EDITORIAL

Citius, Fortius, Altius—Understanding Which Components Drive Exercise Benefits in Parkinson Disease

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The expression "*citius, fortius, altius*" (Latin for "faster, higher, stronger") is the Olympic motto indicating what is required to achieve athletic excellence. Which of these skills is most important to reach an optimal personal performance was not specified by its creator, Pierre de Coubertin, but a combination is presumably optimal. Similar issues are at play when trying to understand the beneficial outcomes of physical activity on general health and motor functioning in people with neurological disorders such as Parkinson disease (PD). One component of physical activity, namely its intensity, has thus far been studied best. For persons with PD, intense physical activity (also referred to as aerobic exercise) has positive associations with aerobic capacity and motor signs.[1] Intense physical activity may also improve nonmotor symptoms, such as cognitive functioning and sleep.[1] In addition to these symptomatic outcomes, there is some early but converging evidence that intense physical activity may also exert disease-modifying effects in PD. Specifically, phase 2 exercise trials have shown stabilization of motor symptoms following 6 months of aerobic exercise.[2,3] A higher intensity was more effective than a moderate intensity.[3] The precise working mechanisms of aerobic exercise in PD remain unknown, although several modes of action have been suggested.[4-6] Specifically, preliminary neuroimaging evidence from a phase 2 trial suggests that engaging in regular high-intensity aerobic exercise may induce preservation of basal ganglia networks.[7] Similar protective effects of aerobic exercise on the basal ganglia network have been observed in rodents with experimental parkinsonism.[8]

Related article page 1446

The challenge is to now translate these encouraging experimental findings into daily practice. Unfortunately, achieving high-intensity aerobic exercise regularly proves challenging for many patients, in particular those with a neurological disease such as PD who are confronted with multiple barriers.[9] First, limitations in gait and balance, often combined with fear of falling, make it difficult to reach high intensity levels. Second, many persons with PD cannot intensify their exercise because of chronotropic incompetence: an inability to increase the heart rate sufficiently during exercise to match the cardiac output to metabolic demands.[10] Third, adherence to high-intensity exercise is difficult, partially because many suitable activities, such as cycling or running, are monotonous in nature and therefore become insufficiently engaging. Finally, high-intensity training requires longer recovery periods, particularly in people with PD, who may experience disproportional fatigue after exercise; this hampers implementation of a sufficiently frequent training program. Light-intensity to moderate-intensity exercise, on the other hand, seems more convenient to implement and easier to adhere to on a daily basis. However, it is unknown if achieving a larger volume of physical activities and not necessarily a higher intensity also provides benefits to people with PD.

In the present issue of *JAMA Neurology*, Yoon et al[11] address this important knowledge gap. These authors prospectively studied the association between physical activity and mortality in a large sample of people newly diagnosed with PD (N = 10 987) who were registered in the Korean National Health Insurance System. Physical activity was measured at 2 points, namely within 2 years before and after PD diagnosis, using a self-reported questionnaire with a 7-day recall. Activity was categorized as being either physically active or not, based on both the type and frequency of activity. Additionally, metabolic equivalent calculations were made to categorize activities into either light-intensity, moderate-intensity, or vigorous-intensity activities. The main result was that people with PD who are physically active have a significantly lower mortality rate compared with their counterparts who are inactive. Furthermore, the study showed an inverse dose-response association between the amount of exercise and mortality rates: a higher amount of activity corresponded with a lower mortality rate. The study also showed that maintenance of physical activity over longer intervals contributes considerably to the inverse association between physical activity and mortality: persons who were active before but not after their PD diagnosis did not have a reduced mortality rate. On the other hand, persons who were inactive before the diagnosis but became active after the diagnosis did have a reduced mortality rate. Persons who were continuously active showed the lowest mortality rate at all intensity levels.

One main advantage of the prospective, observational design used in this study,[11] compared with clinical trials, is the large number of participants who could be followed up over a long interval. Moreover, participants were sampled from a medical claims database that is representative of the study's source population regarding the distribution of age, sex, disease severity, and comorbidities. By contrast, clinical trials are often restricted to specific subgroups of patients. Furthermore, the authors only included participants with a physical health checkup during which body mass index, blood pressure, comorbidities, and other relevant health indicators were measured. Another strength was that the diagnosis of PD was confirmed by a neurologist, although no information on disease symptoms or severity was registered.

An inevitable limitation of the observational nature of this study[11] is that reverse causality may have occurred, in that the level of physical activity may in itself have been determined by underlying conditions that affected the mortality rate. Specifically, people with a more severe phenotype of PD or multiple comorbidities (eg, osteoarthritis and obesity) may be less physically active, and these underlying conditions may have led to a higher mortality rate. By contrast, people without these conditions would have a lower mortality rate. Also, only including participants who had had 2 health checkups may have introduced selection bias. We were also somewhat concerned that the 2 types of categorizations (active vs inactive; with 3 intensity levels) were arbitrary, and the choice for the specific cutoff values may have affected the results. A final challenge is about the assessment of physical activity levels. The authors used a questionnaire with a 7-day recall. Such physical activity questionnaires are generally unreliable because of recall bias and because people find it difficult to quantify their exact activity level. However, it is unlikely that this recall bias disproportionally affected the various subcategories.

Despite these drawbacks, the work of Yoon et al[11] does have potentially important implications. The first is that the sheer amount (volume) of physical activity seems to matter. This benefit was reflected here by a reduced mortality risk, and it remains to be determined whether this also translates into tangible health benefits during life for persons with PD. Should this be demonstrated in further studies, then this would practically mean that people with PD should not necessarily be encouraged to reach high-intensity exercise levels, but that achieving a higher volume of physical activities (eg, by simply taking longer daily walks) would also confer symptomatic improvement. Practically speaking, this could bring the positive associations of physical activity within reach of more people with PD around the world, including the many who now find it difficult to engage in truly high-intensity aerobic exercise.

The second implication is that the findings by Yoon et al[11] provide cautious evidence for a disease-modifying potential of high-volume exercise. To differentiate between true causal effects of exercise on PD progression and reverse causation, we ultimately need phase 3 randomized clinical trials. To pave the way for such trials, pilot studies should first address several remaining knowledge gaps, such as how to mitigate the difficulty of engaging participants in exercise regimens for prolonged periods and identify the optimal dose of the exercise volume. In this regard, a timely development is the emergence of gamification elements through apps on the participants' own smartphones, which can keep them engaged with exercise interventions. This approach is currently being studied in a randomized clinical trial (STEPWISE; NCT04848077). This study also explores the dose-response association between exercise volume and disease progression by randomizing people to different volumes of activity (ie, a 10%, 50%, 100%, or 200% increase relative to baseline). The outcome is also measured completely remotely, by measuring step counts on the smartphone and using the mPower app on the same smartphone. When successful, this remote STEPWISE design is scalable, including to remote areas and in times of isolation (eg, the recent COVID-19 pandemic[12]). Additionally, such a remote approach may also benefit prodromal PD research in the future. Various observational studies in humans have shown that regular physical activity is associated with a reduced PD risk,[13-15] suggesting that the disease-modifying properties of physical activity may extend to the prodromal phase of PD. Therefore, remotely administered and gamification-enhanced exercise volume interventions could be used to delay the onset of clinically manifest PD in people at high risk of the disease, such as those with a mendelian genetic mutation (eg, *LRRK2 G2019S*) or a REM sleep behavior disorder. Randomizing many such individuals across different volumes of activity and following them for a long period (>5 years) could demonstrate whether physical activity could postpone development of PD.

The present study of Yoon et al[11] thus opens up a wide range of new opportunities for people with PD to benefit from physical activity, recognizing that not just the intensity, but also the volume of physical activities, may be an important determinant of reaching forthcoming end points. These future studies will undoubtedly meet with many challenges, which no single researcher can address alone. It is therefore appropriate to return to the Olympic motto, which in July 2021 was changed by the International Olympic Committee to "*citius, altius, fortius—communiter*" ("faster, higher, stronger—together"). This change was implemented to better reflect the fact that we can only go faster, aim higher, and become stronger by standing together in solidarity. The research community can certainly learn from this important perspective, as only a joint collaborative approach will be able to address the research challenges that lie ahead of us.

ARTICLE INFORMATION

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