Review

Exercise Improves Vascular Function, but does this Translate to the Brain?

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Abstract. The number of adults with Alzheimer's disease (AD) or related dementia is expected to increase exponentially. Interventions aimed to reduce the risk and progression of AD and dementia are critical to the prevention and treatment of this devastating disease. Aging and cardiovascular disease risk factors are associated with reduced vascular function, which can have important clinical implications, including brain health. The age-associated increase in blood pressure and impairment in vascular function may be attenuated or even reversed through lifestyle behaviors. Greater volumes of habitual exercise and higher cardiorespiratory fitness are associated with beneficial effects on vascular health and cognition. Exercise and cardiorespiratory fitness may be most important during midlife, as physical activity and cardiorespiratory fitness during the middle-aged years are associated with future cognitive function. The extent to which exercise, and more specifically aerobic exercise, influences the cerebral circulation is not well established. In this review, we present our working hypothesis showing how cerebrovascular function may be a mediating factor underlying the association between exercise and cognition, as well as discuss recent studies evaluating the effect of exercise interventions on the cerebral circulation.

Keywords: Physical activity, cognition, blood pressure, blood flow, blood vessels

INTRODUCTION

According to the Alzheimer's Association, one in three adults over 65 years of age die with Alzheimer's disease (AD) or another related dementia [1]. Between the years 2000 and 2014, mortality from cardiovascular disease, stroke, and HIV declined; however, the number of deaths attributed to AD increased by 89% [1]. By 2025, an estimated 7.1 million adults in the U.S. will have AD, not including other dementias [1]. Because no cure for AD exists, there is a critical need to develop interventions to delay or prevent AD and related dementias.

Adults with cardiovascular disease have a greater incidence of having cognitive impairment compared with adults without cardiovascular disease [2]. Furthermore, even in the absence of established cardiovascular disease, vascular risk factors such as hypertension, diabetes, and obesity during midlife are associated with lower brain volumes and impaired cognitive function 10 years later [3]. The idea that cardiovascular health is relevant to brain structure and function has been highlighted by the American

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Heart Association and American Stroke Association who stated that the same risk factors for stroke are also likely risk factors for AD [4]. Better vascular health during midlife is associated with higher cognitive function [5]. An effective way to improve vascular health and promote healthy vascular aging is through lifestyle modifications, including habitual aerobic exercise, which may act to support cerebrovascular health. Epidemiological evidence has demonstrated that physical activity and exercise are associated with preserved cognitive function [6–8]. In support of this, Barnes & Yaffe calculated population attributable risks that included the prevalence of the risk factor and the strength of association of that risk factor with AD diagnosis. Of all of the modifiable risk factors for AD (including diabetes, hypertension, obesity, smoking, depression, physical inactivity, and cognitive inactivity), increasing the proportion of the population who are physically active by 25% was statistically the most effective measure in countering AD [9]. Thus, although cardiovascular risk factors may be detrimental to brain health, habitual aerobic exercise may be a promising intervention to improve vascular health and in turn prevent or delay the onset of age-related cognitive decline. This review will discuss the hypothesis that regular exercise, and specifically regular exercise associated with improved cardiorespiratory fitness, enhances cognition through the beneficial effects of exercise on vascular health. While we are not the only group of investigators who are actively working on this hypothesis, this area is relatively undeveloped, with many unanswered research questions. Therefore, this review is limited to the available literature and relies on the previous correlative and cross-sectional studies showing associations between exercise and vascular health, as systematic, randomized control trials are currently ongoing and the results are not yet available [10–12].

PHYSICAL ACTIVITY, FITNESS AND COGNITION

To a large extent, the work establishing the link between physical activity and cognition is dependent on subjective information regarding participants' recall of the volume of leisure time physical activity performed or on objective physiological information quantifying the level of cardiorespiratory fitness. Both subjective measures of physical activity participation and objectively measured cardiorespiratory fitness have been positively associated with cog-

nition. For example, older adults who reported walking more blocks per week had a lower risk of cognitive impairment 9 years later [13]. Similarly, cardiorespiratory fitness measured during an incremental exercise test was correlated with executive function test scores [14, 15].

Lifelong physical activity and high levels of cardiorespiratory fitness are important for brain health as humans age. In a recent study by Horder, et al., higher cardiorespiratory fitness in women at midlife was associated with lower risk of dementia approximately 44 years later [16]. In addition, Nyberg et al. reported that greater cardiorespiratory fitness levels at age 18 were associated with a lower hazard ratio for development of mild cognitive impairment (MCI) or dementia [17]. Taken together, these results suggest that cardiorespiratory fitness and lifestyle behaviors during the young and middle-aged years are important in determining future risk of cognitive decline.

Several studies have performed randomized control trials in sedentary adults or adults with low initial physical activity levels in order to measure the effect of increased physical activity participation on cognition. The results of these trials have shown no change [18, 19] or improvements [20–22] in cognition, with improvements occurring specifically in adults with high adherence rates. While there is discrepancy in the literature in regard to the effectiveness of exercise interventions on improving cognition, the majority of studies that measure cardiorespiratory fitness and demonstrate an increase in cardiorespiratory fitness as a result of the intervention, have reported improvement in cognitive outcomes [23, 24]. In fact, a study by Vironi, et al. has shown that the magnitude of change in cardiorespiratory fitness, rather than the dose of exercise administered during the intervention, was a better predictor of cognitive benefit [23]. Thus, while the volume of exercise employed in randomized control trials is important, the improvement in cardiorespiratory fitness may be crucial to achieving improvements in cognitive function.

As mentioned above, greater volumes of physical activity and higher levels of cardiorespiratory fitness are associated with improved cognitive function and decreased risk of cognitive decline. One factor underlying the beneficial effects of physical activity or fitness on cognition is the maintenance of brain volume or reduced atrophy rates [14]. Longitudinal assessments of brain volumes have demonstrated that atrophy occurs with advancing age [25], particularly after 65 years of age [26], and this brain atrophy is accelerated in adults who progress to MCI or AD [27]. Importantly, older adults who reported walking more

than 72 blocks per week demonstrated greater grey matter volume compared with adults who reported walking less [13]. Similarly, higher cardiorespiratory fitness in older adults was positively associated with greater hippocampal volume [28–30] and lower rates of age-related decline in grey matter, particularly in the prefrontal, superior parietal, and temporal cortices [30]. Therefore, physical activity and exercise appear to mitigate the atrophy rates of grey matter, hippocampal, and whole brain volumes, which are considered biomarkers of cognitive decline.

Another factor that could explain some of the beneficial effects of regular exercise on cognition is the maintenance of cerebral blood flow (CBF). Global CBF declines with age [31–33], which may be due to regional atrophy (although reduced CBF has been shown independent of regional atrophy [31]), lower cerebral metabolism, increased cerebrovascular resistance, or vascular dysfunction [33]. In older adults, there is a positive association between self-reported volumes of physical activity and CBF in grey matter regions [34]. Similarly, studies investigating blood flow parameters in the middle cerebral artery (MCA) also report an association between cardiorespiratory fitness and MCA blood velocity [35]. CBF declines with age, and greater global CBF or MCA blood velocity may be protective in reducing the negative impact of aging on brain health. This hypothesis is based on the idea that: 1) greater levels of CBF may prevent or slow the accumulation of neuropathology, in particular amyloid-β [36, 37]; and 2) greater levels of CBF may allow for higher cognitive reserve for a given level of neuropathological burden [38, 39].

While physical activity recall, physical activity tracking (e.g. steps per day using physical activity trackers), and cardiorespiratory fitness (e.g. VO_2max) are used in quantifying physical activity and exercise, the mechanisms underlying the cognitive effects of physical activity vs. fitness may be different. Increasing physical activity participation and reducing sedentary behaviors have a variety of cardiovascular and metabolic benefits; however, higher cardiorespiratory fitness typically observed in lifelong exercisers may provide additional advantages. When comparing healthy middle-aged and older adults who met physical activity guidelines to adults with a history of lifelong endurance exercise, grey matter volumes were statistically higher in lifelong endurance exercisers [40]. Additionally, cortical thickness in these lifelong endurance exercisers was higher in several regions of the brain and cortical thickness was positively correlated with cardiorespi-

ratory fitness [40]. In addition, Voss, et al. has shown that higher cardiorespiratory fitness, but not physical activity, was associated with functional connectivity in several brain regions [41]. Taken together, these results suggest that interventions designed to increase cardiorespiratory fitness, rather than simply increasing physical activity volumes or reducing sedentary behavior, may offer the greatest neuroprotection in middle-aged and older adults.

An important consideration of the aforementioned studies is that cardiorespiratory fitness has substantial variability and heritability, with maximal heritability estimates of ∼50% in sedentary individuals [42]. Thus, the positive association between cardiorespiratory fitness may be partially driven by genetic predisposition in sedentary individuals as cardiorespiratory fitness is not only influenced by the volume and intensity of exercise one participates in. Accordingly, many well-designed studies involving both sedentary and habitually exercising individuals quantify both exercise training volume and cardiorespiratory fitness levels. Even if an individual has a genetic predisposition for a high cardiorespiratory fitness, this potential advantage could be lost in the absence of regular physical activity, especially over the lifespan. In fact, studies that examine trainability of cardiorespiratory fitness have shown that, even in individuals with "low trainability", once a greater volume of exercise is added, cardiorespiratory fitness improves to the levels of individuals with "high trainability" (see reference [43] for review). Therefore, exercise interventions should aim to increase both exercise training volume and cardiorespiratory fitness in adults with a range of initial fitness levels and determine the potential effect on brain health.

One of the hallmarks of regular endurance exercise and endurance exercise training in previously sedentary individuals is enhanced cardiovascular function [44]. Enhanced cardiovascular function is associated with a range of benefits to many organ systems and it is likely that the cardiovascular adaptations associated with exercise also influence brain health. Therefore, the enhancement in cardiovascular function may mediate the relationship between fitness, brain structure, cerebral blood flow and cognition [45].

BLOOD PRESSURE AND COGNITION

There is significant evidence that elevated cardiovascular risk is linked to cognitive decline, highlighting the importance of vascular contributions

to development of AD and dementia. Hypertension, and specifically hypertension during the middle-aged years, is a major vascular risk factor for cognitive decline [4, 46]. Hypertensive adults have a higher propensity for developing cognitive impairment compared with normotensive adults [47, 48]. A murine model of hypertension (transverse aortic coarctation) demonstrated that hypertension led to amyloid- deposition, and reduced learning capacity, likely through oxidative stress pathways [49]. Even in the absence of hypertension, elevated diastolic blood pressure is associated with cognitive impairment in humans [48, 50]. Similarly, pulse pressure (the difference between systolic and diastolic blood pressure) is also linked to cognitive decline [51, 52]. In an angiotensin II (ANG II) model of hypertension in mice, the effect of hypertension on myogenic autoregulation and disruption of the blood-brain barrier is further exacerbated by aging, which suggests a synergistic effect of hypertension and aging on brain health [49, 53].

The association between blood pressure characteristics and cognition illustrates the importance of the structure and function of the vasculature in the development of cognitive decline. Autoregulatory mechanisms should maintain adequate blood flow to the brain while protecting the delicate cerebral microvessels, despite exposure to a high-pressure environment. Yet, isolated systolic hypertension and high pulse pressure may surpass the autoregulatory curve, preventing the necessary protection of the cerebral microvessels [52]. In an ANG II mouse model of hypertension, high blood pressure augmented the progression of brain pathologies [54]. In humans, higher brachial blood pressure is associated with lower CBF, a potential biomarker of cognitive decline [55]. The presence of hypertension also increases cerebral microbleeds [56, 57] and white matter hyperintensities [58, 59], which are also important biomarkers of cognitive risk. Blood pressure measured in the aorta and carotid arteries may be more indicative of the pulsatile exposure experienced by the cerebral circulation, when compared to brachial blood pressure. We and others have shown an association between aortic blood pressure characteristics and white matter hyperintensities in middle-aged adults [60], normotensive postmenopausal women [61] and elderly adults [62].

Importantly, the relationship between blood pressure and cognition is not consistent throughout the lifespan. For example, pulse pressure and its association with cognitive function is highly dependent on both age and baseline systolic blood pressure [63].

Managing blood pressure during midlife is associated with improved cognitive outcomes [64]. Yet, low blood pressure, often due to aggressive pharmacological intervention, is associated with cognitive impairment in older adults [65–67]. The widening of pulse pressure and isolated systolic hypertension with increasing age is due in part to an increase in central arterial stiffness. In young adults, there is a mismatch of vascular impedance between the central elastic arteries and the peripheral muscular arteries [68]. As humans age, the increase in central arterial stiffness reduces the central-to-peripheral impedance mismatch, resulting in greater transmission of the pulsatile energy to the peripheral vasculature. With age-associated increases in arterial stiffness, higher pulsatile flow will reach the microvessels in vulnerable high flow organs such as the brain and kidneys [69, 70], potentially causing damage. Aggressive blood pressure lowering therapy in the elderly, without a concomitant reduction in arterial stiffness, may not have a beneficial effect on cognitive function. Thus, this highlights the complex relationship between blood pressure control and the effect on brain structure and function.

ARTERIAL STIFFNESS AND COGNITION

An increase in age-related blood pressure at rest may be due to a parallel increase in the rigidity of the large arteries. As the structure of the large central arteries stiffens (due to structural characteristics like increased collagen deposition, elastin degeneration, and advanced glycation end-product cross-linking, and/or functional characteristics like increased sympathetic nerve activity or reduced nitric oxide (NO) bioavailability; see [71] for review), the large arteries are less capable of dampening the pulsatile flow from the heart. Thus, with increased arterial stiffness and arteriosclerosis, which may precede clinically-relevant increases in blood pressure, higher pulsatile flow will reach the microvessels [69, 70]. If this happens in highly vascularized tissue like the brain, damage to the microcirculation will ultimately impair organ function, as mentioned above.

Aortic pulse wave velocity (PWV) is the gold standard technique to measure arterial stiffness of the large central arteries in humans [72]. Large epidemiology studies, like Framingham, have shown that higher aortic PWV is associated with lower working memory scores [73] and associated with the progression of cognitive decline [74]. Changes in brain

structure and cerebrovascular function have been suggested to mediate the relationship between arterial stiffness and cognition. Cooper, et al. demonstrated that vascular resistance in the cerebral vessels and white matter hyperintensity fraction explained 41% of the relationship between aortic PWV and memory scores [75]. Thus, interventions aimed to improve or reduce arterial stiffness may be important in mitigating the risk of cognitive decline.

VASCULAR FUNCTION AND COGNITION

Endothelial dysfunction may underlie the age-related increases in arterial stiffness. The endothelial layer of the blood vessels is responsible for producing vasoactive substances, or endothelial-derived relaxing factors (EDRFs). For example, when endothelial cells experience an increase in shear stress, this initiates a signaling cascade resulting in the release of EDRFs, including NO and prostacyclin, which diffuse into the adjacent vascular smooth muscle cells (VSMCs) to cause VSMC relaxation/vasodilation [76]. Peripheral endothelial function is commonly quantified from the magnitude of endothelium-dependent vasodilation (EDD) either using intra-arterial infusions of vasodilating substances (i.e. acetylcholine) and measuring the change in blood flow [77] or by occlusion of blood flow for several minutes and quantifying the magnitude of vasodilation upon release of blood flow restriction (flow-mediated dilation; FMD) [78]. Because endothelial dysfunction is likely systemic, previous studies have evaluated EDD (often in the arm or leg) and determined its association with biomarkers of cognitive decline. In adults with cardiovascular disease, brachial artery FMD was inversely associated with white matter hyperintensities such that individuals with worse FMD demonstrated greater white matter hyperintensity volume [79]. FMD was also positively associated with working memory activation in middle-aged adults [80]. Other studies have shown that patients with AD demonstrated lower brachial artery FMD compared with healthy controls, and that FMD was associated with clinical severity of AD [81]. Similarly, adults with MCI also demonstrated impaired FMD compared with age-matched controls [82]. Taken together, these studies suggest that systemic endothelial dysfunction is present in patients with MCI and AD, and may be important in both the development and progression of cognitive decline.

Although several studies have shown impaired FMD in MCI or AD patients or a relationship between FMD and cognitive variables, this is not consistent across all cognitive domains. In fact, a recent systematic review demonstrated that worsening FMD is associated with lower executive function, but not correlated with global cognition, memory, or processing speed [83]. Some limitations noted in this review state that the studies often are not powered to investigate the confounding effect of medications or traditional cardiovascular disease risk factors. Future studies should evaluate the impact of improving endothelial function, and thereby FMD (via pharmacological or lifestyle interventions), and determine the effect on neuropathology and/or cognition.

While the literature strongly suggests the role of vascular and hemodynamic influences in the development and progression of cognitive decline, studies reporting associations between vascular function or hemodynamic variables and cognition have several notable limitations. First, causality cannot be determined by these correlative relationships. Second, as noted above, many of these studies are underpowered to adjust for the confounding variables, making it difficult to interpret these results. Third, the few studies that have longitudinal data on cognition are subject to practice effects and test-retest variability, which could either underestimate or overestimate the effects of vascular health on cognition. Finally, a single measure of cognitive function is often used to represent a cognitive domain, which may result in an inaccurate or incomplete assessment of cognitive abilities. These limitations highlight the need for systematic, randomized control trials to further establish the role of vascular dysfunction in cognitive decline.

EXERCISE AND VASCULAR FUNCTION

Age-associated impairments in vascular function may be attenuated or even reversed through changing lifestyle behaviors. The association between habitual exercise or cardiorespiratory fitness and cognition may be mediated by the beneficial effect on vascular function. Thus, exercise is a promising potential intervention for individuals at risk for AD or dementia.

Age-associated vascular dysfunction primarily manifests as increased central arterial stiffness and lower EDD, which can have wide-ranging effects on organ function. Fortunately, there is evidence that habitual exercise is able to reduce central arterial stiff-

ness and improve EDD, in addition to attenuating the age-associated impairment in vascular function. For example, exercise-trained middle-aged and older adults demonstrate favorable aortic PWV [84, 85] and EDD [86, 87] when compared to age-matched sedentary adults. Additionally, both aortic PWV and EDD are improved after a short-term exercise intervention in middle-aged adults [86, 88]. Importantly, greater cardiorespiratory fitness is associated with lower aortic PWV [84, 85] and higher EDD [87, 89] in adults throughout the lifespan (Fig. 1).

Despite these promising results in healthy adults, exercise-derived improvements in vascular function may not be universal. Exercise-related changes in peripheral vascular function in women may be estrogen-dependent, as there is evidence that exercise does not enhance FMD in postmenopausal women without impaired endothelial function [90, 91], unless they are given supplemental estradiol [90]. Similarly, a recent review suggests that there are conflicting results on the effect of exercise interventions on vascular function in individuals with type 2 diabetes (T2D) [92]. One study reported no improvement in FMD in adults with T2D after a 6-month supervised exercise intervention, despite improvements in cardiorespiratory fitness [93]. Collectively, these studies suggest that the magnitude of improvement in vascular function may be dependent on the initial health and/or presence of comorbidities in the sample population. Finally, it is important to note that, although many studies suggest that age-associated increases in arterial stiffness precede age-associated elevations in blood pressure [94], arterial stiffness and blood pressure are inter related and could both change in a parallel manner. Due to this association, exercise-induced reductions in arterial stiffness may be partially influenced by exercise-induced reductions in blood pressure.

The majority of published studies in healthy adults demonstrate exercise-related improvements in vascular function, which are likely the result of multiple mechanisms. During exercise, the increase in muscle blood flow increases shear stress in the blood vessels supplying the skeletal muscle, which persists throughout muscle contraction. A local increase in shear stimulus experienced by the endothelial cells enhances NO production through the endothelial NO synthase (eNOS) enzyme. Repeated habitual exercise acutely increases this shear stimulus and results in upregulated NO production. Through repeated exposure, the endothelial cells adapt by increasing eNOS mRNA expression [95] and increas-
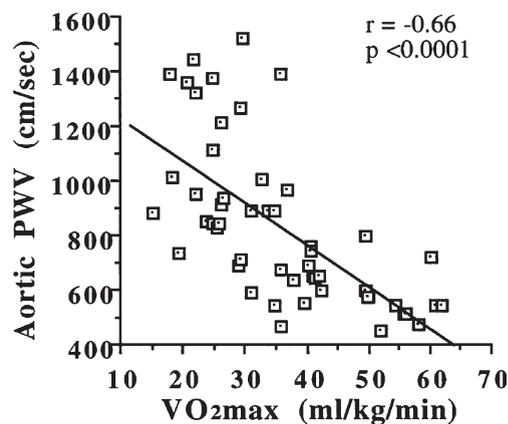

Fig. 1. The relationship between cardiorespiratory fitness (VO_2max) and aortic pulse wave velocity (PWV), a measure of central arterial stiffness, in 53 healthy women. Adapted with permission from Tanaka, et al. [85].

ing eNOS phosphorylation [96]. When compared to light intensity exercise, moderate to vigorous intensity exercise results in the greatest increase in endothelial shear stress [97], and is more efficient at improving cardiorespiratory fitness [98]. In support of this idea, cardiorespiratory fitness is associated with EDD in men and women [87, 89]. Thus, changes in eNOS expression and/or function may underlie the exercise-related adaptations in the brachial artery and resistance vessels as a result of exercise training. Furthermore, this favorable adaptation to exercise is prevented when blood flow (and therefore shear stress) is occluded in one arm during an exercise training intervention [99, 100].

Another mechanism underlying exercise-related adaptations in the peripheral vasculature includes oxidative stress, which increases with advancing age [101], and reduces NO bioavailability (due to combination of NO with reactive oxygen species (ROS) and/or uncoupling the eNOS enzyme). Adults who habitually exercise and have greater cardiorespiratory fitness demonstrate lower oxidative stress and higher antioxidant enzyme expression [101, 102] which are related to EDD [101]. Therefore, the reduction in oxidative stress could be secondary to the upregulation of endogenous antioxidant enzymes, an adaptation that could protect against the excess oxidative stress produced during exercise. Structurally, oxidative stress is associated with disadvantageous arterial wall remodeling, specifically collagen I protein expression [103], which is prevented when cells are treated with an antioxidant enzyme mimetic [103]. In an animal model, aerobic

exercise has been shown to reduce advanced gly-cation end-products, which accumulate with age to increase arterial stiffness [104]. Functionally, supra-physiologic administration of ascorbic acid (a potent antioxidant) acutely reduced arterial stiffness [105] and improved EDD [106], strongly suggesting a role of oxidative stress. Interestingly, the reduction in arterial stiffness and improvement in EDD with ascorbic acid infusion only occurred in older sedentary adults and not in young adults, or those who were already habitually active [106, 107], highlighting the role of ROS in vascular aging and the benefit of habitual exercise in mitigating this effect.

To date, there have been many published reports examining the effect of exercise (particularly aerobic exercise) on arterial stiffness and peripheral vascular function, yet there are still many unresolved questions and further studies are needed. For example, some studies report no improvement in EDD after an exercise training invention, which may be due to methodological/technical limitations in quantifying the shear stimulus. The magnitude of the vasodilatory response should account for the magnitude of the shear stimulus to properly compare the effect of an intervention. Additionally, there is evidence that light intensity exercise involving a large muscle mass may not increase shear stress in vessels of non-exercising tissue [108]. Interventions that utilize light intensity exercise may not detect a significant increase in EDD after training because the increase in shear stress during light intensity is insufficient. Yet another unresolved issue is the contrasting results regarding the effectiveness of an exercise intervention on vascular function in postmenopausal women and adults with T2D, as mentioned above. More research is necessary to determine optimal interventions to improve vascular function in these populations.

An important and often overlooked factor to consider when evaluating the role of exercise on vascular function is the mode and intensity of exercise. Many exercise interventions utilize moderate intensity aerobic exercise; however, there are contrasting results with resistance exercise interventions regarding whether they induce beneficial or maladaptive changes in vascular function. For example, several studies have reported an increase in arterial stiffness in healthy adults as a result of a high intensity resistance exercise intervention [109–111]. Even under the umbrella of aerobic exercise, the mode of aerobic exercise may also be important as arterial stiffness was lower in runners, swimmers, and rowers, compared with age-matched sedentary adults [112,

113], but FMD was not different between swimmers and sedentary adults [113]. Thus, future studies are necessary to elucidate the mechanism underlying exercise-induced adaptations and specify which exercise interventions are most effective and what populations benefit the most from these interventions.

TRANSLATION OF VASCULAR ADAPTATIONS TO THE CEREBRAL CIRCULATION

While the beneficial effects of exercise on the peripheral circulation are more established, there is also evidence that exercise in general enhances the health of the cerebral circulation. Specifically, cardiorespiratory fitness was associated with improved resting MCA blood velocity in men [35, 114]. Similarly, cardiorespiratory fitness was associated with increased MCA cerebral vasodilator responses (a measure of cerebrovascular function) in young [114] and older [114, 115] healthy adults (Fig. 2). There is also evidence that cerebral vasodilator responses to metabolic stimuli are impaired in adults with low cardiorespiratory fitness [116], demonstrating a potential mechanism underlying the association between exercise and cerebrovascular function. Along these lines, Tarumi, et al. reported correlations between measures of cerebral and peripheral vascular function (cerebral vasodilator responses and FMD) and measures of cognition (memory and executive function) [117]. Furthermore, the relationship between cardiorespiratory fitness and measures of cognition in this study were abolished after controlling for cerebral and peripheral vascular function [117], which strongly suggests the link between exercise and cognition may be mediated by improvements in cerebrovascular function.

The effect of higher cardiorespiratory fitness on cerebral vasodilator responses may be due, in part, to the effect of habitual aerobic exercise on the extracranial arteries supplying the brain. As mentioned above, increased arterial stiffness may result in a greater magnitude of hemodynamic forces transmitted to the delicate cerebral microvessels, resulting in microvascular damage and remodeling that ultimately impairs their function. In an animal model of arterial stiffness (mice with reduced elastin content), cerebral vasodilator responses of the MCA were lower when compared to wild type mice, indicating cerebrovascular dysfunction [118]. Over time, impaired cerebral microvessel function may impair
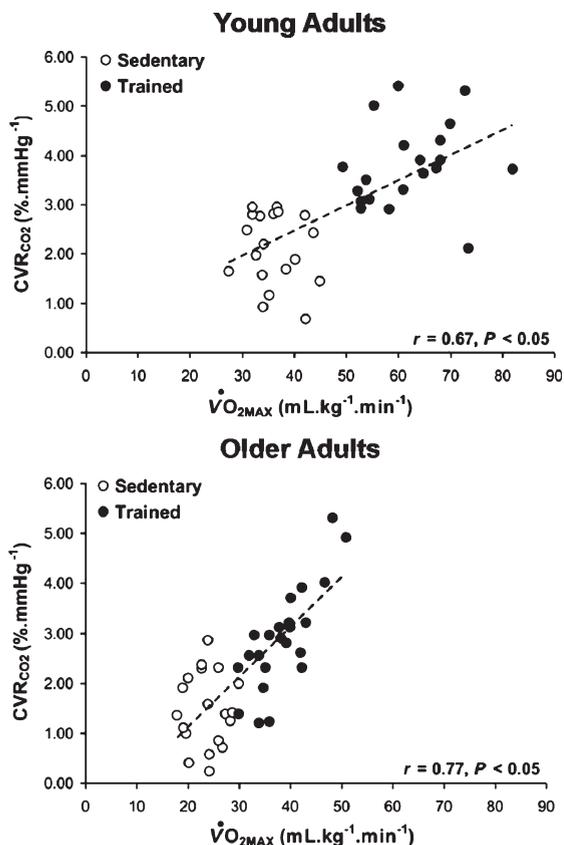
Fig. 2. The relationship between cardiorespiratory fitness (VO_2max) and cerebrovascular function (CVR_{CO2}) in older adults as a function of exercise training status. CVR_{CO2} indicates cerebral vasodilator responses to carbon dioxide. Adapted with permission from Bailey, et al. [114].

neuronal function, limit the clearance of amyloid-β, increase neuropathology, and manifest as reduced cognitive function. Demonstrating this, increased carotid arterial stiffness is associated with increased prevalence of neuropathology and lower cognition [62], which may be mediated by impaired cerebral microvessel function. Additionally, carotid arterial stiffness is associated with the progression of cognitive decline in individuals with MCI [119]. While studies have linked aortic stiffness (PWV) to cognition [73–75], the stiffness of the carotid arteries may be a stronger predictor of cerebrovascular health and cognitive outcomes, as the common carotid arteries branch directly (left) or indirectly (right) off of the aortic arch. Due to the early branching from the aorta, the blood flow that reaches the carotid arteries is considerably pulsatile, with little elastic dampening. With increased stiffness of the carotid arteries, a greater amount of this pulsatile energy may reach the

intracranial arteries. In support of this theory, carotid arterial stiffness, but not aortic stiffness, was inversely associated with cognition in adults [120]. Aerobic exercise has been shown to reduce carotid arterial stiffness [107, 121]; therefore, these beneficial adaptations may result in a more favorable hemodynamic profile, thus enhancing cerebrovascular function.

The improvements in cerebrovascular function in habitually exercising animals or adults may also be due to adaptations as a result of regular increases in blood flow to the brain. Blood flow to the brain increases during aerobic exercise up to approximately 60% VO_2max, then it plateaus, and decreases with any further increases in intensity [122, 123]. The amount of the increase in blood flow is likely dependent on many other factors, such as the amount of muscle mass active, the mode of exercise, and skeletal muscle afferent feedback mechanisms. During these increases in CBF during exercise, the cerebral vessels experience increases in shear stress that parallel the increase in blood flow. With habitual exercise, the cerebrovasculature experiences repeated, acute increases in shear stress that likely result in shear-mediated intracellular signaling cascades similar to the peripheral circulation. While previous studies have shown that age is associated with unfavorable adaptations in the cerebral vessels [124, 125] and impaired cerebral vasodilator responses [126], aerobic exercise may prevent or attenuate these age-associated changes. Evidence of this is limited in humans; however, animal models have demonstrated that habitual exercise may be able to prevent age-associated cerebrovascular dysfunction. We have recently shown that habitually exercising adults do not demonstrate an age-related decline in cerebral vasodilator responses of the MCA [127]. In middle-aged mice with access to voluntary running wheels, there are distinct differences in cerebrovascular structure and function, with greater endothelial cell nuclei size (Fig. 3) compared to sedentary animals [128]. Similarly, mice with access to a running wheel also have greater EDD of the cerebral arteries [129]. If exercise directly improves cerebrovascular function, it may also lead to enhanced astrocyte function. Aging is associated with astrocyte hypertrophy and increased reactivity, which may be due to astrocytes attempting to compensate for impairments in cerebrovascular function. If exercise enhances the function of the cerebrovasculature, it may attenuate the age-associated increases in hypertrophy and reactivity, due to the synergistic relationship between cerebral microves-

sels and astrocytes. This could, in turn, prevent neuronal hypoperfusion and hypometabolism that is a result of impaired blood flow delivery.

In summary, exercise may serve to preserve cerebrovascular function and neuronal function, and subsequently cognition, through multiple mechanisms. Aging is associated with increased blood pressure, arterial stiffness, and endothelial dysfunction. Enhanced vascular function or amelioration in the age-related increases in arterial stiffness and endothelial dysfunction with habitual aerobic exercise likely translates to the cerebral circulation (Fig. 4). Yet, this hypothesis has undergone limited testing.

EXERCISE INTERVENTIONS AND CEREBROVASCULAR FUNCTION

Aerobic exercise and cardiorespiratory fitness may be most important during midlife, as physical activity levels and cardiorespiratory fitness during the middle-aged years are associated with future cognitive function [16, 130]. Large-scale studies are currently underway to evaluate the effect of exercise interventions in older adults without cognitive complaints on cerebrovascular function [10–12]. These will be important in understanding how increasing the volume of exercise may mitigate the effect of aging on cerebrovascular function in sedentary adults. Small-scale studies have shown that cerebral vasodilator responses to carbon dioxide increased after an aerobic training in healthy adults [131, 132] and in patients with stroke [133]. Although more randomized control trials are necessary, the results of these studies suggest that vascular function in the cerebral vessels can be improved with a short-term aerobic exercise intervention. Furthermore, initiating exercise interventions early (i.e. during midlife), before the onset of cognitive decline, may be the most effective way to lower the risk of cognitive decline.

ADDITIONAL MECHANISMS UNDERLYING THE BENEFIT OF EXERCISE

This review discussed the hypothesis that improved vascular health is one mechanism underlying the association between regular aerobic exercise and enhanced cognitive function. In addition to improvements in vascular health, regular aerobic exercise induces numerous cardiac, musculoskeletal, and metabolic adaptations that may also contribute to the brain. A consistent finding is that exercise can induces neurotrophins and growth factors, such as vascular endothelial growth factor (VEGF) or brain-derived neurotrophic factor (BDNF), but the mechanism by which these are activated and affect the cerebral circulation are less clear. During exercise, skeletal muscle contraction causes the release of numerous biologically-active factors into the circulation. These "myokines" can then affect other tissues through endocrine or paracrine mechanisms that may mediate the systemic effects of regular exercise [134–136]. These myokines may also promote neurogenesis, linking skeletal muscle contraction to brain structure and function. Recent studies have shown that cathepsin B (CTSB) mRNA and protein levels are elevated after exercise in mice, and in CTSB-deficient mice, the exercise-induced improvement in spatial memory is absent [137]. Furthermore, treadmill training increased CTSB levels in monkeys and plasma CTSB is associated with spatial memory in humans [137]. Additionally, the PGC-1α/FDNC5 pathway is activated by aerobic exercise in the hippocampus (similar to skeletal muscle) in mice, which leads to increased hippocampal BDNF [138].

During high-intensity exercise, lactate accumulates in the skeletal muscle and blood lactate concentrations increase. Thus, studies have investigated lactate as a potential link between skeletal muscle contraction and brain adaptations. High-intensity exercise in mice, sufficient to elevate blood lactate levels, increases VEGF expression [139]. Lactate injection has been shown to mimic the effect of exercise [139, 140] and increase BDNF concentration in humans [141]. Along these lines, exercise at a high enough intensity to promote lactate production in humans is associated with improved motor memory and executive function [142, 143]. Taken together, these studies demonstrate that numerous byproducts of skeletal muscle contraction may contribute to neurogenesis, cerebral angiogenesis, and enhanced brain function, if the exercise is of sufficient intensity and repeated regularly.

SUMMARY

Advancing age is the largest risk factor for developing AD or other dementias. The epidemiological and experimental evidence strongly suggests that cardiovascular risk factors and/or poor vascular health is positively associated with cognitive
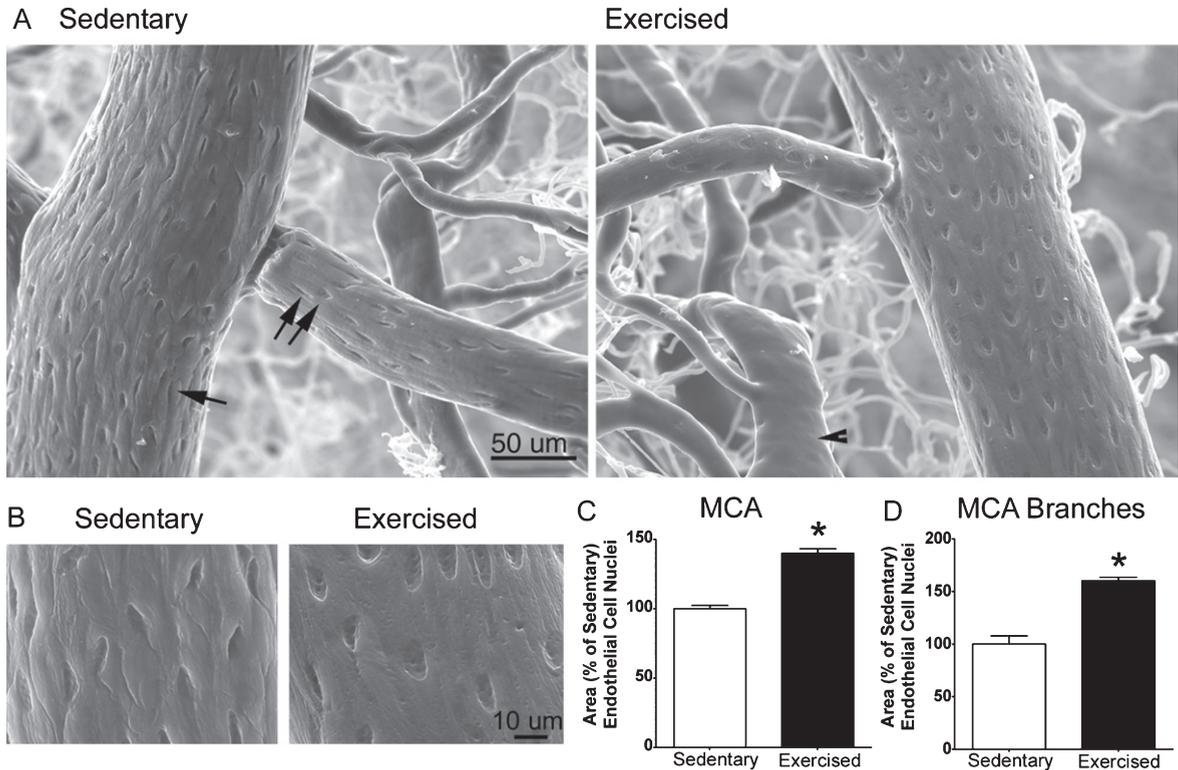
Fig. 3. Scanning electron micrographs comparing cerebrovascular microstructure of sedentary and exercised middle-aged mice. A) Low magnification images of the middle cerebral artery (MCA) (single arrow) with branch (double arrow) in a sedentary (left) and exercised (right) mouse. Arteries are distinguished from veins (arrowhead) by the distinct impressions made by their endothelial cell nuclei (ECN). B) High magnification images of ECN imprints from the MCA in a sedentary (left) and exercised (right) mouse. C and D) Exercise increased the area of ECN in the MCA and its associated branches. *$p < 0.005$, t-test. Adapted with permission from Latimer, et al. [128].
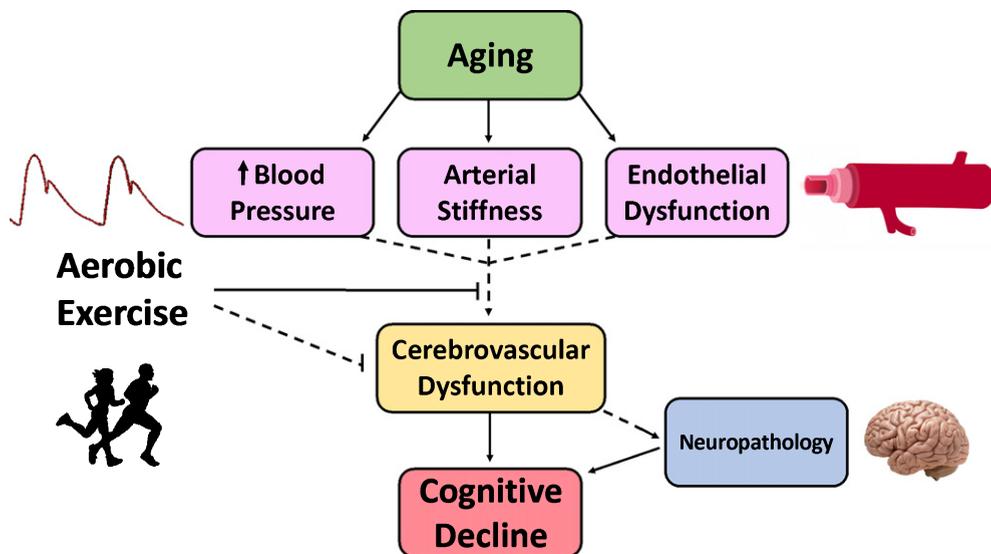

Fig. 4. Our working hypothesis showing that aging is associated with an adverse cardiovascular profile, including increased blood pressure, arterial stiffness, and endothelial dysfunction, which could all contribute to cerebrovascular dysfunction, and ultimately, cognitive decline. Individuals at elevated risk of cognitive decline may experience "accelerated aging". Aerobic exercise appears to attenuate vascular aging and may be directly or indirectly associated with preserved cerebrovascular function throughout the lifespan. Solid lines represent mechanisms with strong support from the literature. Dashed lines represent mechanisms that require further research to be definitively established.

decline. As blood vessel health is associated with both brain structure and brain function, vascular health is likely a key mechanism by which regular aerobic exercise improves cognitive function. The World Health Organization estimates that 25% of adults, globally, are not meeting the minimum physical activity recommendations. The high percentage of adults who are physically inactive will have a substantial impact on future brain health. Importantly, higher volumes of exercise and greater cardiorespiratory fitness are associated with favorable vascular function and the majority of studies show that aerobic exercise interventions improve vascular function in healthy adults. Aerobic exercise could directly increase cerebral angiogenesis, preserve the function of existing cerebral microvessels, or enhance extracranial artery function to protect the cerebral microvasculature from the unfavorable transmission of hemodynamic forces. Because direct evidence on the effect of exercise on cerebrovascular function in humans is currently limited, future studies are necessary to determine the effect of aerobic exercise on cerebrovascular function and elucidate the potential underlying mechanisms. Furthermore, additional research is necessary to optimize and implement exercise interventions early in the treatment or prevention of cognitive decline.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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