise to study in PD prevention trials, who could potentially benefit most, how to monitor exercise engagement and how to measure exercise efficacy on cardiorespiratory fitness and intermediate prodromal PD outcomes.

## WHOM TO TARGET IN PD EXERCISE PREVENTION TRIALS

The prodromal phase of PD emerges up to 15–20 years prior to meeting the PD diagnosis criteria offering potential time to install disease modifying treatments when the pathology is still limited [3–5]. Criteria to diagnose prodromal PD with absolute certainty are not yet available. The MDS research criteria for prodromal PD offer a list of risk markers to help to identify eligible participants for exercise trials aimed at preventing PD [6]. We used these criteria to create an overview (Table 1) in which we provide specific considerations for the design of exercise trials for the prevention of PD. For practical reasons we categorized the MDS risk markers in Table 1 into three groups: low-, medium-, and high risk. We anticipate that the MDS criteria will be continue to be updated in years to come, and future versions may also entail components of the two recent biological classifications of PD [7, 8], which incorporate biological measures such as the presence of $\alpha$-synuclein in the skin or cerebrospinal fluid to further stage and identify the earliest phases of (prodromal) PD [7, 8]. We refer to the work by Crotty et al. for generic considerations regarding the feasibility of trial inclusion for a presumed prodromal cohort carrying these risk markers [9]. Here, we highlight additional considerations that are specific to the design of exercise trials in the context of PD prevention.

Targeting individuals with a high suspicion of prodromal PD (based on the MDS risk criteria) will increase the likelihood of emerging prodromal features within the timeframe of a clinical trial, which is needed to demonstrate disease-modifying effects of exercise [9]. By contrast, targeting individuals with a combination of risk markers likely increases this likelihood even further. Novel frameworks, including biological criteria as mentioned above may help to identify people with prodromal PD with more precision in the future. PD incidence steadily rises with age [10]. Therefore, an overall enrichment factor to increase the likelihood of developing PD could be by including older persons to increase the chance of emerging measurable prodromal symptoms within the time frame of a clinical trial.

### *Who could benefit most from exercise?*

To date, no exercise trials have been performed in individuals with prodromal PD, leaving it uncertain who could benefit most from exercise for PD prevention. Theoretically, one factor that may be of influence is the extent of the underlying PD pathology at the moment of trial inclusion. Those with limited PD pathology (i.e., early stage) may benefit more from the effect of exercise as there is more dopaminergic tissue to preserve, compared to those in whom pathology is more advanced. However, targeting those with presumably more advanced pathology will be more likely to phenoconvert to fully manifest PD, or at least show measurable changes in PD-related prodromal features within the time frame of the clinical trial. In Table 1, we estimated the presumed disease stage of the underlying PD pathology on the moment of onset of risk markers as described in previous work of Darweesh et al. [3], Fereshtehnejad et al. [4], and Schrag et al. [11]. We categorized the presumed underlying PD pathology into three stages, calculated as the number of years that symptoms would appear prior to PD diagnosis: early defined as $>10$ years, in-between as 5–10 years, and advanced as $<5$ years of symptom onset prior to PD diagnosis. Apart from disease stage, an overarching enrichment factor could be to target sedentary people who are more likely to benefit from exercise, but this selection criterion also poses a challenge as these individuals are likely less eager to be recruited into exercise trials (as we demonstrated in the ParkFit trial in patients with clinically manifest PD) [12] and to comply with the exercise intervention [13].

### *Considerations regarding exercise complications*

Engaging in (vigorous) exercise may increase the risk of falls, musculoskeletal injury and sudden cardiac disease, particularly when carried out by unfit individuals [14]. Elderly with concomitant mobility problems, cardiovascular co-morbidities, or those with advanced prodromal pathology have an increased risk of exercise-related complications. During the clinical trial, it is important to monitor potential complications.

Table 1
Whom to include for exercise prevention trials? *Considerations on the selection of suitable trial participants for exercise prevention trials of Parkinson's disease*

| Characteristics | Examples | Generic | | Exercise-specific |
|---|---|---|---|---|
| | | Likelihood of prodromal PD* | Presumed disease stage** | Considerations |
| Prodromal manifestations | DAT-deficit | High | Advanced | – Exercise benefit may be limited due to advanced disease stage<br>– Increased risk for complications due to mobility problems (e.g., falls) |
| | Subthreshold Parkinsonism and neurogenic OH | Medium (subthreshold Parkinsonism) High (OH) | In between | – Increased risk for complications due to mobility problems (e.g., falls) |
| | Other symptoms | Range from high (RBD) to medium (olfactory loss) or low (other features***) | In between | – Symptomatic OH increase risk for falls |
| Non-manifest mutation carriers | Monogenic or polygenic | Range from high (PRKN, PINK1, SNCA, PARK7), medium (LRRK2 or GBA1) or low (polygenic) | Early | – Exercise benefit may be high due to early disease stage, but needs a long trial time-frame for prodromal features to emerge to measure exercise efficacy |
| Environmental markers | Environmental factors**** | Low | Early | – Exercise benefit may be high due to early disease stage, but needs a long trial time-frame for prodromal features to emerge to measure exercise efficacy<br>– Physical inactive individuals may benefit more, but are less eager to be recruited and compliant to an exercise trial [12] and have a small increased risk of acute cardiac disease due to (aerobic) exercise [14]<br>– Older age with co-morbidities increase risk of exercise complications (e.g., falls, cardiovascular risk) |

DAT, Dopamine Active Transporter; OH, orthostatic hypotension; RBD, Rapid Eye Movement sleep Behavior Disorder *Likelihood of prodromal PD defined as low risk with LR < 5, medium risk with LR 5–20 and high risk with LR > 20 based on MDS prodromal research criteria. Of monogenic mutation carriers other than LRRK2 and GBA1 no LR is reported, yet the chance of developing PD at age 80 is 90–100% implying a high risk of developing PD. **Presumed disease stage categorized into 3 stages: early as > 10 years, in-between as 5–10 years and advanced as <5 years of symptom onset prior to PD diagnosis. ***Other symptomatology = excessive daytime somnolence, loss of cognitive function, orthostatic hypotension, constipation, depression and anxiety, erectile- and urinary dysfunction ****Other environmental factors = age, never smoker, physical inactivity, pesticides exposure, non-use of caffeine, first degree relative with PD.

## WHAT: WHICH EXERCISE COMPONENTS ARE SUITABLE FOR PD PREVENTION TRIALS

Exercise is divided into four components: aerobic-, resistance-, flexibility-, and neuromotor exercise [15]. We here describe the available evidence on their effect in PD to determine what type of exercise could potentially bear a disease-modifying effect in prevention trials. Table 2 highlights considerations for each exercise component.

### *Aerobic exercise*

#### *Moderate- to vigorous intensity exercise*

Aerobic exercise classifies into light-, moderate-, or vigorous-intensity exercise. The largest body of evidence is available on moderate- and vigorous exercise. Vigorous exercise stabilizes motor symptoms as measured with the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III by > 4.0 after 6 months of training in PD patients with mild disease severity [16, 17] with similar results for moderate exercise [18]. Trials of shorter duration also showed positive effect on mobility, non-motor symptoms such as depression [19], executive cognitive functioning [20, 21] and quality of life. Furthermore, animal models [22] and neuroimaging data [23] suggest that exercise improves preservation of basal ganglia networks by promoting adaptive plasticity. It remains uncertain whether this merely reflects a symptomatic or compensatory effect. We do not yet fully understand the exact pathophysiology of PD and lack

Table 2
**What exercise to study in exercise prevention trials?** *Considerations on the nature of the exercise intervention in prevention trials of Parkinson's Disease*

| Exercise component | Examples | Pros | Cons |
|---|---|---|---|
| 1. Aerobic exercise | Moderate to vigorous | – Most convincing evidence on symptomatic, neuro-imaging and animal studies on putative neuroprotective properties<br>– Able to be monitored remotely with wearables (see Table 4) | – Not feasible for all (co-morbidities, access to sports facilities)<br>– (Professional) supervision needed to train in specific heart rate zones<br>– Can be monotonous; challenging adherence |
| | Light | – Accessible for those who cannot engage in strenuous exercise (e.g., due to co-morbidity)<br>– No supervision needed<br>– Can be done in home environment<br>– Able to be monitored remotely with wearables (see Table 4) | – Probably needs a higher volume of exercise than moderate- to vigorous intensity exercise<br>– Time consuming, can be monotonous; challenging adherence<br>– No evidence available on effect in clinical studies in PD<br>– When using wearables, other objective monitoring options than walking/step count are not suitable |
| 2. Resistance exercise | Strength | – Considerable evidence on beneficial effect on (non)motor symptoms | – No imaging or animal studies to support potential neuroprotective properties<br>– Access to equipment/weights needed |
| 3. Flexibility exercise | Stretching | – No equipment needed, can be done from home<br>– Can be done at each part of the day | – Too scarce evidence to attribute potential disease-modifying effect |
| 4. Neuromotor exercise | Balance, agility, coordination | – Mostly a multicomponent sport often perceived as fun improving adherence | – Too scarce evidence to attribute potential disease-modifying effect<br>– Often sports that also include other exercise components, impeding to study distinct effect of neuromotor component. |

ultimate biomarkers for disease progression making it difficult to thoroughly investigate the underlying mechanisms and demonstrate potential disease modification through exercise. The ongoing SPARX 3 trial (NCT04284436) will give more insights in the mechanisms by which moderate- and vigorous exercise potentially have a protective effect by studying a selection of blood biomarkers and neuroimaging markers. Overall, we consider the evidence as convincing, making moderate- and vigorous exercise a suitable intervention for exercise prevention trials.

*Light intensity exercise*

In contrast to the evidence on the effect of moderate- and vigorous exercise, little evidence is available on light-intensity aerobic exercise, such as walking. One study showed that a small sample of PD patients with gait impairment improved walking distance after light-intensity exercise, which was a similar result compared to a vigorous exercise group [24]. However, this study lacked necessary potential biomarkers of disease progression to draw a conclusion on disease-modifying potential. Another study that included walking as light-intensity exercise intervention was a combined intervention with moderate- to vigorous exercise components which makes it impossible to draw a conclusion on the effect of light exercise alone [25]. This study, like the one mentioned above, also lacked necessary potential biomarkers of disease progression to draw a conclusion on disease-modifying potential. Despite these drawbacks in prospective controlled studies, epidemiological evidence indicates an inverse association between physical activity and PD risk, regardless of intensity [26]. Therefore, we hypothesize that even exercise of light intensity (but perhaps with a large volume) may impact the pathophysiological processes underlying PD. This could clinically have an enormous impact because exercise of light intensity is highly accessible, even to people who are not able to engage in strenuous exercise (e.g., due to co-morbidity).

*Resistance exercise*

Resistance training, or strength training has many positive effects, including improvements in motor symptoms [27–29], functional mobility (i.e., gait; timed-up and go) [27–32], muscle strength [32–34], balance [33, 34], cognitive functioning [35], quality of life [31], and depression [33]. Bone density has also been shown to improve [30] and preventing muscle weakness may prevent falls and alleviate fear for falling which contributes to reduced mobility and quality of life [36, 37]. However, most strength training studies performed in people with PD had small sample sizes that make it impossible to draw definitive conclusions about effectiveness [38]. In healthy people, increasing muscle strength is associated with lower all-cause mortality, cardiovascular disease and less risk of developing cancer and diabetes; interestingly, these effects appeared to be independent of aerobic activities [39]. These are interesting findings indicating potentially interesting physiological effects of strength training that might be of benefit to the pathological process of PD as well. Several mechanisms of action have been suggested to underlie a disease-modifying effect of resistance training in PD [40], but these assumptions are not yet supported by imaging data, animal studies or other biomarkers. Of note, compared to aerobic exercise, resistance exercise induces a different physiological pathway [41], mainly enhancing anaerobic capacity [42]. While the evidence that aerobic exercise can exert a disease-modifying effect is more convincing, we feel that it is worth exploring the effect of resistance exercise in a PD prevention trial. Subsequently, we believe it is worth investigating whether resistance exercise might offer complementary benefits when combined with aerobic exercise in a PD prevention trial.

*Flexibility exercise*

Aging leads to a reduction of flexibility resulting in reduced range of motion [15]. Regular flexibility training of all major muscle groups is recommended to mitigate the loss of range of motion; this may improve balance and stability [15]. People with PD may especially benefit as range of motion is progressively lost during the course of the disease. However, only a few flexibility trials have been performed in the PD field, and these demonstrated little positive symptomatic effects on gait speed when combined with resistance exercise [24]. Thus far, no study has examined the effect of flexibility exercise as mono-intervention in persons with PD [17, 38] and there are no studies evaluating any type of biomarker or hypothesizing a disease modifying effect. The available evidence is therefore too limited to justify formal testing for a potential disease-modifying potential, and more basic research into the underlying working mechanisms is needed first.

*Neuromotor exercise*

Neuromotor exercise can be defined as exercise combining different motor skills related to functional fitness. It refers to training of balance, agility and coordination [15]. There are many types of neuromotor exercise, and in people with PD, Tai-Chi, dance and adding dual task training are popular examples, that can improve motor functioning, in particular gait [43–46]. Moreover, balance exercise may reduce the risk of falls [47]. Neuromotor exercises, i.e., skill training, is included in many types of activities such as community-based exercise (e.g., boxing). However, these activities also include other exercise components like flexibility, strengthening or, when performed intensely, an aerobic component. Therefore, the effect of the neuromuscular component of those activities remains unclear. While the direct clinical effects of neuromotor exercise are very relevant, there are no studies evaluating any type of biomarker or hypothesizing a disease modifying effect. At this point, we therefore do not recommend using neuromotor exercise to test the neuroprotective effects of exercise.

## HOW TO DESIGN A PD PREVENTION TRIAL AND MEASURE EXERCISE ENGAGEMENT AND EFFICACY

*Methodological considerations*

Previous studies suggest that the putative disease-modifying effects of exercise translate into sustained improvements in clinical outcomes over long intervals (>5 years) [48]. This relatively long interval is relevant for the design of exercise prevention trials considering the prodromal phase of PD extends across several years. Combining different exercise components in research may yield complementary or perhaps even more synergistic effects but comes with the challenge of making it hard to identify which exercise component is responsible for the effects. Also, both placebo and nocebo effects have been described. It is extremely important to describe any intervention under study in detail. Different from pharmacological

trials there are many factors that impact the motivation for and the adherence to the intervention. For example, the expertise of the instructor or the location of the training, can play an important role. The Consensus on Exercise Reporting Template (CERT) [49] helps to standardize and structure the description and monitoring of exercise interventions to allow for replication and to identify confounders that might hamper interpretation of the study results.

Also personal circumstances (e.g., divorce, moving houses) can impact adherence. Moreover, facing stigmatization from being identified as having prodromal PD (e.g., feelings of shame, stress, emotional burden) may impact motivation. The consequence is that the intervention is not performed as intended. These variations in adherence to the prescribed exercise regime (i.e., considering duration, intensity or other type of activities) may confound the study results and create challenges in interpreting the outcomes. It is therefore important to monitor both the intervention and the control group closely.

Including an active control intervention may make it easier to monitor exercise activities in the control group and may be essential to maintain participant's blinding. Blinding is an important aspect of high-quality clinical trials to rule out bias because of expectations about the effectiveness of the used intervention(s). However, it is hardly possible in non-pharmacological interventions. With an active control group an attempt could be made to blind participants to which intervention is expected to be (more) effective. The downside is that an active control group reduces the contrast between both interventions, making it challenging to identify subtle but real exercise effects and making it necessary to include larger samples. One option to deal with this is to first compare exercise to regular care, with maximum contrast, and only in case of a positive outcome, to follow this up with more detailed studies to examine the precise underlying working elements (i.e., types of exercise) and working mechanisms.

Maintaining adequate adherence to the exercise intervention will be a key factor to optimize the chances of finding benefits in PD prevention trials. An important motivator for people with PD to remain engaged in exercise is a perceived positive effect on PD symptoms [13]. Since participants in a PD prevention exercise trial (who by definition have prodromal parkinsonism, and therefore only limited to no symptoms) will likely not experience such a symptomatic benefit, and this may well hamper adherence. To mitigate this, we anticipate that the use of a range of motivational strategies might be helpful to promote adherence, for example by rewarding participants with new knowledge or insight as a reward for reaching their exercise targets [13] or including 'biofeedback' feedbacking information about the body (e.g., physiological parameters) to the participant using an external monitoring device [50]. Another challenge will be to manage adherence of research participants in an active-control group, who will also have to adhere for a long time to whatever program they were assigned to. Again, motivational strategies are potentially promising in this regard and need further study.

A new approach to clinical trials, that fits exercise prevention trials very well, is performing a trial completely remotely (i.e., fully in the participant's own home living environment, without need to travel to more distant institutions to measure the outcomes). This option is interesting, for several reasons. First, home-based exercise may support adherence with a long-term intervention. Second, it is a scalable solution for the inclusion of high numbers of participants, also in potentially geographically harder-to-reach populations. Third, home-based exercise without the need of expensive exercise equipment will enable inclusion of participants from low socioeconomic regions, thereby addressing one of the vexing issues related to diversity in clinical trials [2]. Finally, any intervention that is delivered close to the participant's home gives insight in the real-life effects.

### *Considerations to measure exercise engagement and efficacy*

Because of the long duration of prodromal PD, it will take considerable time before individuals show phenoconversion to clinically manifest PD. Therefore, exercise prevention trials should incorporate intermediate measures of disease progression that can be serially assessed while participants are still in the prodromal phase. Since there are currently no validated clinical scales for quantifying prodromal features, a sensible approach could involve utilizing clinically validated scales for (non)motor symptoms in PD [51], with a particular focus on symptoms emerging in the prodromal phase [3, 4]. Additionally, monitoring exercise adherence and engagement will be crucial. Wearable technology can be used to objectively measure the adherence to exercise [52], as well as study outcomes, over a prolonged period of time. Since these outcomes are not fully validated yet, we can, at this point, only use them as exploratory out-

Table 3
**How to measure exercise in PD prevention trials?** *Considerations on how to measure exercise engagement*

| Exercise component | | Exemplary mode of measurement | | Exercise | | | | |
|---|---|---|---|---|---|---|---|---|
| Aerobic | Parameter | Clinical | Digital | Light | Moderate | Vigorous | Pros | Cons |
| | Heart rate (bpm) [15] | GXT [59] | Wearable sensor [52] | HRmax: 57–63%<br>HRR: 30–39% | HRmax: 64–76%<br>HRR: 40–59% | HRmax: 77–95%<br>HRR: 60–89% | – Usable in range of activities (e.g., cycling, swimming, running) | – Light intensity exercise is hard to distinguish from resting due to consistently beating heart<br>– Autonomic dysfunction may influence heart rate |
| | VO2max (ml/kg/min) [15] | GXT [59] | Wearable sensor [60] | 37–45% | 46–63% | 64–90% | – Reflect the gold standard of metabolic activity and fitness | – GXT is an in-clinic assessment<br>– Expert needed for GXT<br>– GXT requires maximum effort from participant, potentially increasing burden<br>– Wearables estimate VO2max (i.e., not directly measure) |
| | Perceived effort (6–20) [15] | BORG-scale [61] | BORG-scale [61] | 9–11 | 12–13 | 14–17 | – Usable in range of activities (e.g., cycling, swimming, running)<br>– Quick and easy to use | – Subjective measure |
| | Step count (/min) [54, 55] | Count cadence manually | Wearable sensor [52] | <100 | 100–130 | >130 | – Usable in range of activities (e.g., cycling, swimming, running) | – Only usable for walking or running |
| Resistance | Perceived effort (0–10) [15] | OMNI-scale [62] | OMNI-scale [62] | 2–4 | 5–7 | 8–10 | – Quick and easy to use | – Subjective measure |
| | One-repetition maximal [15] | Diary | Diary | 1RM: 30–49% | 1RM: 50–69% | 1RM: 70–84% | – Quick and easy to use | – Personal trainer needed to determine 1RM<br>– Subjective tracking of engaged exercise<br>– Exercise material with measurable, adjustable, resistance needed to measure 1RM |

bpm, beats per minute; GXT, Graded-exercise test; HRmax, maximum heart rate; HRR, heart rate reserve; ml, milliliter; kg, kilogram; min, minute; 1RM, One-repetition maximal.

Table 4
**How to measure exercise efficacy in PD prevention trials?** *Considerations to measure efficacy of exercise intervention*

| | Exemplary outcomes | |
|---|---|---|
| | Clinical | Remote |
| Cardiorespiratory fitness | | |
| VO2max [16, 17] | GXT [59] | Wearable sensor [59] |
| Resting heart rate [60] | GXT [59] | Wearable sensor [52] |
| Motor symptoms | | |
| Bradykinesia (arm swing, dexterity) [16–18] | MDS-UPDRS [51] | Smartphone app [61]<br>Accelerometer [62] |
| Tremor (rest, postural, action) [16–18] | MDS-UPDRS [51] | Smartphone app [61]<br>Accelerometer [62] |
| Gait [16–18] | MDS-UPDRS [51] | Smartphone app [61]<br>Accelerometer [62] |
| Non-motor symptoms | | |
| Olfactory loss [63] | UPSIT [64] | UPSIT [64] |
| Cognition [35, 65, 66] | MoCA [67] | cCOG test battery [68] |
| Depression and anxiety [19] | HADS [69–71] | HADS e-questionnaire |
| Autonomic dysfunction [72] | SCOPA-AUT [51] | SCOPA-AUT e-questionnaire |
| Sleep [72, 74] | SCOPA-Sleep [51] | Wearable sensor [73]<br>SCOPA-Sleep e-questionnaire |

We omitted rigidity from motor symptoms as it currently cannot be accurately measured with wearable sensors. GXT, Graded exercise test; MDS-UPDRS, Movement Disorder Society-Unified Parkinson Disease Rating Scale; UPSIT, University of Pennsylvania Smell Identification Test; MoCA, Montreal Cognitive Assessment; cCOG, computerized cognitive tool; HADS, Hospital Anxiety and Depression Scale; SCOPA-AUT, SCales for Outcomes in PArkinson's disease – Autonomic Dysfunction; SCOPA-Sleep, SCales for Outcomes in PArkinson's disease – Sleep.

comes and not as primary outcome [53]. Using heart rate, VO2max and the perceived exertion during exercise are recommended surrogates to monitor different intensities of aerobic exercise [15]. In Table 3, we highlight our considerations with respect to measures that could be used to document and monitor treatment adherence. Additionally, recent work showed the potential of measuring step counts as a remotely collected measure of the volume of physical activities [54, 55]. For strength training, a percentage of an individual's one-repetition maximum (1RM) and perceived exertion may be used to measure adherence to a resistance training regime [15].

If exercise intervention is not delivered in-clinic but remotely [2], as suggested in the previous paragraph, then exercise engagement and outcome assessments should also be assessed remotely. To achieve this, clinically validated scales for (non)motor symptoms in PD cannot be used. An innovative approach would be to leverage digital biomarkers of emerging prodromal features, to estimate the severity of prodromal pathology and exercise engagement. Digital biomarkers hold the additional benefit of acquiring objective, high-frequency serial data compared to clinical scales [56]. While such digital outcomes are being developed, these still require further validation, and pending this, can be used as exploratory outcomes. In Table 4, we highlight intermediate prodromal outcomes that could potentially measure the outcome of an exercise intervention in the prodromal phase of PD.

However, in order to show a truly disease modifying effect, digital biomarkers are not enough because we need to separate putative disease modifying effects from merely symptomatic improvements. For example, a beneficial effect on constipation may reflect a symptomatic effect of exercise, rather than a protective effect on degeneration of the autonomic nervous system. Therefore, the assessment of digital biomarkers should be complemented by a pre- and post-treatment assessment of fluid blood-based biomarkers (blood/cerebrospinal fluid) and brain imaging biomarkers of the actual underlying neurodegeneration. Measuring these different markers in concert will make it possible to identify the (potentially different) pathways by which exercise may be protective, for example by induction of neuroplasticity or inhibition of neuroinflammation [57] and neurodegeneration. Exercise has demonstrated a beneficial effect on functional connectivity [23], but little is known about the effect of exercise on other specific imaging modalities. Therefore, we rec-

ommend to include generic fluid- and brain imaging markers [58] in PD exercise prevention trials to study exercise-specific effects.

## KEY MESSAGES

- It is possible to use risk biomarkers to identify eligible participants for a future Parkinson prevention study that uses exercise as a possible disease-modifying intervention. A disadvantage to this approach is that these participants enter the trial while still in a very early disease phase, thus reducing the likelihood of finding effect on their prodromal features (if any) within the timeframe of the prevention trial.
- When considering the nature of the exercise intervention in a future Parkinson prevention study, it is logical to start with an intervention that has been shown to not only have symptomatic effects in alleviating (non)motor symptoms, but for which evidence exists for a possible disease-modifying effect as well. The strongest evidence is available for moderate to vigorous aerobic exercise, followed by resistance exercise.
- Combining different exercise components in PD exercise prevention trials may yield complementary or perhaps even more synergistic effects but comes with the challenge of being unable to identify which exercise component is responsible for these effects.
- Ideally, PD exercise prevention trials are performed remotely, in the own living environment of the participants. This includes the need to deliver the intervention remotely, and also to measure the adherence to the intervention as well as the outcomes remotely. This may be achieved by leveraging digital biomarkers (e.g., as collected from wearable sensors), although further validation remains required before this can be used as primary outcomes.
- The outcome assessment in future Parkinson prevention studies should include a pre- and post-exercise assessment of fluid biomarkers (blood/cerebrospinal fluid) and brain imaging biomarkers of mechanisms that could mediate the putative protective effects of exercise.

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## CONFLICT OF INTEREST

BRB currently serves as Editor in Chief for Journal of Parkinson's disease, but was not involved in the peer-review process nor had access to any information regarding its peer review. He also serves on the editorial board of Practical Neurology and Digital Biomarkers; has received honoraria from serving on the scientific advisory board for AbbVie, Biogen, and UCB; has received fees for speaking at conferences from AbbVie, Zambon, Roche, GE Healthcare, and Bial; and has received research support from the Netherlands Organization for Scientific Research, The Michael J. Fox Foundation, UCB, AbbVie, the Stichting Parkinson Fonds, the Hersenstichting Nederland, the Parkinson's Foundation, Verily Life Sciences, Horizon 2020, the Topsector Life Sciences and Health, the Gatsby Foundation, and the Parkinson Vereniging. NMdV is an Editorial Board member for this journal but was not involved in the peer-review process nor had access to any information regarding its peer review. SKLD is an Editorial Board member for Neurology and also for Brain Sciences. He is also Associate Editor for Frontiers of Neurology.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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