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Lifestyle Interventions for the Prevention of Parkinson Disease

A Recipe for Action

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Abstract

The prevalence of Parkinson disease (PD) is growing fast, amplifying the quest for disease-modifying therapies in early disease phases where pathology is still limited. Lifestyle interventions offer a promising avenue for preventing progression from prodromal to manifest PD. We illustrate this primarily for 1 specific lifestyle intervention, namely aerobic exercise because the case for the other main lifestyle factor (dietary interventions) to modify the course of prodromal PD is currently less persuasive. Various observations have hinted at the disease-modifying potential of exercise. First, studies in rodents with experimental parkinsonism showed that exercise elicits adaptive neuroplasticity in basal ganglia circuitries. Second, exercise is associated with a reduced risk of developing PD, suggesting a disease-modifying potential. Third, 2 large trials in persons with manifest PD indicate that exercise can help to stabilize motor parkinsonism, although this could also reflect a symptomatic effect. In addition, exercise seems to be a feasible intervention, given its minimal risk of side effects. Theoretical risks include an increase in fall incidents and cardiovascular complications, but these concerns seem to be acceptably low. Innovative approaches using gamification elements indicate that adequate long-term compliance with regular exercise programs can be achieved, although more work remains necessary to demonstrate enduring adherence for multiple years. Advances in digital technology can be used to deliver the exercise intervention in the participant's own living environment and also to measure the outcomes remotely, which will help to further boost long-term compliance. When delivering exercise to prodromal participants, outcome measures should focus not just on phenoconversion to manifest PD (which may well take many years to occur) but also on measurable intermediate outcomes, such as physical fitness or prodromal nonmotor symptoms. Taken together, there seems to be sufficient evidence to advocate the first judicious attempt of investigating exercise as a disease-modifying treatment in prodromal PD.

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Glossary

PD = Parkinson disease; **RCT** = randomized controlled trial; **SPARX** = Study in Parkinson Disease of Exercise.

Parkinson disease (PD) currently affects more than 6 million people worldwide, and its prevalence is projected to further rise considerably in the next decades.[1] In persons with PD, pathologic processes are already advanced at a time when the clinical diagnosis is made, particularly when realizing that the prodromal period may span up to 2 decades or more.[2] This relatively late timing of the diagnosis likely explains why it has proven so difficult to slow disease progression in persons with clinically manifest PD.[3] Against that background, interest has risen in delaying or even preventing the onset of clinically manifest PD by intervening in a much earlier disease phase, namely in the prodromal phase of PD.

Driven by new insights into the pathophysiology of PD, various pharmacologic interventions have been developed that can potentially modify the course of PD.[4] In this study, we will focus on a complementary approach, namely targeting lifestyle to prevent the onset of manifest PD. Various lifestyle factors have been associated with a reduced risk of developing PD. Probably the most promising and best studied candidate target for disease modification is exercise,[5] primarily referred to in this article as (the volume and intensity of) aerobic exercise. Specifically, various studies have shown that regular physical activity is associated with a reduced PD risk.[6-8] The Park-in-Shape and Study in Parkinson Disease of Exercise (SPARX) trials, both phase 2 exercise trials, have shown stabilization of motor symptoms after 6 months of aerobic exercise.[9,10] Furthermore, preliminary neuroimaging evidence from the Park-in-Shape trial—where both structural and functional magnetic resonance imaging scans were performed before and after exercise—suggests that engaging in regular aerobic exercise can be associated with an improved preservation of the basal ganglia network.[11] These human findings corroborate animal studies in rodents with experimental parkinsonism, which demonstrated that aerobic exercise protects the integrity of the mesencephalic dopaminergic network and can promote adaptive plasticity in basal ganglia circuitries.[12] The precise working mechanisms remain unknown, although several modes of action have been suggested, that will be discussed in more detail in this article.[13,14]

Other lifestyle factors have also been considered, but the case for their disease-modifying potential is less persuasive. Some dietary patterns are associated with a reduced risk of developing PD. Examples include a Mediterranean diet (containing high levels of vegetables, fruits, [poly]unsaturated fats, whole grains and nuts),[15] diets that are low in dairy,[16] moderate in alcohol or high in caffeine,[6] and diets with urate-increasing properties.[17] One concern is the nature of dietary interventions and the resultant careful and fully remote control of meals, which would be necessary over a long period of time to conduct such a study. Additional concerns relate to the difficulty in isolating a single dietary intervention as the solitary factor that affected on the PD risk, particularly in historical studies where recall for dietary habits is challenging and also because healthy diets tend to coincide with other beneficial lifestyle habits. Moreover, unlike exercise, the underlying working mechanisms for these dietary factors are less clear, and there is no good evidence to suggest an effect in persons with manifest PD whether this be symptomatic or disease-modifying.

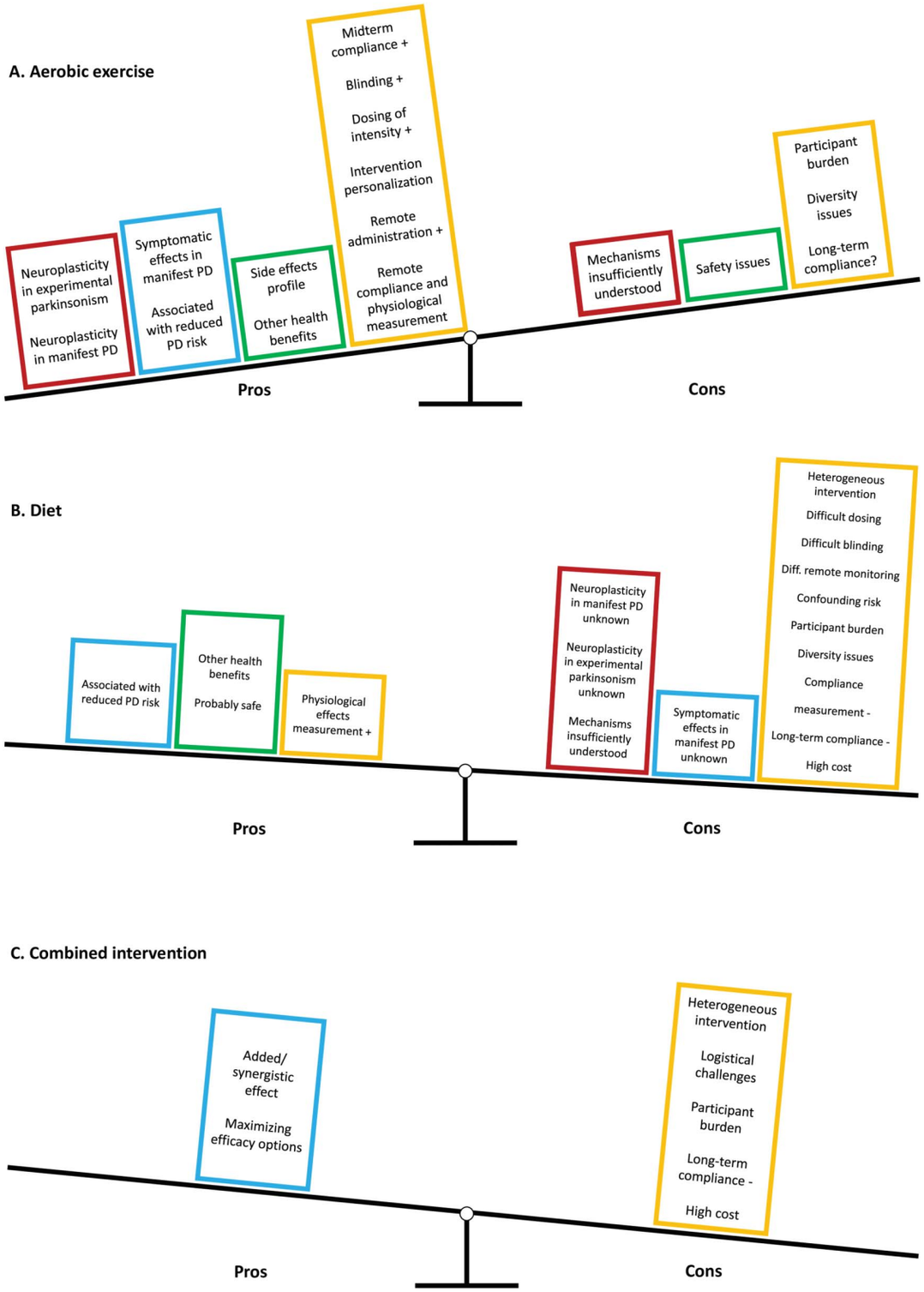
In this article, we focus primarily on exercise as the most promising lifestyle intervention that, when experimentally manipulated in participants in a prodromal phase, could potentially slow down or even prevent progression to manifest PD. Several challenges must be addressed before exercise can qualify as a lifestyle intervention that is sufficiently promising to be taken to the test in a prevention trial of PD. In this study, we critically review 4 of the most important boxes: underlying working mechanisms, presumed efficacy in both prodromal and manifest PD, side effects profile, and issues related to feasibility (Figure 1A). Moreover, we provide a "recipe" for future exercise trials (Figure 2).

Whom to Target?

Other publications in this special issue address this topic in more detail. We only briefly discuss elements that are specifically relevant when considering exercise as an intervention to prevent PD. The most straightforward answer is that it is unknown what subgroups of (prodromal) PD will benefit most from exercise. It is possible that certain (sub)populations in specific phases of disease progression are already at an inevitable risk of developing manifest PD or that exercise is simply not effective in persons with specific causes of PD.[4] However, unlike pharmacologic interventions which are targeting specific pathophysiologic processes, exercise can—at least theoretically—be regarded as a fairly cause-agnostic intervention that may well be effective for a very heterogeneous PD population, regardless of the specific etiology or underlying disease mechanism. When discussing exercise to prevent PD, 2 populations can be considered, each with their specific advantages and challenges: asymptomatic mutation carriers[18,19] and persons with 1 or more prodromal features.[20]

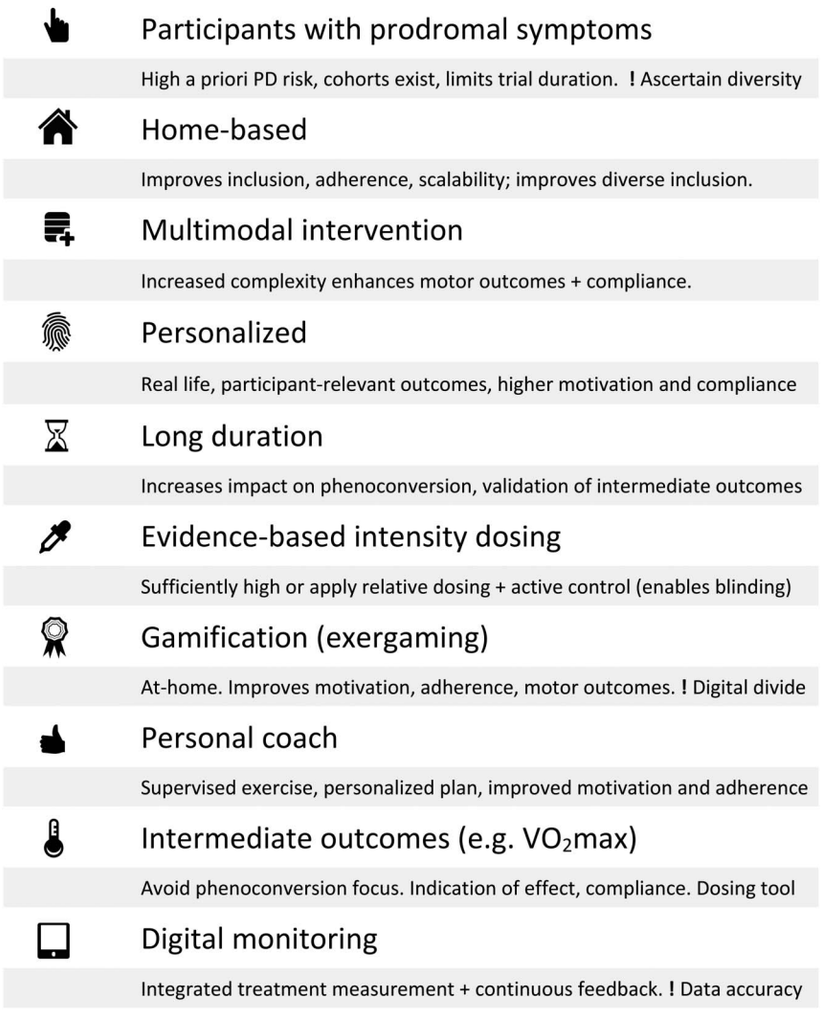
Exercise studies will require an extensive duration of the intervention to achieve a tangible impact on disease progression, which may well be uninviting for mutation carriers because they are usually asymptomatic in early disease phases. Another concern relates to external validity because it is uncertain whether positive findings in mutation carriers can automatically be extended to the broad spectrum of person

Figure 1 Advantages and Disadvantages for 3 Approaches to Lifestyle Interventions in Prevention Trials of PD: Increasing (Aerobic) Exercise (A), Changing the Dietary Pattern (B), or a Combined Multifaceted Intervention (C)



Working mechanism (red), efficacy (blue), side effects profile (green), and feasibility (orange). + and − indicates evidence-based positive or negative performance of the specific (dis)advantage. PD = Parkinson disease.

Figure 2 Recipe for Future Exercise Trials



Exclamation marks indicate important precautions for the recommendation. PD = Parkinson disease.

with prodromal PD, most of whom likely have a multifactorial underlying etiology.[21]

Interventions in these genetically defined cohorts might therefore primarily serve as proof-of-concept trials for cohorts that are more representative of the broad spectrum of persons with PD.

A specific advantage of persons with prodromal symptoms in relation to exercise is the notion that it might be possible to shorten the trial duration because multiple prodromal features seem to develop only a limited number of years before the diagnosis of manifest PD, although with large variability across at-risk individuals.[22]

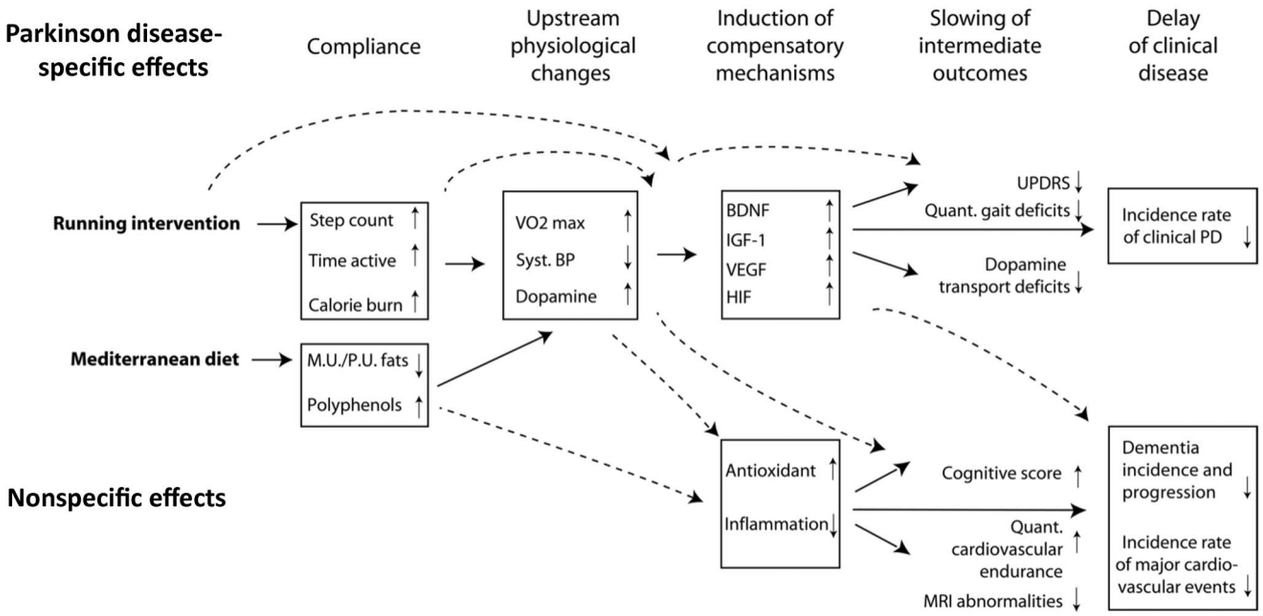
Finally, 1 currently active phase 2 trial investigates the disease-modifying effects of exercise in participants with drug-induced parkinsonism hypothesized to be at an increased risk of manifest PD (ClinicalTrials.gov Identifier NCT02598973). The external validity of this presumed prodromal subgroup to the broader PD spectrum is unclear.

Other Considerations

Having a sedentary lifestyle could be included as enrichment factor, thus ascertaining inclusion of a subgroup with a putatively higher-than-average PD risk and one that is perhaps more likely to benefit from an increase in physical activity levels.[23] A challenge is that particularly those with a sedentary lifestyle are precisely the ones that are least eager to be recruited into trials of physical exercise.[5,24]

Because subgroup differences in effectivity of exercise interventions are not yet elucidated, future PD prevention studies should specifically address diversity, ascertaining inclusion of a representative population by deploying a proactive outreach to typically difficult-to-reach subgroups regarding factors such as geography, socioeconomic status, sex, and race. For example, evidence is increasing that PD presents very differently

Figure 3 Hypothetical Logic Model That Can Be Used for the Evaluation of Lifestyle Intervention Trials for the Prevention of Manifest Parkinson Disease



Dotted lines indicate unknown mediating mechanisms. For physical activity and diet, we have highlighted 1 conceptual pathway through which these interventions may exert their effects. BDNF = brain-derived neurotrophic factor; HIF = hypoxia-inducible factor; IGF-1 = insulin-like growth factor 1; M.U./P.U. = monounsaturated and polyunsaturated; Syst. BP = systolic blood pressure; VEGF = vascular endothelial growth factor.

in men and women[25]; it is conceivable that both the adherence to exercise and the resultant effects may show a relevant sex difference.

Regarding exclusion criteria, individuals deemed unable to achieve a tangible adjustment in lifestyle pattern would presumably have to be excluded. Similarly, medical conditions that markedly hamper mobility should probably be an exclusion criterion for exercise studies.

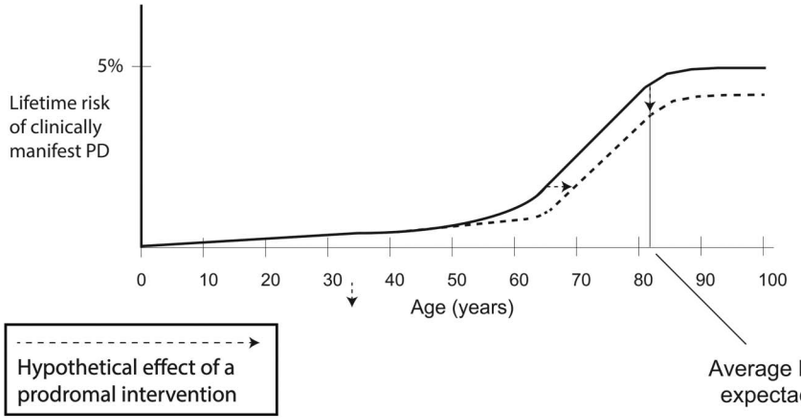
Efficacy and Working Mechanisms

Exercise

Several observational cohorts established an association between physical activity and reduction of future PD risk.[6-8] Whether experimentally manipulating the intensity and frequency of physical activities can slow down progression from prodromal to manifest PD is unclear because no interventions have been performed in at-risk individuals. It is also unknown whether an exercise intervention can slow long-term progression in persons with already manifest PD, although some recent studies have carefully hinted at this possibility. Two phase 2 randomized controlled trials (RCTs; the Park-in-shape and SPARX studies) showed that aerobic exercise for 6 months stabilizes Movement Disorders Society revision of the Unified Parkinson Disease Rating Scale motor symptoms, but the effects beyond that period remain unknown.[9,10] The Park-in-Shape trial additionally showed a significant improvement of VO_2max in the intervention group.[9] The SPARX trial suggested that a higher intensity of exercise (80%–85% of maximum heart rate) is associated with better motor outcomes than a lower dose (60%–65% of maximum heart rate),[10] although this was not seen in an earlier trial.[26] A widely held assumption is that an aerobic component of the exercise intervention is pivotal for establishing clinical effects,[9,10,27] but this is not entirely certain: resistance exercises, balance training, yoga, and dance interventions (even when not necessarily strenuous) can also improve various motor symptoms, although there is less evidence for these interventions.[28] One further RCT directly assessed this by directly comparing aerobic exercise (treadmill walking) and ("non"aerobic) stretching and resistance exercises. As expected, an increase in VO_2max was only seen in the treadmill arm, but an improvement in walking speed after 3 months was seen in the aerobic and nonaerobic arms, without between-group differences.[26]

One further consideration may be relevant for the design of PD prevention studies, and this relates to the complexity of the exercise intervention. Combining aerobic exercise with a dual-task or exergaming component seems effective.[28] For example, the V-TIME trial showed that adding virtual reality components to an aerobic intervention consisting of treadmill exercises was more effective in reducing the frequency of falls than treadmill training alone.[29] This might suggest that a similar multimodal intervention could be tested in future trials to prevent PD.

Figure 4 Illustration of Lifetime Risk of Manifest PD



Introduction of a disease-modifying therapy that delays onset by a few years could result in a significant change in PD incidence in middle and older age. PD = Parkinson disease.

More work remains needed to decipher the mediating mechanisms of the effects of exercise as a putative disease-modifying intervention, although there are some insights stemming from work in rodents with experimental parkinsonism and studies in persons with manifest PD. The animal work identified various pathways as neuroprotective physiologic responses to energetic stress induced by aerobic exercise in rodents, including adaptive changes in brain-derived neurotrophic factor, insulin-like growth factor 1, vascular endothelial growth factor, and hypoxia-inducible factor, inducing angiogenesis, neurogenesis, and synaptogenesis (summarized in a hypothetical logic model Figure 3).[14] These rodent studies also showed that physical activity normalizes dopamine levels in the nigrostriatal axis, but the exact mechanism that underpins this effect remains unknown.[12] Importantly, the translation of these findings to humans remains largely uncertain. In humans with PD, 2 functional MRI studies showed evidence of altered functional connectivity in thalamocortical and basal ganglia networks after intense exercise compared with an active control.[11,30] One of these studies also showed persistence of this strengthened functional connectivity at 1 month postintervention.[30] Taken together, epidemiologic and clinical studies suggest that increasing exercise levels in people at risk for PD might delay the onset of PD. Shifting the disease onset by a few years could already result in a significantly reduced PD incidence in older age,[31] which is shown in Figure 4.

Combined Intervention

When planning future prevention trials, we should decide between either a specific unidimensional intervention such as exercise or to potentially enhance the efficacy by opting for a multidimensional set of healthy lifestyle habits, for example, by combining exercise with a healthy diet. We believe that there is currently insufficient evidence to justify a PD prevention trial using a dietary intervention alone (Figure 1B), but there is an argument to be made for combining it with exercise. Specifically, this combined approach may be more efficient than launching multiple RCTs for individual lifestyle elements. In addition, this could maximize the efficacy of the intervention because the different physiologic mechanisms might have an additive or even synergistic effect. However, without robust baseline research, paradoxical effects—where the different elements of the intervention might modify or even antagonize each other—cannot be ruled out. Such a combined intervention might also introduce greater heterogeneity in baseline variables, such as preintervention activity levels or dietary habits, making outcome measurement more difficult, necessitating high numbers of participants. Furthermore, in the scenario where such a combined intervention is effective, it would be impossible to decide which component ultimately yielded the greatest efficacy. Importantly, combined interventions come with rather drastic changes in daily life and may lead to high participant and partner burden, thereby challenging long-term compliance. Indeed, a lower adherence to a combined lifestyle intervention is likely to compete with its advantages.[32] Multifaceted interventions may also require multimodal monitoring and outcome measurements to document the effect of the various interventional components, creating logistical challenges and causing greater costs (Figure 1C). Finally, interactive effects of the various lifestyle interventions cannot be ruled out at this stage, which makes factorial RCTs unsuitable.

A final important decision to take is whether to make the intervention uniform across all participants or to customize the intervention according to the specific abilities and preferences of each participant. Advantages of uniform interventions are the feasibility and efficiency for therapists and researchers, as well as the more convenient determination and homogeneity of intervention effects. However, individually tailored interventions are by definition more in line with participants' real life, and the treatment response is likely more relevant for the individual. It is conceivable that PD prevention trials will be launched in which the exact nature of the exercise intervention (e.g., running, cycling, or swimming)

is less important than the amount of aerobic workout that is ultimately achieved. Personalized interventions will probably also improve adherence, which is particularly important because PD prevention trials will likely require a time frame of multiple years.

Side Effects Profile

Exercise seems to have few side effects. Fall-related injuries are not expected among participants in the prodromal phase because significant gait disorders that jeopardize balance typically only appear in persons with more advanced disease. The earliest gait abnormality, a reduced arm swing, is unlikely to increase the risk of falls. Another early change in gait is a slowing of walking velocity, which if anything may reduce the risk of injuries. Importantly, there was no increase in number of falls during exercise interventions in individuals with PD.[9,10]

Another theoretical risk is cardiovascular events triggered by strenuous exercise or the inability to adequately adapt the cardiovascular system to the exercise requirements because of autonomic dysfunction.[33] Before inclusion in exercise interventions, cardiovascular screening should therefore be considered.[33] In an earlier exercise study in persons with manifest PD, such cardiovascular screening adequately identified a small number of persons with contraindications for exercise, and no cardiovascular complications were seen in the cohort that safely passed this screening test.[9] Notably, before inclusion, eligible participants should not only hear about the possible risks but also about the potential other beneficial effects of exercise, including improvements in cardiovascular risk.[27,34]

Exercise may also have various beneficial effects on nonmotor functioning. Specifically, beneficial effects of exercise on cognitive function,[35] sleep and fatigue,[13] depressive symptoms,[35,36] and constipation,[35] as suggested in other diseases, may also apply to PD. Therefore, exercise may exert both effects that are unique to PD[11] and effects that are also observed in other conditions. As nonmotor functioning is scarcely included as primary outcome and studies were often underpowered, further research on the effectiveness and mechanisms of exercise interventions for nonmotor functioning is needed.[27] Furthermore, exercise might also alleviate pathologic processes indirectly through its beneficial influence on the gut microbiome and mental stress,[37] both implicated in PD pathogenesis. The fact that exercise likely has multifaceted beneficial working mechanisms makes exercise a relatively complex potential disease-modifying treatment to study.

Feasibility

Blinding

Blinding of participants in exercise interventions to reliably measure outcomes is difficult. In addition to the selection of objective outcome measures and blinded assessment, we currently address the challenge of adequate blinding in a remotely supervised home-based exercise intervention called STEPWISE (ClinicalTrials.gov Identifier: NCT04848077). In this study, we use a relative blinding approach together with an active control group using a customized app on the smartphone: instead of defining the absolute exercise target regarding, for example, number of steps taken, all participants increase their baseline exercise level to a different degree. This ranges from a small proportional increase which serves as control to either a medium-large or very large proportional increase which serves as the active intervention groups. Everyone is rewarded for achieving that relative and personalized target. It should be noted that this control group in an exercise intervention trial should not be required to reduce current physical activity levels. This is, however, unlikely to complicate the formation of a suitable control group because daily activity levels in de novo PD are currently below recommendations for daily physical activity.[38] The feasibility of an active control group was previously shown by a home-based study which compared aerobic exercise on a stationary bicycle with an active control intervention consisting of stretching exercises.[9] Participants in both arms received gamification elements to promote compliance, and both groups were told at baseline that they were receiving an active intervention.[9] Compliance in both groups was excellent, and debriefing after study completion showed that participants in both study arms felt that they had received the active intervention.

The success of blinding should be assessed by asking (blinded) participants and study personnel about their perceived awareness of intervention arm allocation. Researchers should be aware of the risks of this method, most prominently misinterpretation of "flawed" blinding.[39]

Remote Trials

Trials to prevent PD should probably be home-based, for at least 2 reasons. First, in-clinic delivery of interventions jeopardizes the rate of inclusions and hampers adherence to a long-term intervention.[29] Second, the planned trials should probably include large numbers of participants. Remote administration makes lifestyle interventions more scalable and can perhaps also address the issue of diversity, enabling inclusion of more geographically remote and other harder-to-reach populations.

Recent PD trials suggest that home-based therapy can stabilize the progression of motor symptoms.[9,10,40] Importantly, for physical activity interventions, group therapy where participants interact with peers is typically a motivational factor,[41] which cannot be satisfied by a completely remote administration—although the group element can also be reproduced online. One example of a home-based intervention is the Park-in-Shape study, in which exergaming was administered remotely. All participants received a stationary bicycle at home equipped with connected virtual reality software that guided participants through the prescribed exercise. Supervision was kept to a minimum, although a personal coach was available remotely

through telephone. This approach resulted in good compliance for 6 months, which would translate to midterm compliance in PD prevention exercise trials.[9]

In low socioeconomic regions, home-based lifestyle trials can be effective without the need for expensive exercise equipment. One RCT administered a physical activity and dietary intervention using goal setting and education about healthy lifestyles, while remotely available therapists provided support and applied motivational interviewing to improve motivation and adherence. With only 1 baseline and 1 follow-up center visit at 6 months, this resulted in improvement of cardiovascular risk factors in rural adults.[42]

Digital technology can be used to measure the outcome of exercise studies. For example, levels of physical activity can be documented continuously or periodically using body-worn sensors (smartphone, smartwatch, or 1 or more activity trackers) and through connected equipment such as motorized treadmills or stationary bicycles. Automated remote measurement of the achieved level of exercise is important because this enables direct feedback to the participant and between the participant and the supervising therapist.[9] In addition, recording data automatically reduces data collection burden for participants and increases data granularity, allowing for more intelligent data analysis. Alternatively, participants could be instructed to actively register their activities with their own device.[43] This "bring your own device" approach has the advantage of not requiring additional materials, saving costs and lowering the burden of use for participants. The accuracy of tracking activities using wearable sensors is still suboptimal, which has to be taken into account when relying on these measurements.[44] Digital diaries can collect patient-reported outcomes; these have advantages over paper-based diaries, allowing for automatic calculation of compliance, direct communication to the trial supervisor, and direct feedback.

The so-called digital divide, a divide between populations determined by the ability to benefit from digital technology, remains an area of concern. Populations in PD prevention trials will likely be older and cannot be assumed to be proficient in digital technology. In a population of adults older than 40 years, conceptions regarding mobile health included feelings of discomfort, lower efficacy, and lower acceptability.[45] Therefore, the complexity of mobile health should be well-fitted to the study population, and participants should be involved in the design phase of a new mobile health solution, which we have successfully incorporated in STEPWISE (NCT04848077).

Compliance

Good compliance is key for intervention studies that take years, but this is notoriously challenging. Lifestyle interventions differ from other therapies such as medication because they fully depend on active participation and because lifestyle is not a novel intervention but already an integral part of life. Earlier long-duration prevention trials showed good compliance in fields outside neurology.[34] People with PD generally comply well with (remotely) supervised exercise programs in clinical trials,[9,10] but maintaining a physically active lifestyle outside the setting of a clinical trial provides many challenges.[41,46] Motivation could differ significantly across different high-risk populations. For example, this might depend on the perceived risk of actually developing PD, the presence of any prodromal symptoms (which could be perceived as alarming), and presence of symptoms or signs that interfere with long-term compliance, including depressive symptoms, apathy, and joint or muscular pain. Identifying the barriers and motivators to engage in an exercise intervention should be performed for each specific target population to guide the right strategy to optimize compliance.[41]

Various factors can help to promote compliance. Involving participants in the why and what of the research and, importantly, actively involving them already in the design phase is essential for motivation and adherence.[47] This also improves inclusion in trials and ascertains better compliance. Moreover, this allows active participants to assist in identifying clinically relevant research questions and problem-solving, thereby boosting the societal impact of research. For participants, knowing that they contribute to new insights in PD pathophysiology and treatment is a major motivator for participating.[48]

Second, availability of a therapist during the intervention may improve adherence, at the cost of having to deploy more research personnel.[9,40] For example, regular (in-person or telephone) contact with a health care professional motivates participants in exercise trials because they know they are being monitored.[41] Advances in mobile technology also allow for remote monitoring and improving adherence to an active lifestyle,[46] and exergaming is an important exercise-specific example.[9,28,29] Social support is an important motivational factor,[41] and smartphone applications can enhance engagement of participants by providing feedback, rewards, and by involving fellow participants or partners for social support.[43,46] However, research on the cost-effectiveness of regular in-person contact and other mHealth applications is conflicting and remains especially challenging in low-income areas.[49]

Outcome Measurement

Although PD is a steadily progressive disease, phenoconversion is a rather crude outcome that may take years to reach. Lifestyle trials will likely require many years to show an effect on phenoconversion. Therefore, physiologic and functional intermediate outcomes are additionally needed as surrogate markers (Figure 3). For example, cardiorespiratory effects such as VO_2max reflect the physiologic intensity of exercise and estimate the achieved duration and intensity of the intervention. Patient-reported outcome measures or functional tests such as the 6-minute walking test or Timed Up and Go are clinically relevant reflections of symptomatic

effects. This is important because low expectations are an important barrier for participation in exercise.[41] Notably, absence of effect on these intermediate outcomes does not exclude a possible disease-modifying effect nor the opposite.[50]

Conclusion

Of all lifestyle interventions, aerobic exercise seems promising based on current insights into working mechanisms, efficacy, side effects, and feasibility. Challenges include remote and blinded administration, compliance optimization, and outcome measurement. In addition, we provide recommendations (summarized in Figure 2) for organizing exercise interventions as part of PD prevention trials.

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Edo Richard, MD, PhD	Department of Neurology, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behavior; Radboud University Medical Center Alzheimer Center, Nijmegen, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Sirwan K.L. Darweesh, MD, PhD	Department of Neurology, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behavior; Center of Expertise for Parkinson & Movement Disorders, Nijmegen, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Bastiaan R. Bloem, MD, PhD	Department of Neurology, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behavior; Center of Expertise for Parkinson & Movement Disorders, Nijmegen, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

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