

## Physical Exercise as a Preventive or Disease-Modifying Treatment of Dementia and Brain Aging

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A rapidly growing literature strongly suggests that exercise, specifically aerobic exercise, may attenuate cognitive impairment and reduce dementia risk. We used PubMed (keywords *exercise* and *cognition*) and manuscript bibliographies to examine the published evidence of a cognitive neuroprotective effect of exercise. Meta-analyses of prospective studies documented a significantly reduced risk of dementia associated with midlife exercise; similarly, midlife exercise significantly reduced later risks of mild cognitive impairment in several studies. Among patients with dementia or mild cognitive impairment, randomized controlled trials (RCTs) documented better cognitive scores after 6 to 12 months of exercise compared with sedentary controls. Meta-analyses of RCTs of aerobic exercise in healthy adults were also associated with significantly improved cognitive scores. One year of aerobic exercise in a large RCT of seniors was associated with significantly larger hippocampal volumes and better spatial memory; other RCTs in seniors documented attenuation of age-related gray matter volume loss with aerobic exercise. Cross-sectional studies similarly reported significantly larger hippocampal or gray matter volumes among physically fit seniors compared with unfit seniors. Brain cognitive networks studied with functional magnetic resonance imaging display improved connectivity after 6 to 12 months of exercise. Animal studies indicate that exercise facilitates neuroplasticity via a variety of biomechanisms, with improved learning outcomes. Induction of brain neurotrophic factors by exercise has been confirmed in multiple animal studies, with indirect evidence for this process in humans. Besides a brain neuroprotective effect, physical exercise may also attenuate cognitive decline via mitigation of cerebrovascular risk, including the contribution of small vessel disease to dementia. Exercise should not be overlooked as an important therapeutic strategy.

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AD = Alzheimer disease; BDNF = brain-derived neurotrophic factor; fMRI = functional brain magnetic resonance imaging; IGF-1 = insulin-like growth factor 1; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; RCT = randomized controlled trial;  $\dot{V}_{O_2}$  = oxygen consumption per unit time

Dementia is a major threat to our aging population. Besides destroying life quality of affected patients, it affects immediate family, turning spouses or children into caregivers and often straining family finances. Alzheimer disease (AD) accounts for most dementia cases,<sup>1</sup> with contributions from dementia with Lewy bodies, vascular disease, frontotemporal degeneration syndromes, and various other less common disorders. Less devastating but also disrupting life quality is mild cognitive impairment (MCI), documented in more than 10% of seniors older than 70 years, with more than 20% affected after the age of 80 years.<sup>2</sup> Often MCI is a prelude to subsequent dementia.<sup>3</sup>

Notable also is the subtle loss of cognitive skills often accompanying normal aging. Seniors frequently experience reduced memory for names and telephone numbers. Whether the substrate is the progressive loss of gray matter routinely seen with brain magnetic resonance imaging (MRI) of seniors is debatable; indeed, normal brain aging is accompanied by loss of synaptic connections and attenuated neuropil.<sup>4,5</sup>

The neurodegenerative dementias are presumed to be proteinopathies, characterized by aggregation of a specific protein within the brain, such as  $\beta$ -amyloid and microtubule-associated protein tau in AD or  $\alpha$ -synuclein in dementia with Lewy bodies. Despite intensive research directed at these and other neurodegenerative diseases, no drug effectively targets the pathogenic substrates. No medication has been proven to reduce the subsequent risk of dementia or age-related cognitive impairment.

### REGULAR EXERCISE AS NEUROPROTECTIVE THERAPY

Although medications have no proven neuroprotective effect on dementia, an evolving literature documents significant benefit of long-term, regular exercise on cognition, dementia risk, and perhaps dementia progression. These studies suggest an attenuating effect on brain aging and resilience to dementing neurodegenerative mechanisms.

Exercise also favors brain health via the well-known attenuating influences on atherosclerotic cerebrovascular disease. Thus, primary vascular dementia is common and, moreover, cerebrovascular small vessel disease (eg, leukoariosis and lacunar disease) appears additive with

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neurodegenerative processes to cause dementia.<sup>6</sup> These atherosclerotic cerebrovascular mechanisms are distinctive from neurodegeneration and age-related loss of neuropil and synapses. Because the benefit of exercise on atherosclerotic (cerebrovascular) risk seems well established, this contribution to the subject will not be a focus of this article.

Our focus is on the scientific basis for advocating regular exercise as a prophylactic and perhaps disease-slowng treatment of neurodegenerative and age-related dementia and MCI. Although certain studies in humans make it difficult to separate vascular contributions, the literature in the aggregate suggests that exercise may have more direct favorable effects on brain neuroplasticity and resilience to brain aging and neurodegeneration.

A recent National Institutes of Health State-of-the-Science Statement took a nihilistic view of exercise as a disease-modifying influence on cognition or dementing illness.<sup>7,8</sup> However, as pointed out in a subsequent critique of this statement, the conclusions were based on a narrow scope of data.<sup>9</sup>

We present evidence that argues for the benefit of exercise on cognition and the forestalling of later-life cognitive decline. In contrast to the recent National Institutes of Health consensus statement,<sup>7,8</sup> we considered a broad expanse of both animal and human studies relevant to this topic. In an attempt to capture the relevant literature, we reviewed all publications identified by a PubMed search using the keyword *cognition* cross-referenced with *exercise* (identifying 1603 publications, without date limitations) and identified additional relevant articles via review of bibliographies from these and other publications.

### DEFINING REGULAR EXERCISE

The literature on this subject, including animal studies, implies that potential benefits accrue with long-term, regular exercise. The exercise parameters cannot be precisely defined, but the connotation is aerobic physical exercise that is sufficient to increase the heart rate and the need for oxygen. Presumably, this must be sustained (eg, for at least 20-30 minutes per session) and ongoing. Ultimately, this translates into what physiologists characterize as cardiovascular fitness, objectively assessed with measurement of oxygen uptake during peak exercise (such as on a treadmill); this is reported as peak oxygen consumption per unit time ( $\dot{V}O_2$ ), with higher values indicative of better fitness.

Limited studies have also specifically addressed resistance exercise (effort against weighting or resistance) and cognition; however, this literature is currently insufficient to draw conclusions. Hence, we primarily fo-

cus on aerobic-type exercise that potentially leads to physical fitness.

### EXERCISE MODALITIES

Although other medical conditions may limit the extent of exercise, modalities should be available for all people, except perhaps those with major cardiopulmonary disease or major organ failure. There is a wide variety of such aerobic exercise options, including walking, gym or health club routines, driveway basketball, and home activities, such as shoveling snow, raking leaves, or other yard work. Impaired ambulation does not preclude certain sitting exercises, such as use of rowing machines, exercise bicycles, or other gym machines.

### IMPROVEMENT IN COGNITIVE SCORES IN HEALTHY ADULTS

Recent meta-analyses of 29 randomized controlled trials (RCTs) documented significant cognitive benefits from sustained exercise in adults without dementia (although 3 of the 29 trials enrolled patients with MCI).<sup>10</sup> Significantly improved scores were noted in memory, attention, processing speed, and executive function, albeit with only modest improvement. Because the benefits accrued during 1 to 12 months of exercise (except for one 18-month trial), these findings are less easily explained by the secondary influence of exercise on cerebrovascular disease (eg, leukoaraiosis, lacune, or stroke risk).

### FUNCTIONAL MRI COGNITIVE NETWORKS IN HEALTHY SENIORS

Functional brain MRI (fMRI) during cognitive tasks has also documented significantly improved cognitive networks with exercise or fitness. In one 6-month RCT among seniors, aerobic exercise translated into significantly improved cortical connectivity and activation, compared with controls.<sup>11</sup> In a 12-month RCT, aerobic exercise likewise improved cognitive fMRI network connectivity; however, the control group undergoing nonaerobic stretching and toning also had improved fMRI outcomes.<sup>12</sup>

In cross-sectional analyses, physically fit seniors had fMRI evidence of significantly better cortical connectivity and activation during cognitive tasks than unfit seniors (assessed by peak  $\dot{V}O_2$  during exercise).<sup>11,13</sup> Physically fit seniors also performed significantly better on cognitive tasks than unfit seniors in these cross-sectional studies.<sup>11,13,14</sup>

### MRI GRAY MATTER VOLUME LOSS IN SENIORS

Brain gray matter volumes decrease with advancing age, as routinely seen in the clinic with brain MRI. In contrast to neu-

rodegenerative disorders, which are associated with neuronal loss, the reductions of gray matter volumes seen in normal aging primarily reflect loss of neuropil and synapses.<sup>4,5</sup>

A recent RCT in a large cohort of seniors documented significantly larger hippocampal volumes after 1 year of aerobic exercise, compared with the control intervention of simple stretching and toning.<sup>15</sup> This finding was associated with significant improvement in the primary cognitive outcome measure of spatial memory. Similar exercise outcomes have been documented in the neocortex. Thus, two 6-month RCTs of aerobic exercise in seniors without dementia were associated with increased cortical volumes compared with sedentary interventions.<sup>16,17</sup> In a long-term, prospective cohort study, the usual weekly walking distances reported by healthy adults at baseline were positively associated with neocortical and hippocampal MRI volumes 9 years later.<sup>18</sup>

In a large, cross-sectional study of seniors without dementia, physical fitness, assessed by treadmill exercise testing (peak  $\dot{V}O_2$ ), was highly and significantly associated with hippocampal volumes on MRI (controlling for age, sex, and educational level).<sup>19</sup> In other cross-sectional studies, physical fitness (measured by peak  $\dot{V}O_2$ ) was associated with better preservation of gray matter volumes among both cognitively normal seniors<sup>14,20</sup> and patients with early AD.<sup>21,22</sup> The control groups in these latter 2 studies, however, did not generate expected results; in these seniors without dementia, there was no association of cardiorespiratory fitness (peak  $\dot{V}O_2$ ) with gray matter volumes.<sup>21,22</sup>

### MIDLIFE EXERCISE AND REDUCED RISKS OF LATER DEMENTIA AND MCI

Adults who routinely engaged in physical activities, sports, or regular exercise in midlife carried a significantly lower risk of dementia years later, based on a recent meta-analysis of prospective cohort studies.<sup>23</sup> Thus, reduction of dementia risk was documented in 10 of 11 studies, with an estimated relative risk of 0.72 ( $P < .001$ ).<sup>23</sup>

Several prospective cohort investigations have reported significantly reduced subsequent risks of MCI associated with midlife exercise.<sup>24-26</sup> A population-based, case-control study similarly found that moderate exercise retrospectively reported for midlife was associated with a significantly reduced risk of MCI.<sup>27</sup> Reduction of MCI risk with retrospectively reported earlier life exercise was also documented in a cross-sectional study of a large female cohort.<sup>28</sup>

One caveat: the association of midlife exercise with later cognitive preservation could be explained by reverse causality. In other words, those with very early, preclinical neurodegenerative disease might be disinclined to exercise.

### INFLUENCE OF PHYSICAL ACTIVITY ON MORTALITY IN AD PATIENTS

A population-based, prospective cohort study of incident AD patients revealed that those who maintained physical activity had a significantly reduced risk of mortality.<sup>29</sup> This was true even after statistically adjusting for *APOE* genotype, medical comorbidities, and cognitive performance. Again, however, reverse causality cannot be excluded.

### SHORT-TERM COGNITIVE BENEFIT AMONG THOSE WITH MCI OR DEMENTIA

Reverse causality would not explain improved cognitive scores in short-term RCTs. A meta-analysis<sup>30</sup> of RCTs in seniors with MCI or dementia tabulated outcomes with exercise durations spanning 2 to 112 weeks. Among the 12 trials, significant cognitive benefits were documented compared with control outcomes.

Several more recent studies have added to this literature. Most compelling was the Australian trial randomizing 170 subjects with “memory problems” to 6 months of moderate-intensity exercise vs a sedentary routine.<sup>31</sup> The exercise group had significantly better scores on the primary outcome measure after the 6 months, the Alzheimer Disease Assessment Scale–Cognitive Subscale; this benefit persisted at 12 and 18 months. Interestingly, they noted that the extent of improvement on the Alzheimer Disease Assessment Scale–Cognitive Subscale compared favorably to the effect of donepezil documented in another large clinical trial.<sup>32</sup> A similar outcome in seniors with MCI was documented in one smaller 6-month RCT of “high-intensity aerobic exercise” vs sedentary controls (stretching); however, the improvement was predominantly in women.<sup>33</sup> One additional RCT in seniors with MCI identified similar but not statistically significant trends after 1 year of exercise; the investigators commented that the analysis was compromised by suboptimal adherence to the exercise program.<sup>34</sup> In women with dementia, a small RCT of regular exercise for 1 year significantly improved the Mini-Mental State Examination score compared with slight (nonsignificant) worsening in the sedentary control group.<sup>35</sup> Of note, 2 of these trials<sup>31,34</sup> were included in the meta-analysis by Smith et al.<sup>10</sup>

### PLAUSIBILITY FROM ANIMAL STUDIES

The studies in humans suggest that exercise may improve cognition in the short term, reduce risks of dementia or MCI in the long term, and reduce the age-associated progressive loss of brain volume. This issue lends itself to as-

assessment in animal models, in which it is also possible to study putative biological mechanisms.

### EXERCISE IMPROVES COGNITION IN ANIMALS

Exercised rats or mice (eg, treadmills and running wheels) have significantly better scores on memory tests or object recognition compared with their more sedentary counterparts.<sup>36-42</sup> Conversely, immobilization had the opposite effect, with reduced cognitive scores.<sup>43</sup> These findings have been extended to primates; monkeys with scheduled exercise for 5 months had significantly better cognitive scores than sedentary animals.<sup>44</sup>

### EVIDENCE FOR ENHANCED NEUROPLASTICITY INDUCED BY EXERCISE IN ANIMALS

Brain neuroplasticity is a fundamental mechanism for learning, memory, and general cognition. A voluminous literature in rats and mice has documented multiple mechanisms by which exercise may facilitate such neuroplasticity. Thus, exercise has been shown to increase expression of synaptic plasticity genes,<sup>45</sup> gene products such as synapsin I and synaptophysin,<sup>46,47</sup> and various neuroplasticity-related transcription factors such as cyclic adenosine monophosphate response element binding and intracellular kinases.<sup>42,48,49</sup> Hippocampal dendritic length and dendritic spine complexity are enhanced with exercise.<sup>50,51</sup> Neurogenesis within the hippocampal dentate gyrus is also induced by exercise.<sup>50,52-54</sup> Finally, long-term potentiation, which is thought to be a primary neurophysiologic substrate in learning, is potentiated by exercise,<sup>38,41,54</sup> although this effect was confined to male animals in one study.<sup>55</sup>

### BRAIN EXPRESSION OF NEUROTROPHIC FACTORS INDUCED BY EXERCISE IN ANIMALS

Neurotrophic factors appear to be especially involved in learning and neuroplasticity. Brain-derived neurotrophic factor (BDNF) has been most extensively investigated and, *in vitro*, modulates brain plasticity, including increasing neuritic outgrowth and synaptic function. It also promotes *in vitro* survival of a vast array of neurons affected by neurodegenerative conditions, including AD.<sup>56</sup> Numerous investigations in mice or rats have found elevated brain BDNF concentrations and expression with exercise,<sup>36,37,41,42,46,47,49,54,57-60</sup> although with one exception.<sup>55</sup> Insulin-like growth factor 1 (IGF-1) interacts with BDNF and is likewise elevated in the rat brain by exercise.<sup>40,61</sup> Rat brain concentrations of glial-derived neurotrophic factor are similarly upregulated by exercise.<sup>59,62</sup>

### EXERCISE AND HIPPOCAMPAL NEUROGENESIS IN HUMANS

The hippocampus is crucial for memory and progressively degenerates in patients with AD, an effect already apparent in the earliest stages of dementia (MCI).<sup>63</sup> The hippocampal dentate gyrus is also the region most vulnerable to aging.<sup>64</sup> However, this region is one of the few brain regions that supports neurogenesis, and dentate gyrus neurogenesis is significantly facilitated by exercise in animal studies, as previously mentioned.<sup>50,52-54,65</sup>

Regional hippocampal dentate gyrus blood volume can be measured with brain MRI, and this was shown to be a neurogenesis biomarker in mice.<sup>65</sup> Extending this to humans in a small, prospective, uncontrolled trial of young adults, 3 months of aerobic exercise resulted in significantly increased hippocampal dentate gyrus blood volume over baseline; other hippocampal regions were unchanged.<sup>65</sup> This was interpreted as reflective of dentate gyrus angiogenesis and hence neurogenesis. It was associated with mildly improved cognitive scores. Fitness, as measured by peak  $\dot{V}O_2$ , significantly correlated with individual differences in dentate gyrus blood volume.<sup>65</sup>

### NEUROTROPHIC FACTORS, COGNITION, AND EXERCISE IN HUMANS

Theoretically, neurotrophic factors may be important in combating age-related brain atrophy and perhaps neurodegenerative disease. In contrast to laboratory animals, however, brain concentrations of neurotrophic factors cannot easily be studied in humans. Human investigations have focused on circulating levels, which may or may not reflect what is going on within the brain.

BDNF is widely expressed throughout the human adult brain,<sup>56</sup> whereas levels are significantly reduced in the brains of AD patients.<sup>66-69</sup> BDNF is rapidly transported in both directions across the blood-brain barrier,<sup>70,71</sup> and hence measurement of circulating levels could be relevant to the brain. Thus, circulating BDNF levels are reduced in patients with AD<sup>72,73</sup>; moreover, AD patients whose condition is rapidly declining have significantly lower serum BDNF concentrations than those whose condition is slowly declining.<sup>74</sup> Note also that in healthy young adults, BDNF appears to be released from the human brain by both short-term vigorous exercise<sup>75</sup> and long-term endurance training<sup>76</sup> on the basis of arterial and venous measurements.

In cross-sectional studies of seniors, circulating BDNF levels have been significantly associated with cognitive test scores after adjusting for multiple covariables,<sup>77,78</sup> although confined to women in one study.<sup>77</sup> In fact, fitness (peak  $\dot{V}O_2$ ) was significantly correlated with both BDNF

and cognitive improvement in one of these studies.<sup>78</sup> Moreover, in a 1-year RCT of exercise among seniors, increased serum BDNF level was associated with increased hippocampal volume.<sup>15</sup>

The study of aerobic exercise on plasma or serum BDNF levels has generated complex findings. Most investigations in young adults have documented significant transient increases of circulating BDNF with short-term aerobic exercise,<sup>79-82</sup> with one exception.<sup>83</sup> Prospective studies of long-term aerobic exercise, however, have generated negative or inconsistent results. Thus, 5 weeks of chronic aerobic exercise in young adults was associated with increased levels of circulating BDNF in one uncontrolled trial,<sup>84</sup> whereas two trials were negative (8-12 weeks; one controlled).<sup>83,85</sup> In one RCT of patients with MCI, 6 months of “high-intensity aerobic exercise” resulted in a nonsignificant trend toward increased plasma BDNF levels in men but reduced in women (compared with control values).<sup>33</sup> Somewhat paradoxically, 2 cross-sectional studies documented an inverse relationship between physical fitness and serum BDNF concentrations.<sup>86,87</sup>

The few prospective trials of resistance (not aerobic) exercise influences on plasma or serum BDNF levels have generated primarily negative results. In contrast to aerobic exercise, strength and resistance exercise did not elevate circulating BDNF concentrations.<sup>88-90</sup> A prospective, controlled trial of strength training (10 weeks) failed to increase serum BDNF levels.<sup>90</sup> As an exception, 5 weeks of resistance exercise raised serum BDNF levels in one other prospective, uncontrolled trial in young men.<sup>91</sup>

Insulin-like growth factor 1 is widely expressed in the human brain, and IGF-1 insufficiency has been proposed as a risk factor for AD.<sup>92</sup> Patients with AD had significantly lower circulating IGF-1 levels than controls in one small cross-sectional study, and these levels were inversely correlated with the degree of cognitive impairment.<sup>93</sup> Meta-analysis of the predominantly cross-sectional studies assessing circulating IGF-1 levels and cognition in seniors revealed a highly significant positive association.<sup>94</sup> In healthy young adults, circulating IGF-1 is increased by exercise in most<sup>88,95-97</sup> but not all studies.<sup>98</sup> In young adults, long-term aerobic exercise failed to elevate circulating IGF-1 levels in 2 RCTs (12-16 weeks).<sup>85,99</sup> In contrast to aerobic exercise, long-term resistance training elevated serum IGF-1 concentrations in 2 prospective, controlled trials<sup>100,101</sup> but not in another.<sup>102</sup>

### EXERCISE IMPACT ON BRAIN $\beta$ -AMYLOID AND TAU PROTEIN

Alzheimer disease is the most common neurodegenerative dementia and is neuropathologically marked by the accumulation of neuritic plaques, as well as neurofibrillary tangles

containing hyperphosphorylated tau protein. Perhaps a crucial inciting factor for AD development is the brain deposition of  $\beta$ -amyloid, the primary component of neuritic plaques. Brain accumulation of  $\beta$ -amyloid can be assessed in vivo using Pittsburgh compound B positron emission tomography. One recent investigation (cross-sectional design) documented an inverse relationship between long-term exercise levels and brain Pittsburgh compound B imaging density in a large cohort of cognitively normal seniors.<sup>103</sup> These brain imaging findings were mirrored by spinal fluid tau protein and  $\beta$ -amyloid<sub>42</sub> biomarkers. Again, however, reverse causality cannot be excluded. A small RCT of 6 months of exercise in patients with MCI documented a nonsignificant trend toward reduced plasma concentrations of  $\beta$ -amyloid<sub>42</sub> compared with sedentary controls.<sup>33</sup>

Most investigations of exercise and brain  $\beta$ -amyloid deposition, however, have been performed using transgenic mice overexpressing pathogenic amyloid precursor protein (or presenilin 2<sup>104</sup>). The findings have been mixed, with a reduction of brain pathogenic  $\beta$ -amyloid deposition or amyloid plaques in most<sup>104-109</sup> but not all studies.<sup>110-112</sup>

Neurofibrillary tangles are marked by hyperphosphorylated tau protein and are one of the pathological hallmarks of AD. In transgenic mice expressing a human pathogenic tau gene, 9 months of exercise prevented both the development of hippocampal tau disease and memory impairment, which were present in the sedentary control group.<sup>113</sup> In 2 other studies, 12 weeks of exercise significantly reduced tau phosphorylation in transgenic mice expressing pathogenic tau<sup>114</sup> or presenilin 2<sup>104</sup> genes (compared with sedentary controls).

### ATTENUATION OF VASCULAR CONTRIBUTIONS TO NEURODEGENERATIVE DEMENTIA BY EXERCISE

There is a striking overlap of the risk factors for AD and vascular dementia. Glucose intolerance and diabetes mellitus, hypertension, hyperlipidemia, and obesity contribute to not only vascular dementia but also to the risk of neurodegenerative dementia.<sup>6</sup> Intuitively, the influence of these vascular factors may be indirect via superimposed small vessel disease (eg, leukoaraiosis, lacunar strokes, and microbleeds). The added burden of cerebrovascular brain damage may simply superimpose on neurodegeneration. However, a more direct effect of these vascular risk factors on neurodegenerative processes is plausible. Regardless, long-term exercise is well known to attenuate each of these risk factors.<sup>115-117</sup>

### OTHER BENEFICIAL EFFECTS OF EXERCISE

Numerous noncognitive, nonvascular benefits additionally benefit from exercise, which may be especially relevant to

an aging population. This includes reduction of osteoporosis and fracture risk,<sup>118</sup> age-related sarcopenia,<sup>119</sup> and benefits directed at depression<sup>120</sup> and anxiety.<sup>121</sup> An exercise program may improve behavioral management in seniors with dementia<sup>122</sup> and fall risk.<sup>123</sup> Importantly, long-term physical activity and fitness reduce mortality risk in the general population.<sup>117,124</sup>

### ADVERSE EFFECTS OF EXERCISE

Advocating for an intervention (in this case, exercise) should be balanced against possible adverse effects. Exercise may result in orthopedic injuries, increase fall risk, and provoke acute coronary syndromes. Thus, physicians should help patients select exercise programs compatible with their capabilities and cardiopulmonary status. In general, people who have been sedentary for an extended time should begin an exercise program with modest exercise targets, but escalating as fitness is progressively achieved.

### RESISTANCE TRAINING

Although the focus of this article has been on aerobic fitness, limited studies have suggested that regular resistance exercise (pushing or pulling against fixed weighting) may also improve cognition. Indeed, improved cognitive scores were documented in RCTs conducted for 2,<sup>125</sup> 6,<sup>101</sup> and 12<sup>126</sup> months. An additional 1-year follow-up in this last study revealed that cognitive benefits were sustained in the exercise group compared with the sedentary group.<sup>127</sup> However, whole-brain volumes were inexplicably reduced in this 12-month resistance training trial<sup>126</sup>; this is in contrast to previously cited aerobic exercise trials in which cortical and hippocampal volumes were increased.<sup>15-19</sup>

Obviously, resistance training may contribute to aerobic fitness if the focus is on lighter weights (lesser resistance), more repetitions, and brief rest periods. However, the effect of resistance training on cognition has been inadequately studied to date and is difficult to assess in animal studies.

### IS MORE EXERCISE BETTER?

The literature cited herein suggests cognitive benefits from aerobic exercise, but it remains unclear whether there are threshold effects or whether exercise duration and intensity are important variables. In mice, longer durations of exercise were more effective than shorter durations in attenuating the neuropathologic and clinical effects of the dopaminergic neurotoxin, 1-methyl-4-phenyl-1,2,3,6-

tetrahydropyridine.<sup>128,129</sup> In a single human study, serum BDNF levels increased with exercise in proportion to the degree of lactate elevation.<sup>80</sup>

Human clinical trials assessing exercise duration or intensity, however, have been confined to resistance training. In a 6-month RCT in seniors, 2 intensities of resistance exercises (moderate and high) resulted in similar degrees of cognitive benefit.<sup>101</sup> In another RCT, once-weekly resistance exercise significantly improved cognitive scores similar to twice-weekly exercise.<sup>126</sup> However, duration was important in this latter trial in that the cognitive benefit was only documented at 12 but not 6 months. These 2 trials, however, assessed resistance training, not aerobic exercise, per se.

### AEROBIC EXERCISE PRESCRIPTION

Aerobic exercise implies training that elevates heart rate and increases  $\dot{V}O_2$ , but the exercise parameters to recommend are not well delineated. The human trials summarized herein have primarily used moderate aerobic exercise, which typically implies exercise sufficient to elevate heart rate or  $\dot{V}O_2$  to approximately 60% of the maximum. For example, in 2 RCTs, the dose of 150 minutes of moderate aerobic exercise per week was sufficient to be cognitively protective<sup>31</sup> and associated with increased hippocampal volume plus improved spatial memory.<sup>15</sup> Such moderate intensity is a practical exercise target, recognizing that greater exercise intensity might not be tolerated and lead to greater numbers of study dropouts or nonadherence, at least initially.

Regular aerobic exercise gradually increased to achieve 60% of maximal heart rate or  $\dot{V}O_2$  and performed at least 150 minutes weekly seems reasonable as an initial regimen. This is similar to the recommendation of the American Heart Association, which advises "...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"; parenthetically, they also recommended resistance exercises "for a minimum of two days each week."<sup>130</sup> Future research should investigate exercise parameters to better determine the optimal recommendations for preservation of cognition and brain health.

Choice of exercise routines needs to be guided by patients' capabilities. Those with imbalance or lower limb arthritis may take advantage of health facilities that provide exercise machines used in the sitting position. The choice of exercise should also be consonant with patient interests because if too onerous it is likely to be abandoned. For very sedentary individuals, a therapist or knowledgeable trainer may be advisable to gradually

introduce and escalate exercise routines and further reinforce patient effort.

## CONCLUSION

These data suggest that aerobic exercise is associated with a reduced risk of cognitive impairment and dementia; it may slow dementing illness. A compelling argument can be made for this via 2 plausible biologic pathways. First, a convergence of evidence from both animal and human studies suggests that aerobic exercise may attenuate progression of neurodegenerative processes and age-related loss of synapses and neuropil. This may occur via a direct influence on neurodegenerative disease mechanisms or facilitation of neuroprotective neurotrophic factors and neuroplasticity. Not to be overlooked, however, is a second pathway, cerebrovascular disease. Cerebrovascular burden contributes to dementia risk, especially via small vessel disease (eg, lacunes and leukoaraiosis). Vascular risk factors are well known to be reduced by aerobic exercise. Thus, ongoing, moderate-intensity physical exercise should be considered as a prescription for lowering cognitive risks and slowing cognitive decline across the age spectrum.

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