



Aerobic Exercise: Evidence for a Direct Brain Effect to Slow Parkinson Disease Progression

J. Eric Ahlskog, PhD, MD

Abstract

No medications are proven to slow the progression of Parkinson disease (PD). Of special concern with longer-standing PD is cognitive decline, as well as motor symptoms unresponsive to dopamine replacement therapy. Not fully recognized is the substantial accumulating evidence that long-term aerobic exercise may attenuate PD progression. Randomized controlled trial proof will not be forthcoming due to many complicating methodological factors. However, extensive and diverse avenues of scientific investigation converge to argue that aerobic exercise and cardiovascular fitness directly influence cerebral mechanisms mediating PD progression. To objectively assess the evidence for a PD exercise benefit, a comprehensive PubMed literature search was conducted, with an unbiased focus on exercise influences on parkinsonism, cognition, brain structure, and brain function. This aggregate literature provides a compelling argument for regular aerobic-type exercise and cardiovascular fitness attenuating PD progression.

© 2017 Mayo Foundation for Medical Education and Research ■ Mayo Clin Proc. 2018;93(3):360-372



From the Department of Neurology, Mayo Clinic, Rochester, MN.

Parkinson disease (PD) is a relatively common neurologic condition with perhaps 1 million affected people in the United States. Increasingly, their treatment is falling into the hands of primary care physicians, who should be able to provide optimal care to most patients.¹⁻³ As previously described,² appropriate carbidopa/levodopa administration is the single most crucial medication strategy. Herein, the argument is advanced that the other important component of optimal PD treatment is engagement in regular aerobic-type exercise. Although no medications are proven to slow PD progression, there is substantial evidence for vigorous exercise attenuating PD progression, which is the specific focus of this article.

Exercise advice may be skeptically viewed by patients. The lay public is bombarded by health advice, some biologically supported and some that is arbitrary, unsupported, or commercially driven. Exercise is easily dismissed as yet another dictum from health experts. Moreover, regular exercise implies strenuous, time-consuming physical work, which for some people is novel. Thus, an exercise prescription for people with PD is easily discarded, especially in the absence of definite proof.

IMPEDIMENTS TO CLINICAL TRIAL ASSESSMENT OF PD EXERCISE INFLUENCES

Definitive arguments for any health intervention are expected to come from clinical randomized controlled trials (RCTs). The outcome of interest is preventing the slow neurologic decline that occurs with PD. Unfortunately, a valid and reliable RCT of long-term exercise to slow PD progression is not truly feasible for several reasons.

First, PD progression tends to be very slow. Reliable and valid biomarkers of PD progression have yet to be developed. Assessment requires outcome measures that will not be contaminated by medication effects (ie, levodopa and related drugs); this precludes motor outcomes routinely used in PD clinical trials (eg, Unified Parkinson Disease Rating Scale scores). From a patient's perspective, the most important markers of clinical progression are dementia and levodopa-refractory symptoms, which are measurable and not subject to medication influences. However, these problems typically do not develop for many years or decades and, thus, are not amenable to RCTs.

Second is the physical and motivational challenge of longer-term engagement in an

aerobic exercise program. Long-term adherence to a rigorous exercise protocol among senior patients with PD is potentially problematic.

Third, confirmation of exercise effort in such a clinical trial is not easily assessed, although cardiovascular fitness is an objective outcome of long-term aerobic exercise. Not to be overlooked in such clinical trials is off-protocol exercise in the “sedentary” control patients cognizant of the study hypothesis that exercise may slow PD progression.

THE RATIONALE FOR THIS REVIEW

Definitive proof of exercise slowing PD progression is unlikely to be forthcoming from RCTs because of the previously mentioned methodological problems. However, there is a very extensive and diverse literature relating to direct exercise influences in the brain, relevant to PD. At an elementary level, this includes exercise-induced brain neuroplasticity, maintenance of synaptic connections, and preservation of brain integrity. Macroscopically, exercise influences on brain integrity are now measurable with modern brain magnetic imaging technology.

The goal of this article is to review the evidence for long-term aerobic-type exercise as a means for slowing PD progression. Although exercise is well-recognized to attenuate brain atherosclerotic risks (ie, cerebrovascular disease), this focus will be on direct brain influences of aerobic-type exercise. Because subject reviews tend to have agendas that may bias interpretation, a concerted effort was made to survey the entire published literature identified in a PubMed search and report both positive and negative findings. The intent is to provide clinicians with the evidence needed for counseling their patients with PD.

METHODS: LITERATURE SEARCH

This PubMed literature search was performed using 2 search term strategies: *exercise and Parkinson disease* and *exercise and cognition*. *Cognition* was chosen because cognitive impairment/dementia is perhaps the most feared outcome of patients with PD. All the titles from this literature search to January 15, 2017, were reviewed, and relevant papers were read. Mixed results and negative trials are

ARTICLE HIGHLIGHTS

- Parkinson disease is a slowly progressive neurodegenerative condition; after many years, dementia or medication-refractory motor symptoms may develop.
- A myriad of animal studies document a direct, favorable effect of aerobic-type exercise on the brain; this includes liberation of neurotrophic hormones and enhancement of a variety of neuroplasticity mechanisms. Exercise tends to protect animals from neurotoxins that induce parkinsonism.
- Long-term exercise and fitness in healthy humans is associated with greater volumes of cerebral cortex and hippocampus and less age-related white matter pathology.
- Midlife exercise is associated with a significantly reduced later risk of Parkinson disease.
- Conclusion from this evidence: Regular aerobic-type exercise tending to lead to fitness is the single strategy with compelling evidence for slowing Parkinson disease progression. All patients with Parkinson disease should be encouraged to engage in regular such exercise.

cited in this review. The reference list contains all the relevant papers; however, individual studies are not separately addressed when included in cited meta-analyses.

Included in this review are adult human (age >18 years) and animal studies. Aerobic-type exercise was the focus because a preliminary reading of this literature indicated that this is the most robust and comprehensive component of this exercise literature. It also allowed extension to animal studies, where running exercise is a common experimental variable. Although resistance exercise might be relevant to this topic, preliminary review of resistance exercise publications suggested too few articles and too varied methods to reliably assess. Papers reporting exercise outcomes in nonrelevant disease groups were excluded (eg, patients with diabetes, cancer, etc). Only studies of long-term exercise were included, excluding short-term exercise trials. Studies using outcome measures that could be influenced by symptomatic drug treatment were excluded (eg, carbidopa/levodopa for PD). The PubMed search targeting *exercise and Parkinson disease* yielded 1781 titles; *exercise and cognition* yielded 5054 titles.

RESULTS: ANIMAL STUDIES

Exercise Facilitates Neuroplasticity in Animals

Much of the early literature relevant to this topic was from animal studies, which provided the initial scientific rationale for exercise directly enhancing brain neuroplasticity. The term *neuroplasticity* implies the ongoing capacity of the brain to form and modify synaptic connections. This is the basis for motor and cognitive memory and is the fundamental repair and maintenance process tending to counter neurodegenerative disease and brain aging.

Exercised Animals Perform Better on Simple Cognitive Tests. Controlled trials of running exercise in rats and mice use running wheels or treadmills. Many such studies have documented significant exercise-related improvement in spatial memory (maze) or object recognition.⁴⁻¹⁷ Exercised monkeys (1 hour daily of treadmill exercise for 5 months) performed better than sedentary control monkeys.¹⁸

Microscopic and Neurophysiologic Evidence of Exercise-Related Neuroplasticity. The hippocampus is crucial to memory and is one of the very few brain regions where new neurons are generated: neurogenesis. Many published studies in rats/mice have consistently documented enhanced hippocampal neurogenesis associated with long-term running exercise.^{9,11,14,19-28} The putative neurophysiologic substrate of memory is hippocampal long-term-potential, which was significantly enhanced by running exercise in rodents,^{13,15,23} although only in male and not female rats in 1 study.²⁹ Learning involves restructuring of synaptic connections, and several rodent studies documented enhanced dendritic length and complexity and increased dendritic spines after long-term running exercise.^{7,21,30-32}

Exercise Facilitates Biochemical Markers of Neuroplasticity. Long-term running exercise in rodents increased brain factors known to mediate neuroplasticity, including CREB and intracellular kinases.^{5,10,33,34} Long-term running exercise also enhanced the expression

of synaptic plasticity genes³⁵ and synaptic proteins such as synapsin I and synaptophysin.^{7,17,32,36,37}

Exercise Influences on Brain Neurotrophic Factors

Neurotrophic factors have long been proposed as a potential therapeutic target for neurodegenerative diseases, including PD.^{38,39} Applied in vitro, they enhance neuron vitality, survival, and neuritic outgrowth; they tend to protect neurons from biologic insults (neurotoxins).^{39,40} Intuitively, enhanced brain neurotrophic factor concentrations should benefit neurodegenerative disease, ie, PD.

Brain Neurotrophic Factor Levels Increase With Exercise in Animals. Perhaps the most studied neuroplasticity factor is brain-derived neurotrophic factor (BDNF). Many animal studies have documented significantly increased brain BDNF levels with exercise.^{4-6,9,10,12-14,17,19,23,26,33,36,37,41-44} Brain insulin-like growth factor I interacts with BDNF and increases with exercise.⁸

Glial cell line—derived neurotrophic factor (GDNF) caught the attention of PD researchers when it was recognized to promote the survival and differentiation of dopaminergic neurons in vitro.⁴⁵ It attenuates neurotoxin-induced parkinsonism in rodents.⁴⁶ Several studies have reported increased brain concentrations of GDNF in animals exercised long-term.⁴⁷⁻⁴⁹

Animal Models of Neurotoxin-Induced Parkinsonism, Attenuated by Exercise

Parkinson disease symptoms are primarily mediated by neurodegeneration of the dopaminergic nigrostriatal system, and dopamine replenishment with levodopa therapy is the most efficacious symptomatic treatment. Although PD is not simply a dopamine disorder, selective neurotoxin-induced destruction of the dopaminergic nigrostriatal system has been used as a treatment model. This is done with either nigrostriatal infusion of 6-hydroxydopamine (6-OH-DA) or systemic administration of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP). Rodent studies using these neurotoxins have assessed possible neuroprotective effects of exercise.

Exercise Increases Neurotrophic Factor Levels and Attenuates 6-OH-DA Nigrostriatal Neurotoxicity. Multiple studies in rodents have reported that the parkinsonian motor deficits from unilateral nigrostriatal injection of 6-OH-DA are markedly attenuated or reversed by exercise,^{44,49-55} although with 3 negative trials.⁵⁶⁻⁵⁸ In this unilateral condition, forced use of the affected limb also attenuated the deficit (cast immobilization of the unaffected limb).^{47,59} Conversely, preventing use of the 6-OH-DA-affected limb by casting exacerbated the motor deficit.⁶⁰ In these studies, postmortem histologic analysis documented partial restoration of histologic markers of striatal dopaminergic terminals^{20,49-51,53-55,59-62} or neurons,^{20,49,62} although not confirmed in 1 study.⁵² In controlled studies, daily exercise in 6-OH-DA animals increased striatal BDNF and GDNF levels⁴⁹ or BDNF levels,^{42,53,55} postulated as relevant to the neuroprotective outcomes. Forced overuse of a limb before 6-OH-DA injection elevated striatal GDNF levels, attenuated the motor deficit, and reduced the striatal dopamine loss.⁴⁷

Exercise Tends to Reduce MPTP Nigrostriatal Neurotoxicity. Mice systemically injected with MPTP develop bilateral parkinsonism due to selective neurotoxic destruction of the dopaminergic nigrostriatal system. Exercise attenuated MPTP-induced parkinsonism in 7 studies,^{48,54,63-67} but not in 2 others.^{68,69} Cast immobilization exacerbated the motor deficit.⁷⁰

Histochemical markers of the dopaminergic nigrostriatal system were inconsistently protected in these studies. Evidence of preserved or restored (sprouted) dopaminergic terminals were found in the minority of investigations,^{48,54,65,70} with 7 of 11 reports documenting no change in the dopaminergic terminal markers.^{63,68,69,71-74} Midbrain dopaminergic neuron counts were partially preserved with exercise in most,^{48,64,66,75} but not all,^{67,73} studies. A dose-effect was documented in 2 investigations,^{64,75} with greater exercise duration and intensity associated with incremental attenuation of parkinsonism and histochemical results.

In other MPTP studies, exercise attenuated postsynaptic changes caused by loss of

dopaminergic input to striatal neurons. Specifically, exercise reversed striatal neuron hyperexcitability⁷⁶ and tended to restore glutamate (AMPA) receptors⁷⁷ and dendritic spine density.³¹

RESULTS: HUMAN STUDIES

Humans and Neurotrophic Factors

As cited previously herein, animal studies have consistently documented increased brain concentrations of neurotrophic factors with long-term exercise (eg, BDNF, GDNF). Neurotrophic factors are proposed as neuroprotective for neurodegenerative disease (ie, PD).

Exercise Increases BDNF in Humans. Brain-derived neurotrophic factor is a small molecule and crosses the blood-brain barrier.^{78,79} Hence, circulating BDNF concentrations should correlate with brain levels in humans. Most studies in normal humans have documented increased serum BDNF concentrations, both after acute exercise and with long-term exercise, as summarized in a recent meta-analysis.⁸⁰

Exercise Increases Serum BDNF in Patients With PD. Serum BDNF levels significantly increased after 1 month of treadmill exercise in a cohort of patients with PD; the levels were unchanged in the unexercised control patients with PD.⁸¹ In 2 other uncontrolled studies, 8 weeks of cycling exercise significantly increased serum BDNF levels.^{82,83} Perhaps relevant is the finding that low serum BDNF concentrations were significantly associated with reduced cognitive scores in a cohort of patients with PD.⁸⁴

Side Story: Direct Brain Administration of GDNF in Patients With PD. As mentioned previously herein, the neurotrophic factor GDNF protects dopaminergic neurons and promotes their survival *in vitro*⁴⁵; *in vivo*, it attenuates the neurotoxic effects in animal models of parkinsonism.⁴⁶ However, unlike BDNF, the large GDNF molecule does not cross the blood-brain barrier, and blood levels are independent of brain concentrations.

Laboratory studies documenting neurotrophic effects of GDNF on dopaminergic neurons were the basis for brain infusion trials in patients with PD. Because GDNF does not

cross the blood-brain barrier it was administered via cannulas implanted in the brains (striata) of patients with PD.^{38,46} Trials of these direct infusions yielded mixed results. An initial open-label trial revealed parkinsonian benefit, but this was not replicated in an RCT.⁸⁵ The failure in the controlled trial was possibly attributed to the limited distribution or poor retrograde neuronal transport of GDNF from the striatal injection site; this large molecule diffuses poorly in brain tissue.³⁸

Exercise and PD

Midlife Exercise Reduces Later PD Risk. In a meta-analysis of prospective studies, midlife exercise conferred a significantly lower subsequent risk of developing PD.⁸⁶ Subsequently, this outcome was similarly reported in 2 individual large cohorts^{87,88} and in 1 cross-sectional analysis.⁸⁹ Obviously, reverse causation cannot be excluded; ie, before PD, patients might have been less inclined to exercise due to subclinical PD-related factors.

Exercise in Early PD and Later Dementia. No clinical trials have assessed whether exercise in early PD reduces later risks of dementia. This would be a difficult investigation for the reasons discussed at the beginning of this article. However, limited studies suggest favorable trends.

In a cross-sectional study involving 2252 patients with PD, questionnaire-based regular exercise was associated with less cognitive decline after 1 year.⁹⁰ Again, reverse causation could have explained this finding (ie, those with more severe PD may have been disinclined to exercise).

Numerous small trials assessing 1 to 6 months of aerobic-type exercise by patients with PD have documented statistically significant cognitive improvement; however, the outcomes have been modest, limited, or inconsistent across cognitive measures. Most of these studies included a nonexercise control group,⁹¹⁻⁹⁶ but 2 were uncontrolled^{97,98} and 2 others assessed only 1 or 2 patients with PD.^{99,100}

Non-PD Human Clinical Studies: Exercise and Cognition

Although studies addressing exercise and cognition in PD are limited, there is a

substantial literature relating to exercise influences on cognition in the general population. Note, however, that exercise-related cognitive enhancement in healthy adults may be limited by a ceiling effect and may fundamentally differ from biological mechanisms counteracting a very slow PD neurodegenerative process.

Prospective Exercise Trials in Healthy Adults: Limited Cognitive Benefits.

Numerous clinical trials have assessed cognitive outcomes after several months of aerobic-type exercise in healthy adults. In the aggregate, the benefits have been modest and inconsistent. These findings may be summarized as follows.

The first of several meta-analyses assessed 16 prospective RCTs of 1 to 18 months of aerobic-type exercise and documented significant, but modest cognitive benefit in healthy adults (some seniors).¹⁰¹ In contrast, 2 subsequent meta-analyses of prospective RCTs of long-term exercise in healthy seniors revealed no aggregate benefit.^{102,103} Subsequently, 6 of 8 individual RCTs assessing long-term aerobic-type exercise documented significant cognitive improvement¹⁰⁴⁻¹⁰⁹; the 2 negative studies assessed 1 to 2 years of regular walking.^{110,111} Complicating interpretation of these findings is uncertain exercise engagement in the exercise group. Even when attendance is monitored, there is no assurance that vigorous and persistent exercise is performed. Moreover, off-protocol exercise in the sedentary control groups is never monitored.

Recent cross-sectional exercise studies in seniors have also generated inconsistent cognitive findings. On the one hand, better cognitive scores were associated with greater physical activity, either questionnaire based^{112,113} or tabulated by a 6-day accelerometer assessment.¹¹⁴ In contrast, 2 decades of high-effort endurance exercise reported by older adults documented no cognitive differences compared with a nonsedentary control group of similar age.¹¹⁵

Some of the limitations of the prospective exercise trials may be better addressed when the independent variable is fitness, which is the intended outcome of aerobic exercise. Fitness can be physiologically defined by the measured oxygen uptake during maximum exercise. There is a voluminous literature

relating to fitness and cognition, with compelling evidence favoring fitness.

Fitness Is Associated With Better Cognition in Healthy Adults. Several large studies measured fitness at baseline and assessed later cognitive outcomes. The largest of these studied 1.2 million Swedish men aged 18 years inducted into the military.¹¹⁶ Fitness was measured at the time of induction, revealing highly significant positive correlations between cardiovascular fitness and cognitive test scores; the findings were similar when the assessment was confined to the 1432 monozygotic twins among their inductees. Also, in this cohort, fitness at age 18 years predicted educational outcomes 10 to 36 years later,¹¹⁶ whereas lower fitness was associated with a greater risk of dementia, with follow-up to 42 years.¹¹⁷ Similar outcomes were documented in 2 community-based studies. In the first study, baseline fitness predicted cognition 25 years later¹¹⁸; in the other, baseline fitness was associated with slower cognitive decline over decades of aging.¹¹⁹ In a cohort of military veterans, better baseline fitness predicted a significantly lower risk of cognitive impairment at mean follow-up of 10 years.¹²⁰ Several cross-sectional studies have reported that better fitness was concurrently associated with better cognitive scores,¹²¹⁻¹²⁵ although in another study, this was found only in seniors and not in young adults.¹²⁶ Masters athletes performed significantly better on 2 of 4 cognitive tests than sedentary control subjects.¹²⁷

One recent publication cautions about reverse causation in these fitness studies, arguing that early socioeconomic or inherited advantages may confer both healthier lifestyles and better cognition; or, that those with better cognition tend to choose healthier lifestyles.¹²⁸

Regular Exercise Reduces the Risk of Later Dementia, Cognitive Decline. Meta-analyses of midlife-documented exercise/physical activity found a significantly reduced frequency of later cognitive decline¹²⁹ and dementia.¹³⁰ More recent similar prospective studies have reported similar significant outcomes,¹³¹⁻¹³⁴ although this trend in 1 other study was only marginally significant.¹³⁵ Midlife vigorous leisure activity (ie, more vigorous

than walking) was associated with a significantly lower risk of a death certificate diagnosis of dementia at 29 years of follow-up.¹³⁶

Cross-sectional studies found midlife fitness to be associated with a reduced risk of later dementia,¹³⁷ and higher reported lifetime physical activity was associated with better cognitive scores.¹¹³ Multiple studies have found midlife exercise to be linked to a reduced risk of later mild cognitive impairment,^{116,138-145} which is recognized to be a frequent prelude to dementia.

Established Dementia/Mild Cognitive Impairment: Aerobic-Type Exercise Generally Provides Cognitive Benefits. Among those already cognitively impaired, most prospective exercise trials documented significant cognitive benefits¹⁴⁶⁻¹⁵⁵; however, a few reported only modest outcomes,¹⁵⁶⁻¹⁵⁸ with 1 negative study.¹⁵⁹ The most recent meta-analysis assessing RCTs of aerobic exercise in demented patients reported significant positive effects on cognition.¹⁶⁰ Although 2 earlier meta-analyses of long-term exercise in demented patients were negative, they included numerous trials using nonaerobic interventions.^{161,162}

Aerobic-Type Exercise Favorably Influences Brain Volumes, Integrity, and Connectivity

Parkinson disease is a brain neurodegenerative condition that is most likely to develop in middle age and beyond. Note that normal aging is associated with brain atrophy and attrition, apparent on routine brain magnetic resonance imaging (MRI). Advances in brain MRI software allow precise measurement of neuroanatomical features, as well as brain activation and connectivity. In this era of advanced brain MRI technology, clinical trial evidence has documented that long-term aerobic exercise tends to induce favorable changes in brain structure and function, paralleling cognitive benefits.

Fitness and Exercise Are Associated With Hippocampus Volumes. The hippocampus is a crucial component of brain memory circuits. Hippocampal atrophy is not only a marker of Alzheimer disease but also is found in PD with dementia.^{163,164} In cross-sectional analyses controlling for relevant variables,

larger hippocampal volumes were significantly associated with cardiovascular fitness.^{124,165} The volume of the entorhinal cortex (which encompasses the hippocampus) was similarly correlated with fitness, at least on 1 side.¹⁶⁶

In prospective RCTs, hippocampal volumes increased with 1 to 2 years of aerobic exercise.^{167,168} Likewise, in a shorter treadmill exercise RCT (3 months), hippocampal volumes were significantly larger in proportion to the measured change in fitness.¹⁶⁹

Fitness and Exercise Are Associated With Neocortical (Gray Matter) Volumes. In the Framingham Heart Study, poor fitness at age 40 years was associated with a smaller overall brain volume 20 years later.¹⁷⁰ Several studies documented that physically fit seniors have significantly less age-related cortical volume loss.^{121,123,171,172}

Prospective 6-month RCTs of exercise documented increased neocortical volumes in 2 studies,^{173,174} but not in 1 walking exercise trial.¹⁷⁵ Reported physical activity has concurrently been associated with greater gray matter volumes,^{176,177} whereas reported walking distances prospectively correlated with cortical volumes 9 years later.¹⁷⁸

Fitness Is Associated With White Matter Integrity. Diffusion tensor imaging (DTI) MRI measures white matter integrity and microstructure. One DTI measure of white matter health is fractional anisotropy, with high values indicating greater microstructural integrity. Among seniors, fitness was associated with greater brain DTI fractional anisotropy,¹⁷⁹⁻¹⁸² and in 1 study fitness correlated with fractional anisotropy measured 5 years later.¹⁸³ Seniors who improved fitness after 1 year of walking exercise improved brain white matter fractional anisotropy.¹¹¹ Estimated physical activity in advanced seniors (mean age, 87 years) was associated with higher DTI fractional anisotropy.¹⁸⁴

Brain White Matter Hyperintensities (Leukoariosis) Are Less With Fitness. Normal aging is variably associated with white matter hyperintensities (leukoariosis). These lesions are thought to reduce brain reserve and at least mildly contribute to deficits from

neurodegenerative disease. Increased fitness is associated with reduced volumes of these white matter hyperintensities (ie, less leukoariosis),^{185,186} although in 1 study this significant relationship was found only in men.¹⁸⁷ Masters athletes had 83% less leukoariosis volume compared with a matched sedentary control group.¹⁸⁸

Functional-MRI: Brain Activation and Connections Improvement With Exercise. Brain functional MRI (fMRI) assesses cortical activation and connectivity during cognitive tasks. In healthy seniors, aerobic fitness has been associated with better fMRI connectivity and cortical activation compared with unfit seniors.^{122,189,190} Prospective (6-12 months) exercise in healthy seniors improved fMRI cortical connectivity and activation in cognitive networks.^{189,191}

fMRI Brain Activation and Connectivity Improved With Exercise in PD. In patients with PD, brain fMRI connectivity declines with progressing PD and correlates with cognitive decline.¹⁹² A prospective, 3-month cycling exercise trial in patients with PD revealed increased brain activation in several relevant nuclei.¹⁹³ In another fMRI study in exercising patients with PD, long-term cycle pedaling rates strongly correlated with improved thalamus-cortex connectivity.¹⁹⁴

SYNOPSIS

An initial rationale for considering exercise to slow PD progression came from animal studies, where long-term running exercise consistently improved cognitive outcomes, increased brain neurotrophic factor concentrations, enhanced biomarkers and microscopic evidence of neuroplasticity, and attenuated neurotoxin-induced parkinsonism. These findings suggested a direct beneficial effect of exercise on the brain, relevant to PD.

In patients with PD, as well as healthy adults, exercise increased BDNF levels. In prospective studies, midlife exercise consistently has been associated with a reduced later risk of PD.

Progression to dementia is the most feared PD complication, but it does not lend itself to clinical trial assessment of exercise influence. However, adults without PD who engage in

midlife exercise have significantly reduced subsequent risks of dementia and mild cognitive impairment. Cardiovascular fitness in midlife is associated with better cognition many years later. Finally, brain volumes (hippocampus, neocortex), brain connectivity and activation, and white matter integrity are significantly favored by exercise and fitness.

ADVICE TO PATIENTS

If regular exercise slows PD progression, what exercise(s) to choose? In animal studies, the focus was on running exercise because this is what rats and mice voluntarily will do. Extrapolating from that to humans suggests that aerobic-type exercises, in general, may accomplish similar outcomes. This is corroborated by the many studies documenting associations between cardiovascular fitness (the outcome of long-term aerobic exercise) and favorable cognitive outcomes, greater brain volumes, brain connectivity, and white matter integrity. This literature would suggest that any exercise routine that potentially leads to fitness should be appropriate. Thus, not only running may serve this purpose, but also countless aerobic routines that tend to increase heart rate, induce perspiration, and generate fatigue. This includes many exercise routines that can be done by those with gait problems or arthritic lower limb joints.

Unfortunately, there are no investigations that provide insight into the ideal exercise duration. Perhaps the American Heart Association exercise guidelines^{195,196} are a good starting point when advising patients: "...moderate-intensity aerobic physical activity for a minimum of 30 minutes on five days each week or vigorous-intensity aerobic activity for a minimum of 20 minutes on three days each week." That guideline also advises resistance exercises "for a minimum of two days each week." However, it seems reasonable to direct patients to gradually increase exercise intensity and duration to improve fitness.

Whereas this literature suggests that fitness, per se, is neuroprotective, this may not be sufficient if not maintained by ongoing exercise. Note that the cited animal literature suggests that exercise triggers brain surges of neurotrophic hormones and induction of neuroplasticity mechanisms. Will these abate if exercise is not maintained? Will the fit patient

with PD who abandons exercise still benefit? Because this is unresolved, it would be appropriate to counsel continued engagement in exercise regardless of baseline fitness.

The evidence for exercise favoring PD progression has implications for carbidopa/levodopa treatment. Engagement in vigorous exercise by those with PD usually requires an appropriately optimized levodopa treatment program. Arbitrarily delayed or underdosed levodopa treatment compromises both the ability and motivation to exercise. Carbidopa/levodopa may be deferred in those who can remain active, and whose quality of life is not substantially affected by PD symptoms. However, there is nothing to be gained by the admonition to defer or limit carbidopa/levodopa in the hope of "saving it for later." Carbidopa/levodopa treatment guidelines have previously been clearly delineated and should be easily adopted by primary care physicians.¹⁻³

CONCLUSION

No medications are proven to slow the progression of PD. After years of living with PD, patients develop symptoms that do not have a dopamine substrate and do not benefit from dopamine replacement, notably, dementia and levodopa-refractory motor symptoms. However, evidence from many avenues of scientific investigation argues for ongoing aerobic exercise as a means to slow PD progression. This should be routine advice to patients with PD.

Abbreviations and Acronyms: BDNF = brain-derived neurotrophic factor; DTI = diffusion tensor imaging; fMRI = functional magnetic resonance imaging; GDNF = glial cell line-derived neurotrophic factor; MRI = magnetic resonance imaging; MPTP = 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; PD = Parkinson disease; RCT = randomized controlled trial; 6-OH-DA = 6-hydroxydopamine

Potential Competing Interests: The authors report no competing interests.

Correspondence: Address to J. Eric Ahlskog, PhD, MD, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (eahlskog@Mayo.edu).

REFERENCES

1. Ahlskog JE. *Parkinson's Disease Treatment Guide for Physicians*. New York, NY: Oxford University Press; 2009.
2. Ahlskog JE. Cheaper, simpler, and better: tips for treating seniors with Parkinson disease. *Mayo Clin Proc*. 2011;86(12):1211-1216.

3. Ahlskog JE. *The New Parkinson's Disease Treatment Book*. New York, NY: Oxford University Press; 2015.
4. Adlard PA, Perreau VM, Engesser-Cesar C, Cotman CW. The timecourse of induction of brain-derived neurotrophic factor mRNA and protein in the rat hippocampus following voluntary exercise. *Neurosci Lett*. 2004;363(1):43-48.
5. Aguiar AS Jr, Castro AA, Moreira EL, et al. Short bouts of mild-intensity physical exercise improve spatial learning and memory in aging rats: involvement of hippocampal plasticity via AKT, CREB and BDNF signaling. *Mech Ageing Dev*. 2011;132(11-12):560-567.
6. Berchtold NC, Castello N, Cotman CW. Exercise and time-dependent benefits to learning and memory. *Neuroscience*. 2010;167(3):588-597.
7. Brockett AT, LaMarca EA, Gould E. Physical exercise enhances cognitive flexibility as well as astrocytic and synaptic markers in the medial prefrontal cortex. *PLoS One*. 2015;10(5):e0124859.
8. Ding Q, Vaynman S, Akhavan M, Ying Z, Gomez-Pinilla F. Insulin-like growth factor I interfaces with brain-derived neurotrophic factor-mediated synaptic plasticity to modulate aspects of exercise-induced cognitive function. *Neuroscience*. 2006;140(3):823-833.
9. Gibbons TE, Pence BD, Petr G, et al. Voluntary wheel running, but not a diet containing (-)-epigallocatechin-3-gallate and beta-alanine, improves learning, memory and hippocampal neurogenesis in aged mice. *Behav Brain Res*. 2014;272C:131-140.
10. Lee MC, Okamoto M, Liu YF, et al. Voluntary resistance running with short distance enhances spatial memory related to hippocampal BDNF signaling. *J Appl Physiol (1985)*. 2012;113(8):1260-1266.
11. Mustroph ML, Chen S, Desai SC, Cay EB, DeYoung EK, Rhodes JS. Aerobic exercise is the critical variable in an enriched environment that increases hippocampal neurogenesis and water maze learning in male C57BL/6j mice. *Neuroscience*. 2012;219:62-71.
12. Noble EE, Mavanji V, Little MR, Billington CJ, Kotz CM, Wang C. Exercise reduces diet-induced cognitive decline and increases hippocampal brain-derived neurotrophic factor in CA3 neurons. *Neurobiol Learn Mem*. 2014;114:40-50.
13. O'Callaghan RM, Ohle R, Kelly AM. The effects of forced exercise on hippocampal plasticity in the rat: a comparison of LTP, spatial- and non-spatial learning. *Behav Brain Res*. 2007;176(2):362-366.
14. Uysal N, Kiray M, Sisman AR, et al. Effects of voluntary and involuntary exercise on cognitive functions, and VEGF and BDNF levels in adolescent rats. *Biotech Histochem*. 2015;90(1):55-68.
15. van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci U S A*. 1999;96(23):13427-13431.
16. van Praag H, Shubert T, Zhao C, Gage FH. Exercise enhances learning and hippocampal neurogenesis in aged mice. *J Neurosci*. 2005;25(38):8680-8685.
17. Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *Eur J Neurosci*. 2004;20(10):2580-2590.
18. Rhyu JI, Bytheway JA, Kohler SJ, et al. Effects of aerobic exercise training on cognitive function and cortical vascularity in monkeys. *Neuroscience*. 2010;167(4):1239-1248.
19. Bechara RG, Kelly AM. Exercise improves object recognition memory and induces BDNF expression and cell proliferation in cognitively enriched rats. *Behav Brain Res*. 2013;245:96-100.
20. Cho HS, Shin MS, Song W, et al. Treadmill exercise alleviates short-term memory impairment in 6-hydroxydopamine-induced Parkinson's rats. *J Exerc Rehabil*. 2013;9(3):354-361.
21. Eadie BD, Redila VA, Christie BR. Voluntary exercise alters the cytoarchitecture of the adult dentate gyrus by increasing cellular proliferation, dendritic complexity, and spine density. *J Comp Neurol*. 2005;486(1):39-47.
22. Fabel K, Fabel K, Tam B, et al. VEGF is necessary for exercise-induced adult hippocampal neurogenesis. *Eur J Neurosci*. 2003;18(10):2803-2812.
23. Farmer J, Zhao X, van Praag H, Wodtke K, Gage FH, Christie BR. Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. *Neuroscience*. 2004;124(1):71-79.
24. Kodali M, Megahed T, Mishra V, Shuai B, Hattiangady B, Shetty AK. Voluntary running exercise-mediated enhanced neurogenesis does not obliterate retrograde spatial memory. *J Neurosci*. 2016;36(31):8112-8122.
25. Okamoto M, Hojo Y, Inoue K, et al. Mild exercise increases dihydrotestosterone in hippocampus providing evidence for androgenic mediation of neurogenesis. *Proc Natl Acad Sci U S A*. 2012;109(32):13100-13105.
26. Sung YH. Effects of treadmill exercise on hippocampal neurogenesis in an MPTP/probenecid-induced Parkinson's disease mouse model. *J Phys Ther Sci*. 2015;27(10):3203-3206.
27. Trejo JL, Carro E, Torres-Aleman I. Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. *J Neurosci*. 2001;21(5):1628-1634.
28. Vivar C, Peterson BD, van Praag H. Running rewires the neuronal network of adult-born dentate granule cells. *Neuroimage*. 2016;131:29-41.
29. Titterness AK, Wiebe E, Kwasnica A, Keyes G, Christie BR. Voluntary exercise does not enhance long-term potentiation in the adolescent female dentate gyrus. *Neuroscience*. 2011;183:25-31.
30. Redila VA, Christie BR. Exercise-induced changes in dendritic structure and complexity in the adult hippocampal dentate gyrus. *Neuroscience*. 2006;137(4):1299-1307.
31. Toy WA, Petzinger GM, Leshon BJ, et al. Treadmill exercise reverses dendritic spine loss in direct and indirect striatal medium spiny neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease. *Neurobiol Dis*. 2014;63:201-209.
32. Shin MS, Jeong HY, An DI, Lee HY, Sung YH. Treadmill exercise facilitates synaptic plasticity on dopaminergic neurons and fibers in the mouse model with Parkinson's disease. *Neurosci Lett*. 2016;621:28-33.
33. Gomez-Pinilla F, Vaynman S, Ying Z. Brain-derived neurotrophic factor functions as a metabotrophin to mediate the effects of exercise on cognition. *Eur J Neurosci*. 2008;28(11):2278-2287.
34. Shen H, Tong L, Balazs R, Cotman CW. Physical activity elicits sustained activation of the cyclic AMP response element-binding protein and mitogen-activated protein kinase in the rat hippocampus. *Neuroscience*. 2001;107(2):219-229.
35. Stranahan AM, Lee K, Becker KG, et al. Hippocampal gene expression patterns underlying the enhancement of memory by running in aged mice. *Neurobiol Aging*. 2010;31(11):1937-1949.
36. Vaynman S, Ying Z, Gomez-Pinilla F. Exercise induces BDNF and synapsin I to specific hippocampal subfields. *J Neurosci Res*. 2004;76(3):356-362.
37. Vaynman SS, Ying Z, Yin D, Gomez-Pinilla F. Exercise differentially regulates synaptic proteins associated to the function of BDNF. *Brain Res*. 2006;1070(1):124-130.
38. Olanow CW, Bartus RT, Volpicelli-Daley LA, Kordower JH. Trophic factors for Parkinson's disease: to live or let die. *Mov Disord*. 2015;30(13):1715-1724.
39. Sampaio TB, Savall AS, Gutierrez MEZ, Pinton S. Neurotrophic factors in Alzheimer's and Parkinson's diseases: implications for pathogenesis and therapy. *Neural Regen Res*. 2017;12(4):549-557.
40. Murer MG, Yan Q, Raisman-Vozari R. Brain-derived neurotrophic factor in the control human brain, and in Alzheimer's disease and Parkinson's disease. *Prog Neurobiol*. 2001;63(1):71-124.

41. Berchtold NC, Chinn G, Chou M, Kessler JP, Cotman CW. Exercise primes a molecular memory for brain-derived neurotrophic factor protein induction in the rat hippocampus. *Neuroscience*. 2005;133(3):853-861.
42. Hopkins ME, Nitecki R, Bucci DJ. Physical exercise during adolescence versus adulthood: differential effects on object recognition memory and brain-derived neurotrophic factor levels. *Neuroscience*. 2011;194:84-94.
43. Neeper SA, Gomez-Pinilla F, Choi J, Cotman CW. Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Brain Res*. 1996;726(1-2):49-56.
44. Tuon T, Valvassori SS, Dal Pont GC, et al. Physical training prevents depressive symptoms and a decrease in brain-derived neurotrophic factor in Parkinson's disease. *Brain Res Bull*. 2014;108:106-112.
45. Lin LF, Doherty DH, Lile JD, Bektesh S, Collins F. GDNF: a glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons. *Science*. 1993;260(5111):1130-1132.
46. Kordower JH, Bjorklund A. Trophic factor gene therapy for Parkinson's disease. *Mov Disord*. 2013;28(1):96-109.
47. Cohen AD, Tillerson JL, Smith AD, Schallert T, Zigmond MJ. Neuroprotective effects of prior limb use in 6-hydroxydopamine-treated rats: possible role of GDNF. *J Neurochem*. 2003;85(2):299-305.
48. Lau YS, Patki G, Das-Panja K, Le WD, Ahmad SO. Neuroprotective effects and mechanisms of exercise in a chronic mouse model of Parkinson's disease with moderate neurodegeneration. *Eur J Neurosci*. 2011;33(7):1264-1274.
49. Tajiri N, Yasuhara T, Shingo T, et al. Exercise exerts neuroprotective effects on Parkinson's disease model of rats. *Brain Res*. 2010;1310:200-207.
50. Aguiar AS Jr, Duzzioni M, Remor AP, et al. Moderate-intensity physical exercise protects against experimental 6-hydroxydopamine-induced hemiparkinsonism through Nrf2-antioxidant response element pathway. *Neurochem Res*. 2016;41(1-2):64-72.
51. Goes AT, Souza LC, Filho CB, et al. Neuroprotective effects of swimming training in a mouse model of Parkinson's disease induced by 6-hydroxydopamine. *Neuroscience*. 2014;256:61-71.
52. O'Dell SJ, Gross NB, Fricks AN, Casiano BD, Nguyen TB, Marshall JF. Running wheel exercise enhances recovery from nigrostriatal dopamine injury without inducing neuroprotection. *Neuroscience*. 2007;144(3):1141-1151.
53. Real CC, Ferreira AF, Chaves-Kirsten GP, Torrao AS, Pires RS, Britto LR. BDNF receptor blockade hinders the beneficial effects of exercise in a rat model of Parkinson's disease. *Neuroscience*. 2013;237:118-129.
54. Tillerson JL, Caudle WM, Revere ME, Miller GW. Exercise induces behavioral recovery and attenuates neurochemical deficits in rodent models of Parkinson's disease. *Neuroscience*. 2003;119:899-911.
55. Tuon T, Valvassori SS, Lopes-Borges J, et al. Physical training exerts neuroprotective effects in the regulation of neurochemical factors in an animal model of Parkinson's disease. *Neuroscience*. 2012;227:305-312.
56. Landers MR, Kinney JW, Allen DN, van Breukelen F. A comparison of voluntary and forced exercise in protecting against behavioral asymmetry in a juvenile hemiparkinsonian rat model. *Behav Brain Res*. 2013;248:121-128.
57. Landers MR, Kinney JW, van Breukelen F. Forced exercise before or after induction of 6-OHDA-mediated nigrostriatal insult does not mitigate behavioral asymmetry in a hemiparkinsonian rat model. *Brain Res*. 2014;1543:263-270.
58. Poulton NP, Muir GD. Treadmill training ameliorates dopamine loss but not behavioral deficits in hemiparkinsonian rats. *Exp Neurol*. 2005;193:181-197.
59. Tillerson JL, Cohen AD, Philhower J, Miller GW, Zigmond MJ, Schallert T. Forced limb-use effects on the behavioral and neurochemical effects of 6-hydroxydopamine. *J Neurosci*. 2001;21(12):4427-4435.
60. Tillerson JL, Cohen AD, Caudle WM, Zigmond MJ, Schallert T, Miller GW. Forced nonuse in unilateral parkinsonian rats exacerbates injury. *J Neurosci*. 2002;22(15):6790-6799.
61. Choe MA, Koo BS, An GJ, Jeon S. Effects of treadmill exercise on the recovery of dopaminergic neuron loss and muscle atrophy in the 6-OHDA lesioned Parkinson's disease rat model. *Korean J Physiol Pharmacol*. 2012;16(5):305-312.
62. Shi K, Liu X, Qiao D, Hou L. Effects of treadmill exercise on spontaneous firing activities of striatal neurons in a rat model of Parkinson's disease. *Motor Control*. 2017;21(1):58-71.
63. Fisher BE, Petzinger GM, Nixon K, et al. Exercise-induced behavioral recovery and neuroplasticity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse basal ganglia. *J Neurosci Res*. 2004;77:378-390.
64. Gerecke KM, Jiao Y, Pani A, Pagala V, Smeys RJ. Exercise protects against MPTP-induced neurotoxicity in mice. *Brain Res*. 2010;1341:72-83.
65. Jang Y, Koo JH, Kwon I, et al. Neuroprotective effects of endurance exercise against neuroinflammation in MPTP-induced Parkinson's disease mice. *Brain Res*. 2017;1655:186-193.
66. Koo JH, Cho JY, Lee UB. Treadmill exercise alleviates motor deficits and improves mitochondrial import machinery in an MPTP-induced mouse model of Parkinson's disease. *Exp Gerontol*. 2017;89:20-29.
67. Pothakos K, Kurz M, Lau Y-S. Restorative effect of endurance exercise on behavioral deficits in the chronic mouse model of Parkinson's disease with severe neurodegeneration. *BMC Neurosci*. 2009;10(1):6.
68. Aguiar AS Jr, Tristao FS, Amar M, et al. Six weeks of voluntary exercise don't protect C57BL/6 mice against neurotoxicity of MPTP and MPP(+). *Neurotox Res*. 2014;25(2):147-152.
69. Aguiar AS Jr, Lopes SC, Tristao FS, et al. Exercise improves cognitive impairment and dopamine metabolism in MPTP-treated mice. *Neurotox Res*. 2016;29(1):118-125.
70. Caudle WM, Tillerson JL, Revere ME, Miller GW. Use-dependent behavioral and neurochemical asymmetry in MPTP mice. *Neurosci Lett*. 2007;418(3):213-216.
71. Al-Jarrah M, Pothakos K, Novikova L, et al. Endurance exercise promotes cardiorespiratory rehabilitation without neurorestoration in the chronic mouse model of Parkinsonism with severe neurodegeneration. *Neuroscience*. 2007;149:28-37.
72. Hood RL, Liguore WA, Moore C, Pflibsen L, Meshul CK. Exercise intervention increases spontaneous locomotion but fails to attenuate dopaminergic system loss in a progressive MPTP model in aged mice. *Brain Res*. 2016;1646:535-542.
73. Petzinger GM, Walsh JP, Akopian G, et al. Effects of treadmill exercise on dopaminergic transmission in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury. *J Neurosci*. 2007;27(20):5291-5300.
74. Sconce MD, Churchill MJ, Greene RE, Meshul CK. Intervention with exercise restores motor deficits but not nigrostriatal loss in a progressive MPTP mouse model of Parkinson's disease. *Neuroscience*. 2015;299:156-174.
75. Ahmad SO, Park JH, Stenho-Bittel L, Lau YS. Effects of endurance exercise on ventral tegmental area neurons in the chronic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and probenecid-treated mice. *Neurosci Lett*. 2009;450(2):102-105.
76. VanLeeuwen JE, Petzinger GM, Walsh JP, Akopian GK, Vuckovic M, Jakowec MW. Altered AMPA receptor expression with treadmill exercise in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury. *J Neurosci Res*. 2010;88(3):650-668.
77. Kintz N, Petzinger GM, Akopian G, et al. Exercise modifies alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor expression in striatopallidal neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse. *J Neurosci Res*. 2013;91(11):1492-1507.

78. Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ. Transport of brain-derived neurotrophic factor across the blood-brain barrier. *Neuropharmacology*. 1998;37(12):1553-1561.
79. Poduslo JF, Curran GL. Permeability at the blood-brain and blood-nerve barriers of the neurotrophic factors: NGF, CNTF, NT-3, BDNF. *Brain Res Mol Brain Res*. 1996;36(2):280-286.
80. Szuhany KL, Bugatti M, Otto MW. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. *J Psychiatr Res*. 2015;60:56-64.
81. Frazzitta G, Maestri R, Ghilardi MF, et al. Intensive rehabilitation increases BDNF serum levels in parkinsonian patients: a randomized study. *Neurorehabil Neural Repair*. 2014;28(2):163-168.
82. Marusiak J, Zeligowska E, Mencil J, et al. Interval training-induced alleviation of rigidity and hypertonia in patients with Parkinson's disease is accompanied by increased basal serum brain-derived neurotrophic factor. *J Rehabil Med*. 2015;47(4):372-375.
83. Zoladz JA, Majerczak J, Zeligowska E, et al. Moderate-intensity interval training increases serum brain-derived neurotrophic factor level and decreases inflammation in Parkinson's disease patients. *J Physiol Pharmacol*. 2014;65(3):441-448.
84. Wang Y, Liu H, Zhang BS, Soares JC, Zhang XY. Low BDNF is associated with cognitive impairments in patients with Parkinson's disease. *Parkinsonism Relat Disord*. 2016;29:66-71.
85. Lang AE, Gill S, Patel NK, et al. Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease. *Ann Neurol*. 2006;59(3):459-466.
86. Xu Q, Park Y, Huang X, et al. Physical activities and future risk of Parkinson disease. *Neurology*. 2010;75(4):341-348.
87. Saaksjarvi K, Knekt P, Mannisto S, et al. Reduced risk of Parkinson's disease associated with lower body mass index and heavy leisure-time physical activity. *Eur J Epidemiol*. 2014;29(4):285-292.
88. Yang F, Trolle Lageros Y, Bellocco R, et al. Physical activity and risk of Parkinson's disease in the Swedish National March Cohort. *Brain*. 2015;138(pt 2):269-275.
89. Shih IF, Liew Z, Krause N, Ritz B. Lifetime occupational and leisure time physical activity and risk of Parkinson's disease. *Parkinsonism Relat Disord*. 2016;28:112-117.
90. Oguh O, Eisenstein A, Kwasny M, Simuni T. Back to the basics: regular exercise matters in Parkinson's disease: results from the National Parkinson Foundation Qll registry study. *Parkinsonism Relat Disord*. 2014;20(11):1221-1225.
91. Altmann LJ, Stegemoller E, Hazamy AA, et al. Aerobic exercise improves mood, cognition, and language function in Parkinson's disease: results of a controlled study. *J Int Neuropsychol Soc*. 2016;22(9):878-889.
92. Cruise KE, Bucks RS, Loftus AM, Newton RU, Pegoraro R, Thomas MG. Exercise and Parkinson's: benefits for cognition and quality of life. *Acta Neurol Scand*. 2011;123(1):13-19.
93. de Oliveira RT, Felipe LA, Bucken Gobbi LT, Barbieri FA, Christoforetti G. Benefits of exercise on the executive functions in people with Parkinson disease: a controlled clinical trial. *Am J Phys Med Rehabil*. 2017;96(5):301-306.
94. Picelli A, Varalta V, Melotti C, et al. Effects of treadmill training on cognitive and motor features of patients with mild to moderate Parkinson's disease: a pilot, single-blind, randomized controlled trial. *Funct Neurol*. 2016;31(1):25-31.
95. Tanaka K, Quadros AC Jr, Santos RF, Stella F, Gobbi LT, Gobbi S. Benefits of physical exercise on executive functions in older people with Parkinson's disease. *Brain Cogn*. 2009;69(2):435-441.
96. Uc EY, Doerschug KC, Magnotta V, et al. Phase I/II randomized trial of aerobic exercise in Parkinson disease in a community setting. *Neurology*. 2014;83(5):413-425.
97. Duchesne C, Lungu O, Nadeau A, et al. Enhancing both motor and cognitive functioning in Parkinson's disease: aerobic exercise as a rehabilitative intervention. *Brain Cogn*. 2015;99:68-77.
98. Nadeau A, Lungu O, Duchesne C, et al. A 12-week cycling training regimen improves gait and executive functions concomitantly in people with Parkinson's disease. *Front Hum Neurosci*. 2016;10:690.
99. Nocera JR, Altmann LJ, Sapienza C, Okun MS, Hass CJ. Can exercise improve language and cognition in Parkinson's disease? a case report. *Neurocase*. 2010;16(4):301-306.
100. Tabak R, Aquije G, Fisher BE. Aerobic exercise to improve executive function in Parkinson disease: a case series. *J Neural Phys Ther*. 2013;37(2):58-64.
101. Smith PJ, Blumenthal JA, Hoffman BM, et al. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosom Med*. 2010;72(3):239-252.
102. Kelly ME, Loughrey D, Lawlor BA, Robertson IH, Walsh C, Brennan S. The impact of exercise on the cognitive functioning of healthy older adults: a systematic review and meta-analysis. *Ageing Res Rev*. 2014;16:12-31.
103. Young J, Angevaren M, Rusted J, Tabet N. Aerobic exercise to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev*. 2015;4:CD005381.
104. Griffin EW, Mullally S, Foley C, Warrington SA, O'Mara SM, Kelly AM. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiol Behav*. 2011;104(5):934-941.
105. Iuliano E, di Cagno A, Aquino G, et al. Effects of different types of physical activity on the cognitive functions and attention in older people: a randomized controlled study. *Exp Gerontol*. 2015;70:105-110.
106. Linde K, Alfemenn D. Single versus combined cognitive and physical activity effects on fluid cognitive abilities of healthy older adults: a 4-month randomized controlled trial with follow-up. *J Aging Phys Act*. 2014;22(3):302-313.
107. Nouchi R, Taki Y, Takeuchi H, et al. Four weeks of combination exercise training improved executive functions, episodic memory, and processing speed in healthy elderly people: evidence from a randomized controlled trial. *Age (Dordr)*. 2014;36(2):787-799.
108. Vaughan S, Wallis M, Polit D, Steele M, Shum D, Morris N. The effects of multimodal exercise on cognitive and physical functioning and brain-derived neurotrophic factor in older women: a randomised controlled trial. *Age Ageing*. 2014;43(5):623-629.
109. Vidoni ED, Johnson DK, Morris JK, et al. Dose-response of aerobic exercise on cognition: a community-based, pilot randomized controlled trial. *PLoS One*. 2015;10(7):e0131647.
110. Sink KM, Espeland MA, Castro CM, et al. Effect of a 24-month physical activity intervention vs health education on cognitive outcomes in sedentary older adults: the LIFE Randomized Trial. *JAMA*. 2015;314(8):781-790.
111. Voss MW, Heo S, Prakash RS, et al. The influence of aerobic fitness on cerebral white matter integrity and cognitive function in older adults: results of a one-year exercise intervention. *Hum Brain Mapp*. 2013;34(11):2972-2985.
112. de Souto Barreto P, Delrieu J, Andrieu S, Vellas B, Rolland Y. Physical activity and cognitive function in middle-aged and older adults: an analysis of 104,909 people from 20 countries. *Mayo Clin Proc*. 2016;91(11):1515-1524.
113. Gill SJ, Friedenreich CM, Sajobi TT, et al. Association between lifetime physical activity and cognitive functioning in middle-aged and older community dwelling adults: results from the Brain in Motion Study. *J Int Neuropsychol Soc*. 2015;21(10):816-830.
114. Hayes SM, Alosco ML, Hayes JP, et al. Physical activity is positively associated with episodic memory in aging. *J Int Neuropsychol Soc*. 2015;21(10):780-790.
115. Young JC, Dowell NG, Watt PW, Tabet N, Rusted JM. Long-term high-effort endurance exercise in older adults: diminishing returns for cognitive and brain aging. *J Aging Phys Act*. 2016;24(4):659-675.

116. Aberg MA, Pedersen NL, Toren K, et al. Cardiovascular fitness is associated with cognition in young adulthood. *Proc Natl Acad Sci U S A*. 2009;106(49):20906-20911.
117. Nyberg J, Aberg MA, Schioler L, et al. Cardiovascular and cognitive fitness at age 18 and risk of early-onset dementia. *Brain*. 2014;137(pt 5):1514-1523.
118. Zhu N, Jacobs DR Jr, Schreiner PJ, et al. Cardiorespiratory fitness and cognitive function in middle age: the CARDIA study. *Neurology*. 2014;82(15):1339-1346.
119. Wendell CR, Gunstad J, Waldstein SR, Wright JG, Ferrucci L, Zonderman AB. Cardiorespiratory fitness and accelerated cognitive decline with aging. *J Gerontol*. 2014;69(4):455-462.
120. Muller J, Chan K, Myers JN. Association between exercise capacity and late onset of dementia, Alzheimer disease, and cognitive impairment. *Mayo Clin Proc*. 2017;92(2):211-217.
121. Gordon BA, Rykhlevskaia EI, Brumback CR, et al. Neuroanatomical correlates of aging, cardiopulmonary fitness level, and education. *Psychophysiology*. 2008;45(5):825-838.
122. Voss MW, Erickson KI, Prakash RS, et al. Functional connectivity: a source of variance in the association between cardiorespiratory fitness and cognition? *Neuropsychologia*. 2010;48(5):1394-1406.
123. Weinstein AM, Voss MW, Prakash RS, et al. The association between aerobic fitness and executive function is mediated by prefrontal cortex volume. *Brain Behav Immun*. 2012;26(5):811-819.
124. McAuley E, Szabo AN, Mailey EL, et al. Non-exercise estimated cardiorespiratory fitness: associations with brain structure, cognition, and memory complaints in older adults. *Ment Health Phys Act*. 2011;4(1):5-11.
125. Freudenberger P, Petrovic K, Sen A, et al. Fitness and cognition in the elderly: the Austrian Stroke Prevention Study. *Neurology*. 2016;86(5):418-424.
126. Hayes SM, Forman DE, Verfaellie M. Cardiorespiratory fitness is associated with cognitive performance in older but not younger adults. *J Gerontol B Psychol Sci Soc Sci*. 2016;71(3):474-482.
127. Zhao E, Tranovich MJ, DeAngelo R, Kontos AP, Wright VJ. Chronic exercise preserves brain function in masters athletes when compared to sedentary counterparts. *Phys Sports Med*. 2016;44(1):8-13.
128. Belsky DW, Caspi A, Israel S, Blumenthal JA, Poulton R, Moffitt TE. Cardiorespiratory fitness and cognitive function in midlife: neuroprotection or neuroselection? *Ann Neurol*. 2015;77(4):607-617.
129. Sofi F, Valecchi D, Bacci D, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *J Intern Med*. 2011;269(1):107-117.
130. Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. *Psychol Med*. 2009;39(1):3-11.
131. Buchman AS, Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA. Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology*. 2012;78(17):1323-1329.
132. Iso-Markku P, Waller K, Vuoksimaa E, et al. Midlife physical activity and cognition later in life: a prospective twin study. *J Alzheimers Dis*. 2016;54(4):1303-1317.
133. Tolppanen AM, Solomon A, Kulmala J, et al. Leisure-time physical activity from mid- to late life, body mass index, and risk of dementia. *Alzheimers Dement*. 2015;11(4):434-443.e6.
134. Verdelho A, Madureira S, Ferro JM, et al. Physical activity prevents progression for cognitive impairment and vascular dementia: results from the LADIS (Leukoaraiosis and Disability) study. *Stroke*. 2012;43(12):3331-3335.
135. de Bruijn RF, Schrijvers EM, de Groot KA, et al. The association between physical activity and dementia in an elderly population: the Rotterdam Study. *Eur J Epidemiol*. 2013;28(3):277-283.
136. Iso-Markku P, Waller K, Kujala UM, Kaprio J. Physical activity and dementia: long-term follow-up study of adult twins. *Ann Med*. 2015;47(2):81-87.
137. Defina LF, Willis BL, Radford NB, et al. The association between midlife cardiorespiratory fitness levels and later-life dementia: a cohort study. *Ann Intern Med*. 2013;158(3):162-168.
138. Geda YE, Roberts RO, Knopman DS, et al. Physical exercise, aging, and mild cognitive impairment: a population-based study. *Arch Neurol*. 2010;67(1):80-86.
139. Jedrzewski MK, Ewbank DC, Wang H, Trojanowski JQ. Exercise and cognition: results from the National Long Term Care Survey. *Alzheimers Dement*. 2010;6(6):448-455.
140. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol*. 2001;58(3):498-504.
141. Middleton LE, Barnes DE, Lui LY, Yaffe K. Physical activity over the life course and its association with cognitive performance and impairment in old age. *J Am Geriatr Soc*. 2010;58(7):1322-1326.
142. Middleton LE, Manini TM, Simonsick EM, et al. Activity energy expenditure and incident cognitive impairment in older adults. *Arch Intern Med*. 2011;171(14):1251-1257.
143. Singh-Manoux A, Hillsdon M, Brunner E, Marmot M. Effects of physical activity on cognitive functioning in middle age: evidence from the Whitehall II prospective cohort study. *Am J Public Health*. 2005;95(12):2252-2258.
144. Vercambre MN, Grodstein F, Manson JE, Stampfer MJ, Kang JH. Physical activity and cognition in women with vascular conditions. *Arch Intern Med*. 2011;171(14):1244-1250.
145. Zhu W, Wadley VG, Howard VJ, Hutto B, Blair SN, Hooker SP. Objectively measured physical activity and cognitive function in older adults. *Med Sci Sports Exerc*. 2017;49(1):47-53.
146. Baker LD, Frank LL, Foster-Schubert K, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch Neurol*. 2010;67(1):71-79.
147. Kwak YS, Um SY, Son TG, Kim DJ. Effect of regular exercise on senile dementia patients. *Int J Sports Med*. 2008;29(6):471-474.
148. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA*. 2008;300(9):1027-1037.
149. Arcoverde C, Deslandes A, Moraes H, et al. Treadmill training as an augmentation treatment for Alzheimer's disease: a pilot randomized controlled study. *Arq Neuropsiquiatr*. 2014;72(3):190-196.
150. Cancela JM, Ayan C, Varela S, Seijo M. Effects of a long-term aerobic exercise intervention on institutionalized patients with dementia. *J Sci Med Sport*. 2016;19(4):293-298.
151. Kim MJ, Han CW, Min KY, et al. Physical exercise with multi-component cognitive intervention for older adults with Alzheimer's disease: a 6-month randomized controlled trial. *Dement Geriatr Cogn Dis Extra*. 2016;6(2):222-232.
152. Morris JK, Vidoni ED, Johnson DK, et al. Aerobic exercise for Alzheimer's disease: a randomized controlled pilot trial. *PLoS One*. 2017;12(2):e0170547.
153. Nagamatsu LS, Chan A, Davis JC, et al. Physical activity improves verbal and spatial memory in older adults with probable mild cognitive impairment: a 6-month randomized controlled trial. *J Aging Res*. 2013;2013:861893.
154. Suzuki T, Shimada H, Makizako H, et al. A randomized controlled trial of multicomponent exercise in older adults with mild cognitive impairment. *PLoS One*. 2013;8(4):e61483.
155. Yang SY, Shan CL, Qing H, et al. The effects of aerobic exercise on cognitive function of Alzheimer's disease patients. *CNS Neurol Disord Drug Targets*. 2015;14(10):1292-1297.
156. Bossers VJ, van der Woude LH, Boersma F, Hortobagyi T, Scherder EJ, van Heuvelen MJ. A 9-week aerobic and strength training program improves cognitive and motor function in

- patients with dementia: a randomized, controlled trial. *Am J Geriatr Psychiatry*. 2015;23(11):1106-1116.
157. Hoffmann K, Sobol NA, Frederiksen KS, et al. Moderate-to-high intensity physical exercise in patients with Alzheimer's disease: a randomized controlled trial. *J Alzheimers Dis*. 2016;50(2):443-453.
 158. Venturelli M, Scarsini R, Schena F. Six-month walking program changes cognitive and ADL performance in patients with Alzheimer. *Am J Alzheimers Dis Other Demen*. 2011;26(5):381-388.
 159. Miller LA, Spitznagel MB, Busko S, et al. Structured exercise does not stabilize cognitive function in individuals with mild cognitive impairment residing in a structured living facility. *Int J Neurosci*. 2011;121(4):218-223.
 160. Groot C, Hooghiemstra AM, Raijmakers PG, et al. The effect of physical activity on cognitive function in patients with dementia: a meta-analysis of randomized control trials. *Ageing Res Rev*. 2016;25:13-23.
 161. Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S. Exercise programs for brain diffusion with dementia. *Cochrane Database Syst Rev*. 2015;4:CD006489.
 162. Ohman H, Savikko N, Strandberg TE, Pitkala KH. Effect of physical exercise on cognitive performance in older adults with mild cognitive impairment or dementia: a systematic review. *Dement Geriatr Cogn Disord*. 2014;38(5-6):347-365.
 163. Kandiah N, Zainal NH, Narasimhalu K, et al. Hippocampal volume and white matter disease in the prediction of dementia in Parkinson's disease. *Parkinsonism Relat Disord*. 2014;20(11):1203-1208.
 164. Kantarci K, Lesnick T, Ferman TJ, et al. Hippocampal volumes predict risk of dementia with Lewy bodies in mild cognitive impairment. *Neurology*. 2016;87(22):2317-2323.
 165. Erickson KI, Prakash RS, Voss MW, et al. Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus*. 2009;19(10):1030-1039.
 166. Whiteman AS, Young DE, Budson AE, Stern CE, Schon K. Entorhinal volume, aerobic fitness, and recognition memory in healthy young adults: a voxel-based morphometry study. *Neuroimage*. 2016;126:229-238.
 167. Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*. 2011;108(7):3017-3022.
 168. Rosano C, Guralnik J, Pahor M, et al. Hippocampal response to a 24-month physical activity intervention in sedentary older adults. *Am J Geriatr Psychiatry*. 2017;25(3):209-217.
 169. Maass A, Duzel S, Goerke M, et al. Vascular hippocampal plasticity after aerobic exercise in older adults. *Mol Psychiatry*. 2015;20(5):585-593.
 170. Spartano NL, Himali JJ, Beiser AS, et al. Midlife exercise blood pressure, heart rate, and fitness relate to brain volume 2 decades later. *Neurology*. 2016;86(14):1313-1319.
 171. Colcombe SJ, Erickson KI, Raz N, et al. Aerobic fitness reduces brain tissue loss in aging humans. *J Gerontol*. 2003;58(2):176-180.
 172. Vidoni ED, Honea RA, Billinger SA, Swerdlow RH, Burns JM. Cardiorespiratory fitness is associated with atrophy in Alzheimer's and aging over 2 years. *Neurobiol Aging*. 2012;33(8):1624-1632.
 173. Colcombe SJ, Erickson KI, Scalf PE, et al. Aerobic exercise training increases brain volume in aging humans. *J Gerontol*. 2006;61(11):1166-1170.
 174. Ruscheweyh R, Willemer C, Kruger K, et al. Physical activity and memory functions: an interventional study. *Neurobiol Aging*. 2011;32(7):1304-1319.
 175. Mortimer JA, Ding D, Borenstein AR, et al. Changes in brain volume and cognition in a randomized trial of exercise and social interaction in a community-based sample of non-demented Chinese elders. *J Alzheimers Dis*. 2012;30(4):757-766.
 176. Bugg JM, Head D. Exercise moderates age-related atrophy of the medial temporal lobe. *Neurobiol Aging*. 2011;32(3):506-514.
 177. Gow AJ, Bastin ME, Munoz Maniega S, et al. Neuroprotective lifestyles and the aging brain: activity, atrophy, and white matter integrity. *Neurology*. 2012;79(17):1802-1808.
 178. Erickson KI, Raji CA, Lopez OL, et al. Physical activity predicts gray matter volume in late adulthood: the Cardiovascular Health Study. *Neurology*. 2010;75(16):1415-1422.
 179. Hayes SM, Salat DH, Forman DE, Sperling RA, Verfaellie M. Cardiorespiratory fitness is associated with white matter integrity in aging. *Ann Clin Transl Neurol*. 2015;2(6):688-698.
 180. Johnson NF, Kim C, Clasey JL, Bailey A, Gold BT. Cardiorespiratory fitness is positively correlated with cerebral white matter integrity in healthy seniors. *Neuroimage*. 2012;59(2):1514-1523.
 181. Oberlin LE, Verstynen TD, Burzynska AZ, et al. White matter microstructure mediates the relationship between cardiorespiratory fitness and spatial working memory in older adults. *Neuroimage*. 2016;131:91-101.
 182. Tian Q, Simonsick EM, Erickson KI, et al. Cardiorespiratory fitness and brain diffusion tensor imaging in adults over 80 years of age. *Brain Res*. 2014;1588:63-72.
 183. Zhu N, Jacobs DR Jr, Schreiner PJ, et al. Cardiorespiratory fitness and brain volume and white matter integrity: the CARDIA study. *Neurology*. 2015;84(23):2347-2353.
 184. Tian Q, Glynn NW, Erickson KI, et al. Objective measures of physical activity, white matter integrity and cognitive status in adults over age 80. *Behav Brain Res*. 2015;284:51-57.
 185. Boots EA, Schultz SA, Oh JM, et al. Cardiorespiratory fitness is associated with brain structure, cognition, and mood in a middle-aged cohort at risk for Alzheimer's disease. *Brain Imaging Behav*. 2015;9(3):639-649.
 186. Burzynska AZ, Chaddock-Heyman L, Voss MW, et al. Physical activity and cardiorespiratory fitness are beneficial for white matter in low-fit older adults. *PLoS One*. 2014;9(9):e107413.
 187. Sen A, Gider P, Cavalieri M, et al. Association of cardiorespiratory fitness and morphological brain changes in the elderly: results of the Austrian Stroke Prevention Study. *Neurodegener Dis*. 2012;10(1-4):135-137.
 188. Tseng BY, Gundapuneedi T, Khan MA, et al. White matter integrity in physically fit older adults. *Neuroimage*. 2013;82:510-516.
 189. Colcombe SJ, Kramer AF, Erickson KI, et al. Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci U S A*. 2004;101(9):3316-3321.
 190. Hayes SM, Hayes JP, Williams VJ, Liu H, Verfaellie M. fMRI activity during associative encoding is correlated with cardiorespiratory fitness and source memory performance in older adults. *Cortex*. 2017;91:208-220.
 191. Voss MW, Prakash RS, Erickson KI, et al. Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Front Aging Neurosci*. 2010;2:32.
 192. Olde Dubbelink KT, Schoonheim MM, Deijen JB, Twisk JW, Barkhof F, Berendse HW. Functional connectivity and cognitive decline over 3 years in Parkinson disease. *Neurology*. 2014;83(22):2046-2053.
 193. Duchesne C, Gheysen F, Bore A, et al. Influence of aerobic exercise training on the neural correlates of motor learning in Parkinson's disease individuals. *Neuroimage Clin*. 2016;12:559-569.
 194. Shah C, Beall EB, Frankemolle AM, et al. Exercise therapy for Parkinson's disease: pedaling rate is related to changes in motor connectivity. *Brain Connect*. 2016;6(1):25-36.
 195. Nelson ME, Rejeski WJ, Blair SN, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116(9):1094-1105.
 196. Ross R, Blair SN, Arena R, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation*. 2016;134(24):e653-e699.