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Aerobic Exercise Training for the Aging Brain: Effective Dosing and Vascular Mechanism

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TARUMI, T., T. TOMOTO, J. SUGAWARA, and R. ZHANG. Aerobic exercise training for the aging brain: effective dosing and vascular mechanism. *Exerc. Sport Sci. Rev.*, Vol. 53, No. 1, pp. 31–40, 2025. *This article presents evidence supporting the hypothesis that starting aerobic exercise in early adulthood and continuing it throughout life leads to significant neurocognitive benefits compared with starting exercise later in life. Regular aerobic exercise at moderate-to-vigorous intensity during midlife is associated with significant improvement in cardiorespiratory fitness, which may create a favorable brain microenvironment promoting neuroplasticity through enhanced vascular function.*
Key Words: aging, brain, aerobic exercise training, cognitive function, brain structure, midlife, vascular function

KEY POINTS

- Cognitive decline with aging is a significant risk factor for late-life dementia.
- Alzheimer disease (AD), the most prevalent form of dementia, currently lacks a cure. However, it exhibits a decades-long asymptomatic phase, providing a critical time window for primary prevention.
- Vascular dysfunction is proposed as the earliest brain abnormality preceding the pathological and clinical features of AD and could be a modifiable target for effective prevention.
- Aerobic exercise training at moderate-to-vigorous intensity is a potent lifestyle intervention to improve cardiorespiratory fitness and vascular function, potentially yielding significant benefits for brain health.
- We hypothesize that increasing the cumulative dose of aerobic exercise training by initiating it in earlier adulthood and sustaining it at moderate-to-vigorous intensity would yield significant neurocognitive benefits compared with initiating the training later in life. Mechanistically, improved vascular function may mediate the relation between aerobic exercise and its neurocognitive benefits.

INTRODUCTION

The global population is aging at an unprecedented rate. Between 2025 and 2050, the number of adults over 65 is projected to almost double, reaching 1.6 billion globally and comprising 16.7% of the world population (1). Rapid medical advancements in developed countries have significantly extended our average lifespan. For instance, in the United States, life expectancy after age 65 has nearly doubled in the last century (1). However, this extended longevity has presented a unique challenge in addressing noncommunicable diseases in later life, including neurological and cardiovascular diseases (1).

Normal aging is associated with continuous and dynamic changes in neurocognitive and cardiovascular functions (Fig. 1). These changes begin in early midlife and gradually increase the risk of noncommunicable diseases in later life. Alzheimer disease (AD) and related dementias (ADRDs) are among the primary causes of mortality, disability, and the need for nursing care in older adults (2). Currently, there are only a few treatment options available to alleviate symptoms or modify the pathological progression in the early disease stage (3,4). Particularly, AD is the most common type of dementia, with pathology preceding symptomatic onset by decades, providing a valuable window of opportunity for effective prevention to delay pathological progression in those with preclinical symptoms

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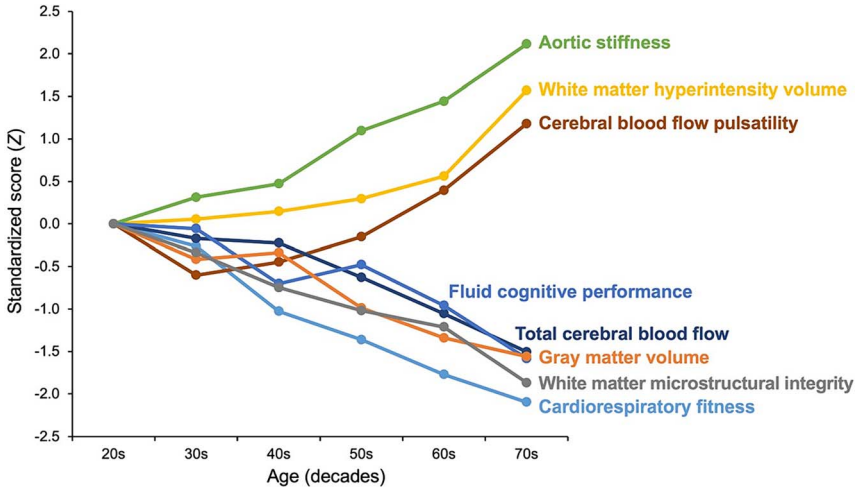

Figure 1. Age-related changes in brain and cardiovascular functions. All data were collected from 179 normal aging adults in our previous studies (age range of 21–79 yr, 63% women). Standardized scores were calculated by general linear model adjusted for sex, averaged in each decade, and zeroed to the mean score of age 20s as reference. Carotid-femoral pulse wave velocity, maximal oxygen uptake, pulsatility index of the middle cerebral arterial blood velocity recorded by transcranial Doppler, neuropsychological battery, T1 MPRAGE MRI, phase-contrast MRI of the bilateral internal carotid and vertebral arteries, T2 FLAIR MRI, and global fractional anisotropy calculated from diffusion tensor imaging measured the aortic stiffness, cardiorespiratory fitness, cerebral blood flow pulsatility, fluid cognitive performance, gray matter volume, total cerebral blood flow, and white matter hyperintensity volume and microstructural integrity, respectively.

and reduce the number of future patients (2). Cerebrovascular dysfunction, which can occur with aging and the presence of cardiovascular disease and risk factors such as midlife hypertension and obesity (5), is suggested as the earliest brain abnormality preceding AD pathologies and may represent a modifiable target for effective prevention (6).

Aerobic exercise is an established lifestyle approach to enhance cardiovascular function, which may translate to significant benefits for promoting brain health in normal aging adults. During aerobic exercise, dynamic contractions of large skeletal muscles elicit robust physiological responses at the systemic level. The increased metabolic demand of working muscles elevates cardiac output and oxygen consumption (7). Simultaneously, the brain coordinates limb movements, adjusts the cardiorespiratory system to meet metabolic demand, and processes an increased amount of information about the environment. With endurance training, repeated exposure to environmental and physiological stimuli may aggregate over time, leading to significant brain and cardiovascular adaptations and potentially reducing age-related cognitive decline and ADRD risk in later life. Notably, regular aerobic exercise at moderate-to-vigorous intensity is effective in increasing cardiorespiratory fitness (CRF), which is associated with improved vascular function, such as reduced central arterial stiffness and improved endothelial function (8). This may trigger and sustain, over time, a cascade of physiological events creating a favorable brain microenvironment that promotes neuroplasticity.

This brief review aims to provide an overview of how and to what extent aerobic exercise training can modify neurocognitive changes with aging and the physiological roles of vascular function in mediating these effects. Specifically, this review discusses 1) current evidence from randomized controlled trials (RCTs) investigating the effects of aerobic exercise intervention on cognitive function and brain structure in the context of contemporary pharmacological treatment for AD, 2) findings from observational studies on the association between long-term aerobic exercise training and neurocognitive function in midlife, and 3) vascular mechanisms by which aerobic exercise may improve the aging brain's function. As illustrated in Figure 2, we hypothesize that increasing the cumulative dose of aerobic exercise training by initiating it in earlier adulthood and sustaining it at moderate-to-vigorous intensity would yield more significant neurocognitive benefits than initiating the training later in life. Mechanistically, improved vascular function may mediate the relation between aerobic exercise and neurocognitive enhancement.

INTERVENTION EFFECTS OF AEROBIC EXERCISE TRAINING

Cognitive Function

Normal cognitive aging is characterized by increased general knowledge and decreased fluid intelligence (9). The fluid cognitive ability encompasses abstract thinking, reasoning, and problem-solving skills, which are composed of processing speed, executive function, and episodic and working memory (9). Fluid cognitive decline begins in young adulthood and persists through mid and later life (Fig. 1), with the rate of decline varying across domains and individuals. Impaired fluid cognition is a clinical hallmark of ADRDs (2), making it a primary outcome in exercise intervention trials. Numerous trials have investigated the impact of aerobic exercise training on cognitive function across diverse age groups and clinical conditions. However, the sample size in each trial was relatively small, limiting statistical power in detecting potential benefits. In this regard, meta-analysis aggregating the results of individual studies may reveal the overall effect of aerobic training on cognitive function.

Results from recent meta-analyses and systematic reviews collectively suggest a modest benefit of aerobic exercise training for fluid cognitive function in aging adults (10–13). A meta-regression analysis of 80 RCTs indicated a small but significant positive effect of exercise intervention on cognitive function comprising attention, executive function, and memory, with an effect size of ~0.2 (Hedges *g*) for aerobic training in healthy

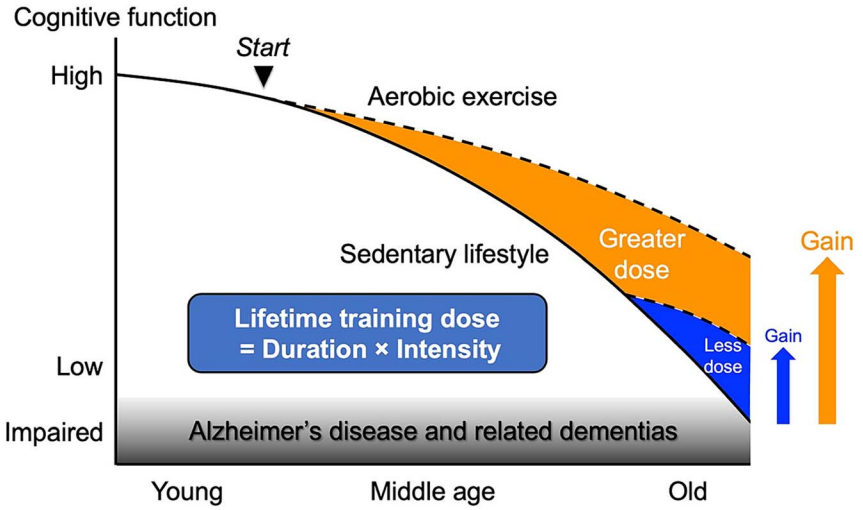

Figure 2. Hypothetical diagram illustrating that increasing the lifetime dose of aerobic exercise training by initiating it in earlier adulthood and sustaining it at moderate-to-vigorous intensity yields significant neurocognitive benefits than initiating the training later in life.

individuals with a mean age 48 (10). In community-dwelling adults aged over 50, a meta-analysis of 33 RCTs reported an effect size of 0.24 standardized mean difference (SMD) on global cognition favoring aerobic training compared with the control condition (11). Another meta-analysis of 29 RCTs in adults aged over age 18 found that supervised aerobic training for more than 1 month modestly improved attention, processing speed, executive function, and memory (g = 0.123~0.158) (12). Conversely, a Cochrane review of 12 RCTs found no evidence of cognitive benefits from aerobic training that lasted for 8 to 26 wk in adults aged over 55 without known cognitive impairment (13).

In our recent RCTs, 1 yr of aerobic exercise did not significantly improve fluid cognitive performance in sedentary healthy older adults and patients with amnestic mild cognitive impairment (MCI) compared with the stretching group (14,15). However, the secondary individual-level analysis revealed that participants with a greater increase in maximal oxygen uptake ($\dot{V}O_{2max}$), the gold standard measure of CRF, exhibited greater cognitive improvement in both the aerobic and stretching groups (14). As illustrated in Figure 1, CRF measured by $\dot{V}O_{2max}$ decreases with age, and it is an important indicator of systemic health due to its strong association with all-cause and cardiovascular mortalities (16). Moderate-to-vigorous aerobic exercise performed regularly over several months to 1 yr can significantly increase $\dot{V}O_{2max}$ in those with a sedentary lifestyle, and the increased level of $\dot{V}O_{2max}$ can be sustained over a lifetime with continuous engagement in moderate-to-vigorous intensity exercise (17,18). A high level of $\dot{V}O_{2max}$ reflects systemic physiological adaptations and enhancements, including cardiovascular, respiratory, and neuromuscular functions (7). Previous meta-analyses suggested that a higher training dose (*i.e.*, duration, frequency, intensity) accompanied by CRF gain may result in greater improvements in cognitive function over 12–18 months (10–13). Therefore, these findings collectively suggest that initiation and continuous participation in aerobic exercise over several months to 1 yr may modestly benefit fluid cognitive performance, with effects potentially enhanced by the associated improvement in CRF. However, the potential dose-dependent effects of aerobic training on neurocognitive function are still not well understood (19). In this regard, a recently completed 1-yr clinical trial (the IGNITE study) may shed light on this question (20). Regardless of the outcome of this particular study, we hypothesize that the cumulative effects of aerobic training at moderate-to-vigorous intensity, associated with a higher level of CRF and improvement in both systemic and cerebrovascular functions over the adult lifespan, will result in greater neurocognitive benefits in later life (Fig. 2).

The U.S. Food and Drug Administration (FDA) recently approved the use of antiamyloid monoclonal antibodies (*e.g.*, lecanemab, donanemab) to treat patients with early AD and MCI who have elevated amyloid β-protein (Aβ) in the brain (3,4). These antibodies can remove aggregated Aβ from the brain and have demonstrated modest clinical benefits in slowing cognitive decline over 18–24 months (3,4). A recent meta-analysis of phase 3 results of aducanumab, lecanemab, donanemab, and gantenerumab showed a reduction of the Clinical Dementia Rating-Sum of Boxes scale by 0.33 points on an 18-point scale (21). However, these FDA-approved antiamyloid treatments are expensive and have significant adverse effects such as amyloid-related imaging abnormalities (ARIA) (22). The likelihood of ARIA can increase with factors like older age, prior stroke, cerebral amyloid angiography and microhemorrhages, antithrombotic use, and apolipoprotein E4 allele carrier status, which are frequently observed in patients with AD and MCI (23). Additionally, only a small fraction of patients may be eligible for these therapies due to the FDA guidelines on the exclusion and inclusion criteria for drug administration (24). Therefore, given the challenges of the current antiamyloid immunotherapies, lifestyle interventions, such as aerobic exercise, present a low-cost, safe approach likely essential for preventing or delaying the onset of AD, especially if started in earlier adulthood (25).

Brain Structure

Aerobic exercise enhances cognitive function through a complex interplay of mechanisms at cellular, molecular, physiological, and psychosocial levels (26). These mechanisms likely operate on different

time scales and interact with the individual genetic background, demographics, and health status (26). In the short term, aerobic exercise may transiently upregulate the release of circulating neurotrophic factors (*e.g.*, brain-derived neurotrophic factor) that promote neuronal survival, growth, and stronger synaptic connections (27). Aerobic exercise also improves mood and reduces psychological stress and depressive symptoms, partly by mitigating inflammation, oxidative stress, and dysfunction in the hypothalamic-pituitary-adrenal axis (28). Additionally, exercise training can enhance sleep quality (29), which is crucial for the brain's restorative processes that maintain mood, cognitive performance, and motor function (30).

Although the short-term cognitive benefits of aerobic exercise may be small or moderate, and potentially masked by the practice or learning effects of conventional neuropsychological testing, chronic exposure to exercise stimuli can lead to structural changes in the brain at both macro and microscopic levels. These changes consequently shape individual cognitive function through long-term interactions with aging and exercise. In the adult brain, there are approximately 170 billion cells, including neurons and glial cells, distributed across the gray and white matter (31). Gray matter primarily comprises neuronal soma on the cortical surface and in the subcortical area, whereas white matter mainly consists of myelinated axons that connect distributed gray matter regions and play a crucial role in neuronal communication and information exchange. The following section discusses findings from neuroimaging studies that revealed how aerobic exercise interventions can modify brain structural changes during aging.

Gray matter volume

Brain volume undergoes dynamic changes throughout the lifespan with substantial regional variability. Pediatric neuroimaging studies revealed that total gray matter volume peaks before age 20, with the frontal, parietal, and temporal lobes reaching peak volumes between ages 10 and 18, whereas the occipital volume increases through age 20 (32). On the other hand, white matter volume increases until around age 30, likely due to increased myelination (32). Thus, change in brain volume during development and young adulthood is characterized by synaptic pruning and optimization of neural circuits that enhance the brain's efficiency based on experience and activity (33). Following young adulthood, brain volume gradually decreases in mid and later life (Fig. 1). At the regional level, the hippocampus and prefrontal cortex (PFC) are among the key regions associated with age-related cognitive decline and frequently studied in exercise intervention trials. With normal aging, the hippocampus, a part of the medial temporal lobe crucial for memory and learning, keeps a relatively stable volume until age ~60 followed by an accelerated shrinkage in later life (34). The PFC, a control center of the brain responsible for higher-order functions such as executive function and working memory, shrinks linearly with aging during the adult lifespan (34).

Early evidence suggesting that aerobic exercise may prevent age-related hippocampal shrinkage originated from animal studies. In aged mice, voluntary wheel running enhanced cell proliferation and neurogenesis in the dentate gyrus of the hippocampus (35), followed by a prominent study in humans showing that 1-yr aerobic exercise (walking) increased the size of the hippocampus while improving spatial memory in older adults (36). Until now, many studies have investigated whether aerobic exercise intervention can enlarge or prevent age-related shrinkage of the hippocampus in normal aging adults and patients with cognitive impairment. Recent findings from meta-analyses and systematic reviews collectively suggest a modest benefit of aerobic exercise programs lasting from a few months up to 5 yr to increase the hippocampal volume in aging adults (37–39). In a meta-analysis of 14 RCTs, 3 to 24 months of aerobic training showed no significant benefit for total hippocampal volume, but a significant positive effect was observed for the left ($g = 0.265$) but not the right hippocampus (37). In another meta-analysis of 22 RCTs, a significant positive effect of aerobic exercise intervention was observed for total hippocampal volume ($g = 0.13$), with a marginally significant effect on the right, but not the left hippocampus (38). *Post hoc* analysis further revealed that the effect was mainly driven by significant shrinkage in the control group, suggesting that aerobic exercise may prevent age-related hippocampal loss (38). Conversely, a meta-analysis of eight RCTs showed no significant effects of aerobic exercise programs lasting longer than 4 wk on hippocampal volume despite a significant CRF improvement (39).

Besides the hippocampus, aerobic exercise training may increase the thickness of the PFC and other cortical areas, with considerable variability observed between individual studies and cortical regions. In cognitively normal adults aged 20–67, 6 months of moderate-intensity aerobic exercise increased the thickness of the left caudal middle frontal cortex, a part of the PFC, accompanied by improved executive function (40). In adults aged 18–20, 9 months of exercise intervention, consisting of running and competitive and noncompetitive sports and games to increase social interactions, increased the thickness of the left lateral occipital cortex and the left precuneus while improving $\dot{V}O_{2max}$ (41). Furthermore, an increase in medial frontal gyrus volume was found to mediate the effects of improved $\dot{V}O_{2max}$ on executive function (41).

In our recent RCTs, we did not find a significant effect of 1-yr aerobic exercise on total brain volume or hippocampal volume in sedentary older adults (14) or patients with MCI (15). However, we did observe a weak but statistically significant correlation between increases in $\dot{V}O_{2max}$ and cortical thickness in the right inferior parietal lobule (14). These findings suggest two things. First, the studies may not have included enough participants to capture the potentially subtle effects of exercise interventions (14,15). Second, the results are consistent with previous research on how exercise training may influence cortical thickness (41), as well as a longitudinal study that found higher CRF predicted greater whole-brain volume 5 yr later in middle-aged adults (42). Therefore, the benefits of aerobic exercise interventions for brain volume and cortical thickness may require a longer duration, as brain structure changes slowly with aging. Moreover, increased CRF with exercise training may enhance resilience, protect the brain from stress and diseases associated with aging (43), and facilitate brain structural changes through various mechanisms, including improved vascular function discussed later in this review.

White matter integrity

The structural integrity of brain white matter can be assessed through various magnetic resonance imaging (MRI) protocols. At the macroscopic level, the volumes of normal-appearing

white matter and white matter hyperintensities (WMH as shown in Fig. 1) can be quantified by T1- and T2-weighted imaging, respectively. At the microscopic level, structural integrity and organization of white matter fibers can be evaluated by diffusion tensor MRI (DTI). DTI quantifies water molecular diffusion inside the brain tissue and calculates several metrics sensitive to white matter microstructural integrity and organization. Specifically, fractional anisotropy (FA) and mean diffusivity (MD), representing the directionality and magnitude of water diffusions, are widely used in clinical neuroscience research, with higher FA and lower MD generally interpreted as higher integrity and organization of the white matter fibers (43). Normal aging is associated with decreased FA in the global white matter (Fig. 1) along with increased MD. This age-related FA reduction is linked to reduced fluid cognitive abilities, particularly decreases in processing speed, memory, and executive function (44).

Current evidence suggests that white matter microstructural integrity benefits from CRF improvement rather than participating in aerobic exercise training alone. One of the first DTI studies investigating the effect of aerobic training on white matter microstructure showed no significant group-level effect compared with stretching in healthy older adults over 1 yr, but CRF improvement achieved through training was associated with increased FA in the prefrontal and temporal lobes (45). Consistently in patients with MCI, we found no significant group effect of 1-yr aerobic exercise on DTI metrics, but CRF gain after intervention was associated with reduced MD in the genu and body of the corpus callosum (CC) (46). Also, 5 yr of supervised aerobic training, one of the longest exercise intervention trials in the literature, found no significant group effect in older adults, but CRF gain and higher self-reported training intensity (Borg scores) were associated with increased FA and decreased MD in the CC at 1- and 3-yr follow-ups (47).

Conversely, RCTs with aerobic training programs lasting less than 6 months showed neither the effect of intervention nor CRF gain on white matter microstructure (48–50). This suggests that structural change in white matter is also a slow process similar to brain volumetric change. Further, CRF gain expected from several months to 1 yr of aerobic training is small, roughly 10% gain from the baseline, according to our 1-yr intervention at the moderate-to-vigorous intensity in previously sedentary older adults (14,46). This magnitude of CRF improvement may not be sufficient to elicit significant brain structural and functional changes over a short intervention period.

Anatomically, the CC may be sensitive to the benefits of aerobic exercise training and CRF gain (51). The CC is the largest white matter bundle in the human brain, enabling sensory, motor, and cognitive integration and communication between the left and right cerebral hemispheres (52). Age-related FA reduction and MD elevation in the CC, particularly the anterior tract (genu) connected to the PFC, are associated with slower processing time, potentially subserving the reduced executive function in older adults (53). Therefore, microstructural enhancement of the CC fibers with aerobic training and CRF gain may contribute to better cognitive health in older adults.

MIDLIFE AEROBIC EXERCISE AND NEUROCOGNITIVE FUNCTION

Aerobic exercise training initiated in midlife or earlier and continuing throughout the lifespan may yield greater neurocognitive benefits than training later in life (Fig. 2). This may be attributed to cumulative effects and higher neuroplasticity at a younger age (9). To test this hypothesis, we conducted a series of cross-sectional studies comparing neurocognitive and vascular functions among three groups: 1) aerobically trained middle-aged group, 2) sedentary middle-aged group, and 3) young sedentary group (54–56). These three groups were similar in sex, educational attainment, and ethnicity. The primary inclusion criteria for the trained group mandated at least 10 yr of aerobic training and ongoing participation in competitive events (*e.g.*, marathons). Thirty well-trained adults aged 45–64 yr participated in the study, with a mean age of 54 and an average $\dot{V}O_{2max}$ exceeding the 90th percentile compared with the general population. The trained group on average reported ~25 yr of physical exercise training before study participation.

Brain structural analysis unveiled a significant enhancement of white matter microstructural integrity in aerobically trained middle-aged adults compared with age-matched sedentary adults (Fig. 3) (54). With DTI, FA of the global white matter in the trained group was significantly higher than that in the age-matched sedentary group, resembling the level observed in the young group. When plotted against age, the global FA exhibited a decline in sedentary adults, while maintaining a higher level in the trained individuals. Moreover, whole-brain voxelwise analysis adjusted for age and sex revealed a significant positive association between $\dot{V}O_{2max}$ and FA, with significant voxels located mainly in the CC, corona radiata, internal capsule, superior longitudinal fasciculus, and external capsule. General cognitive performance scores were also higher in the trained group than population normative values (54).

In contrast to white matter, gray matter showed modest differences between the trained and sedentary groups (54). In the trained group, cortical thickness of the sensorimotor and visual areas was significantly greater than in sedentary groups of middle-aged and young adults, whereas mean cortical thickness was lower in both middle-aged groups than in the young group. Total brain and hippocampal volumes were similar among all three groups. Thus, these findings suggest that long-term aerobic training in midlife may not prevent age-related cortical thinning while supporting the concept of "*use it or lose it*," implying that long-term exercise training induces specific cortical adaptations. The thicker motor cortex in the trained group is anticipated due to its role in controlling voluntary movement during exercise. The visual cortical areas process visuospatial information during exercises such as running and cycling, whereas the adjacent sensory area connected to the motor cortex through corticocortical projections may contribute to motor learning (57).

These cross-sectional findings warrant cautious interpretation. Potential confounding factors other than exercise, such as lifestyle choices (*e.g.*, diet, sleep) and genetic differences, may have influenced brain structure and function in trained individuals compared with sedentary adults. Also, observational findings cannot establish the causality of long-term training. Future RCTs of long-term exercise intervention need to be conducted while addressing anticipated challenges in testing middle-aged adults. Middle-aged individuals often have familial and work-related commitments, making their study enrollment and training more challenging than older adults who may already be retired. Supervising and monitoring their training adherence also pose difficulties that may need to be addressed

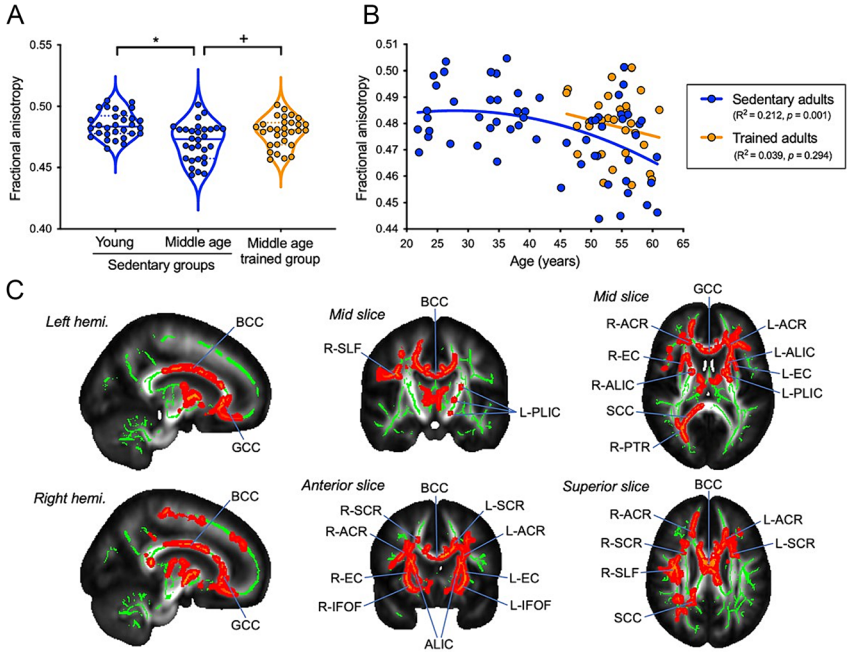

Figure 3. Results from diffusion tensor imaging data analysis exhibiting the significant enhancement of white matter microstructural integrity in aerobically trained middle-aged adults. A, Global fractional anisotropy (FA) compared among sedentary young and middle-aged groups and aerobically trained middle-aged group ($P < 0.001$ for group effect). Each group includes 30 participants (15 women). *$P < 0.05$ versus young group, +$P < 0.05$ versus middle-aged sedentary group. B, Global FA plotted against age separately for sedentary and trained groups. C, Association between $\dot{V}O_{2max}$ and FA in all participants with adjustment for age and sex. Red areas show significant positive associations. ACR/SCR indicates anterior/superior corona radiata; ALIC/PLIC, anterior/posterior limbs of the internal capsule; EC, external capsule; GCC/BCC/SCC, genu/body/splenium of the corpus callosum; IFOF, inferior fronto-occipital fasciculus; L/R, left/right; PTR, posterior thalamic radiation; SLF, superior longitudinal fasciculus. [Adapted from Tarumi T, Tomoto T, Repshas J, *et al*. Midlife aerobic exercise and brain structural integrity: associations with age and cardiorespiratory fitness. *Neuroimage*. 2021;225:117512. Copyright © 2021 Elsevier. Used with permission.]

through the development and effective use of remotely accessible devices. For example, mobile health technology implementing a two-way system that allows the clinical team and trainer to remotely deliver and adapt exercise prescriptions, monitor exercise progress, and communicate with participants may be useful in facilitating exercise intervention studies in middle-aged adults (58). Overcoming these feasibility issues will enable us to determine whether long-term aerobic exercise in midlife can yield greater benefits for neurocognitive function than training later in life.

The long-term effects of exercise training may also be influenced by the mode and environment of the exercise. For instance, our study participants primarily engaged in running, cycling, or swimming to compete in endurance events (54–56). However, many also incorporated resistance exercises, yoga, or group fitness activities such as boot camp, cross-training, or barre workouts into their routines (54). Although multicomponent exercise including aerobic activity has been shown to improve cognition in patients with MCI and dementia (59), the long-term effects remain unclear in cognitively normal adults. Studies have also suggested that athletes participating in open-skill sports involving motor tasks in unpredictable environments (*e.g.*, tennis, basketball) exhibit higher executive function performance than those in closed-skill sports (*e.g.*, running, swimming) (60). The environment in which exercise is performed may also affect the cognitive benefits. Several studies suggest that exercising outdoors in natural settings has greater benefits for brain health compared with exercising indoors (61). Future studies may need to incorporate these additional factors to determine whether training effects can be modulated or enhanced to reduce age-related neurocognitive decline and the risk of dementia.

VASCULAR MECHANISM

The vascular supply of oxygen and nutrients (*e.g.*, glucose) is the primary source of energy for the brain to sustain neuronal activity and cognitive function. Despite having one of the highest metabolic rates among all organs, the brain lacks fuel stores. In healthy adults, the brain accounts for ~20% of the whole-body metabolic rate, a significant proportion considering its weight of only ~2% of body mass (62). As a result, ~15% of cardiac output is continuously perfused to the brain, making it known as a *high-flow, low-resistance* organ. A constant supply of cerebral blood flow (CBF) is achieved in part by the brain's unique vascular functions, such as autoregulation and vasomotor reactivity to carbon dioxide. With aging, vascular function decreases gradually, which may trigger neuropathological changes associated with ADRDs (6). Conversely, aerobic exercise training may enhance this vascular-neurocognitive coupling. This section discusses the physiological roles of central arterial stiffness, pulsatility, and CBF, which have been shown to change significantly with aging, associated with ADRD pathologies, and modified by aerobic exercise training.

Arterial Stiffness and Pulsatility

Central arterial stiffening is a hallmark of vascular aging and associated with cognitive decline and impairment in older adults (Fig. 4). Central arteries, such as the aorta and carotid arteries, deliver blood flow to the brain while dampening its pulsatility through the distension of compliant arterial walls.

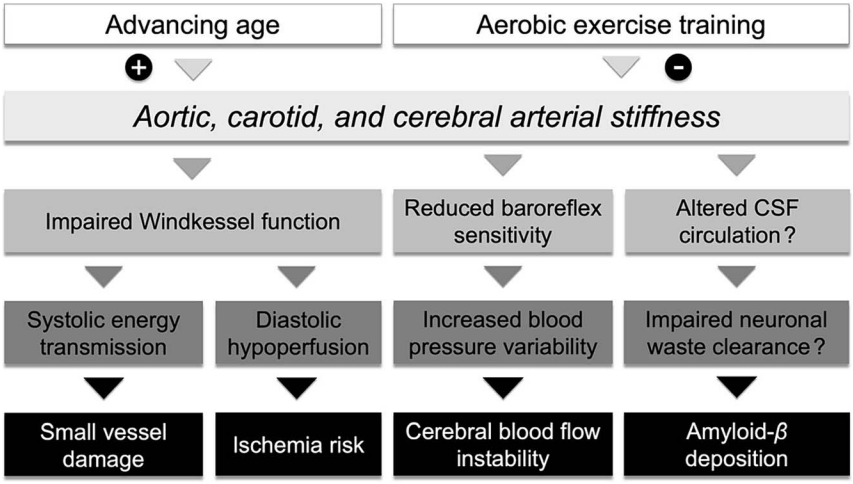

Figure 4. Hypothetical vascular mechanism by which advancing age increases and aerobic exercise training decreases the risk of Alzheimer disease and related dementias through changes in aortic and local arterial stiffness. CSF indicates cerebrospinal fluid.

The proximal ascending aorta, directly connected to the heart, expands with the ejection of stroke volume during systole and recoils during diastole to forward blood stored in the aortic chamber to peripheral circulation (63). This aortic Windkessel function likely protects the brain from the mechanical stress of excess systolic pressure energy being transmitted to the microcirculation while maintaining diastolic perfusion.

As shown in Figure 1, normal aging is associated with aortic stiffening, elevated CBF pulsatility, and reduced diastolic CBF (64). These hemodynamic changes are correlated with reduced white matter integrity in older adults (65). Consistent with these findings, intensive treatment to lower systolic blood pressure showed reduced aortic stiffening (66), decreased occurrence of MCI (67), and a smaller increase in white matter lesion volume (68). Thus, these findings collectively support a hypothesis that excess systolic pressure energy transmitted to the brain may damage cerebral microcirculation and neural tissues, consequently increasing the risk of cognitive decline and impairment in older adults.

Normal aging is also associated with a local increase in carotid and cerebral arterial stiffness (69,70), which may significantly impact brain microenvironmental homeostasis and the risk of ADRDs. For example, arterial baroreceptors located in the walls of the carotid sinus and aortic arch sense changes in arterial wall distension and control arterial pressure via the autonomic nervous system (7). With aging, increased aortic and carotid stiffness can blunt baroreflex sensitivity (71), which may increase blood pressure variability and the risk of cerebral hypoperfusion (72). Higher aortic stiffness and lower baroreflex sensitivity are also associated with reduced white matter perfusion (73) and integrity (74).

Recent animal studies suggest that pulsatility of the cerebral arterial wall drives cerebrospinal fluid (CSF) flow through the perivascular space, clearing waste products like Aβ and tau from the brain through fluid exchange with interstitial fluid (75). Thus, it can be hypothesized that reduced cerebral arterial compliance may alter CSF flow dynamics and impair waste clearance. Although this hypothesis needs further investigation, higher carotid stiffness is associated with brain Aβ deposition in patients with MCI (76), supporting the potential role of cerebrovascular distension for brain waste clearance. Therefore, existing literature collectively suggests that reducing age-related aortic and local arterial stiffening may mitigate the pathophysiological risk of ADRDs.

Regular aerobic exercise is a potent lifestyle intervention to counteract central arterial stiffening in normal aging adults. A recent meta-analysis revealed that aerobic training programs effectively decreased carotid-femoral pulse wave velocity (cfPWV), the gold standard measure of aortic stiffness, in middle-aged and older adults compared with controls (8). Notably, greater reductions in cfPWV were associated with vigorous exercise intensity, younger age, and healthier baseline demographics (8). These findings also align with our cross-sectional studies showing significantly higher carotid arterial distensibility in aerobically trained middle-aged adults compared with sedentary counterparts of the same age (77). Additionally, higher carotid distensibility was correlated with higher $\dot{V}O_{2max}$, better performance on attention, executive function, and memory tests, and higher CBF in the occipitoparietal cortex (77). A noninvasive estimation of cerebral arterial stiffness using vascular impedance measurement also showed that aerobic exercise training was associated with a lower impedance modulus in middle-aged and older adults (56,78). Therefore, although more evidence is still needed from RCTs, reducing central and cerebral arterial stiffness accompanied by increased CRF through aerobic exercise training may decrease the risk of cognitive decline and impairment in middle-aged and older adults.

Cerebral Blood Flow

Cerebrovascular dysregulation, indicated by reduced CBF, has been suggested as the earliest brain abnormality preceding AD pathologies, such as Aβ deposition (6). Therefore, lifestyle interventions that can enhance CBF and cerebrovascular function may reduce the risk of ADRDs in later life. Normal aging is associated with a gradual reduction in CBF (Fig. 1), accompanied by increased cerebrovascular resistance (CVR) (79). These age-related CBF and CVR changes may result from decreased cerebral metabolism, cerebrovascular dysfunction, or both. The cerebral metabolic rates of glucose and oxygen decrease by 5%–6% per decade, which may co-occur with reductions in CBF in normal aging adults (80,81). Additionally,

cerebrovascular dysfunction with aging and the presence of vascular risk factors may lead to neurovascular decoupling, a mismatch between cerebral metabolic demand and CBF supply (82).

In the brains of older adults, chronic exposure to increased systolic pressure resulting from aortic stiffening may lead to structural remodeling of cerebral resistance vessels with concentric hypertrophy (*i.e.*, an increased wall-to-lumen ratio) (83), which may subsequently increase the risk of hypoperfusion and structural brain tissue damage, especially in deep white matter areas supplied with low perfusion pressure, lack of collateral circulation, and impaired cerebral autoregulation (84,85). Additionally, reduced cerebral vasodilatory function may increase the risk of hypoperfusion and ischemia in older adults (86).

Our recent RCTs have demonstrated that aerobic exercise training increases CBF in older adults, possibly enhancing neuronal vitality and reducing the risk of cognitive decline and impairment in later life (87–89). In cognitively normal older adults and patients with MCI, 1-yr aerobic exercise led to significant elevations in global CBF measured by color-coded duplex ultrasonography (87,88). This CBF elevation was accompanied by reductions in CVR and carotid artery stiffness, as well as improvements in $\dot{V}O_{2max}$ and memory performance (87,88). Improved memory was correlated with reduced CVR and carotid stiffness in cognitively normal older adults (87). In patients with MCI, 1-yr aerobic exercise increased hippocampal perfusion and reduced age-related decline in anterior cingulate perfusion measured by arterial spin labeling MRI (89).

Consistent with the findings above, a recent meta-analysis showed a significant negative association between CRF and CVR, supporting the benefits of aerobic fitness for cerebrovascular function (90). However, no significant effect of aerobic training on CBF was observed when using transcranial Doppler (90). These inconsistencies may be linked to the methodological variability of CBF measurements, which currently lack a gold standard procedure for achieving both high spatial and temporal resolutions (79). Therefore, although current evidence favors the benefits of aerobic exercise training and increased CRF for improving CBF in older adults, future studies need to confirm these results by using multiple modalities of CBF measurement in the same participants, as well as developing a novel method that can achieve both high temporal and high spatial resolutions (79).

SUMMARY AND RECOMMENDATION

Aerobic exercise interventions lasting from several months to 1 yr showed modest benefits for fluid cognitive performance and its neural substrates, including regional brain volume (*e.g.*, hippocampus, PFC) and white matter microstructural integrity. Although the effect sizes are relatively small, they may be increased with a larger gain in CRF through higher-intensity or longer-duration training or both. Middle-aged adults engaging in moderate-to-vigorous aerobic training for decades exhibited significant improvements in CRF, which correlated with improved white matter integrity. Trained adults also showed increased sensorimotor and visual cortical thickness, likely representing specific adaptations to long-term exercise training, although there may not be a linear relation between the doses of exercise training and improvements in brain structure and function (19). An optimal training dose for brain health may need to be determined individually based on biological (*e.g.*, sex, genetics) and environmental (*e.g.*, lifestyle, social) factors. Mechanistically, exercise- and CRF-related improvements in central arterial stiffness and CBF may promote neuroplasticity and waste clearance in the aging brain. Therefore, these findings collectively support our hypothesis that increasing the lifetime dose of aerobic exercise leads to cumulative neurocognitive benefits mediated by improved vascular function.

CRF improvement and environmental enrichment are likely the key factors in promoting brain health through aerobic exercise training. To accomplish them, sedentary but otherwise healthy adults are recommended to start with moderate-intensity exercise (*e.g.*, 65%–75% of the maximal heart rate) 3 to 5 d a week with each session lasting for 30–45 min and a total weekly exercise time of ≥150 min, and gradually progress to higher intensities after a period of adaptation, as the risk of cardiovascular or orthopedic complications is greater at higher exercise intensities (17,18). For trained adults, higher-intensity or near-maximal-intensity exercise (*e.g.*, interval training) may be necessary to increase and maintain CRF, as higher-fit individuals experience less $\dot{V}O_{2max}$ gain than lower-fit individuals at any given intensity (17). Cumulative benefits are likely best achieved through long-term continuous participation in moderate-to-vigorous aerobic training. The training effects may further be modulated or enhanced by multiple exercise modalities and environmental enrichment, such as incorporating other exercise modes (*e.g.*, strength, balance, and flexibility), sport-specific exercises (*e.g.*, open and closed skills), indoor/outdoor exercise, and group activities. Exercise programs should be tailored to each person based on their initial fitness level and preferred modes of exercise that can be sustained long term without feeling obligated or psychologically burdened.

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