Journal of Neurochemistry

JOURNAL OF NEUROCHEMISTRY | 2017

doi: 10.1111/jnc.14153

REVIEW

The role of exercise in mitigating subcortical ischemic vascular cognitive impairment

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Abstract

Subcortical ischemic vascular cognitive impairment (SIVCI) is the most preventable form of cognitive dysfunction. There is converging evidence from animal and human studies that indicate vascular injury as the primary cause of SIVCI. Currently, there are no curative pharmaceutical treatments for vascular dementia; however, exercise may be a promising strategy to combat SIVCI. This review will focus on the role of exercise as a strategy to prevent or slow the progression of SIVCI, with particular emphasis on the mechanisms by which exercise may improve cerebrovascular function. We propose that exercise may be an effective strategy to combat SIVCI by improving cognitive function, increasing the bioavailability of neurotrophins, stimulating endothelial function, and controlling vascular risk factors.

Keywords: endothelial function, exercise, subcortical ischemic vascular cognitive impairment, white matter hyperintensities.

J. Neurochem. (2017) https://doi.org/10.1111/jnc.14153

This article is part of the Special Issue "Vascular Dementia"

The World Health Organization estimates that 47.5 million people worldwide are living with dementia with an expected increase of 7.7 million new cases each year (World Health Organization 2012). Dementia is a common cause of disability and dependency among older adults; thus, the high prevalence and incidence of dementia is a great burden to health, social, and financial systems (World Health Organization 2012). Vascular cognitive impairment (VCI) is the second leading cause of cognitive impairment and dementia (van Norden *et al.* 2012). Vascular cognitive impairment is an umbrella term that encompasses the full spectrum of cognitive and functional impairments associated with cerebrovascular disease, from frank dementia to mild cognitive deficits (Gorelick *et al.* 2011). Subcortical ischemic vascular cognitive impairment (SIVCI) is the most common form of VCI and is caused by cerebral small vessel disease (SVD) (Moorhouse and Rockwood 2008). Cerebral SVD is caused by chronic and diffuse ischemia and is most often associated with damage to cerebral white matter. Specifically, it manifests as white matter hyperintensities (WMH), lacunes, enlarged perivascular spaces, and microbleeds (Wardlaw *et al.* 2013b).

Overall, there is converging evidence from animal and human studies that indicate vascular injury as the primary cause of SIVCI (Iadecola 2013). Vascular risk factors such as

Received May 29, 2017; revised manuscript received August 9, 2017; accepted August 11, 2017.

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Abbreviations used: ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; BDNF, brain-derived neurotrophic factor; CBF, cerebral blood flow; eNOS, endothelial nitric oxide synthase; fMRI, functional magnetic resonance imaging MRI; IGF-1, insulin-like growth factor 1; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NO, nitric oxide; NOS, nitric oxide synthase; OPC, oligodendrocyte precursor cells; RCT, randomized controlled trials; SIVCI, subcortical ischemic vascular cognitive impairment; SVD, small vessel disease; VCI, vascular cognitive impairment; VEGF, vascular endothelial growth factor; WMH, white matter hyperintensities.

hypertension, diabetes mellitus, hypercholesteremia, smoking, and obesity are implicated in the vascular pathology associated with SIVCI (Gorelick *et al.* 2011). Currently, there are no curative pharmaceutical treatments for vascular dementia. However, exercise may be a promising primary and secondary prevention strategy. We propose that exercise may be an effective method to combat SIVCI by improving cognitive function, increasing the bioavailability of neurotrophins, stimulating endothelial function, and controlling vascular risk factors. First, we begin by reviewing the biological networks and pathophysiology of SIVCI.

The vascular network and cerebral white matter

Subcortical ischemic vascular cognitive impairment is caused by vascular injury in the wall or lumen of cerebral small vessels. Vascular lesions can include arteriolosclerosis, lipohyalinosis, fibrinoid necrosis, and small vessel atherosclerosis in perforating cerebral arterioles and capillaries (Sachdev *et al.* 2014). Arteriolosclerosis is the most common form of SVD and is highly correlated with aging, hypertension, diabetes, and is directly associated with WMH (Erkinjuntti *et al.* 1996; Schmidt *et al.* 2004; van Swieten *et al.* 1991; Hainsworth *et al.* 2015). It is characterized by smooth muscle loss and collagenization of small arteries and arterioles. These vessels become elongated and tortuous causing chronic and diffuse ischemia. Together, these changes cause endothelial dysfunction, which has been proposed as the primary pathogenesis in SVD (Hainsworth *et al.* 2015).

The endothelium is a thin, flat cellular monolayer that lines the entire vascular tree. These cells have many important functions that include: (i) diffusion of oxygen and carbon-dioxide across capillary walls; (ii) sprouting and revascularization in response to cell signaling molecules such as vascular endothelial growth factor (VEGF) and forms of fibroblast growth factor, and (iii) autoregulation of local cerebral blood flow (CBF), which is a special feature of the brain vasculature (Hainsworth *et al.* 2015). Autoregulation protects cerebral blood vessels from changes in arterial pressure associated with daily activities and provides a stable CBF baseline (Iadecola 2013). The endothelium has the ability to increase or decrease vessel diameter and distal blood flow by modulating vascular smooth muscle tone. It does this by releasing several effectors, most notably nitric oxide (NO). Nitric oxide is produced by NO synthase (NOS) proteins, of which the dominant form in endothelial cells is endothelial NOS (eNOS). Nitric oxide is one of the most important vasodilator mechanisms; it causes contractile smooth muscle cells to relax allowing the vessels to dilate. Dysfunctional endothelial cells may synthesize less NOS resulting in reduced vascular dilation affecting local CBF (Griendling *et al.* 2011).

Endothelial dysfunction is also associated with smooth muscle cell proliferation on the abluminal side and platelet adhesion on the luminal side. This can cause platelet aggregation, white blood cell adhesion, and inflammation, which may initiate and advance vascular pathology (Rajani and Williams 2017). Dysfunctional endothelial cells secrete factors such as VEGF, tumor necrosis factor-α, and endothelin 1 that may have negative effects on other brain cells (Griendling *et al.* 2011; Rajani and Williams 2017). In addition, it can cause leakiness of the blood–brain barrier, which is associated with WMH and lacunar strokes (Wardlaw *et al.* 2008; Iadecola 2013). Vascular risk factors associated with SIVCI including hypertension, hypercholesterolemia, diabetes, and aging all result in identical endothelial damage (Brunner *et al.* 2005). Thus, the preservation of endothelial function is a potential strategy for the prevention of SIVCI.

Endothelial cells can also have a direct impact on oligodendrocytes, which are derived from oligodendrocyte precursor cells (OPC) (Rajani and Williams 2017). Oligodendrocyte precursor cells arise from many different regions of the brain during development and are also present throughout the adult brain. The main function of oligodendrocytes is to form the myelin sheath around axons, which make up the bulk of white matter. It forms the myelin by wrapping its membrane around the axon several times to form short segments called nodes of Ranvier. Myelin is necessary for fast transmission of electrical signals through the axon, as the signal can 'jump' between the nodes of Ranvier by saltatory conduction (Baumann and Pham-Dinh 2001). Oligodendrocytes are also involved in the trophic support of axons by secreting insulin-like growth factor 1 (IGF-1) and brain-derived neurotrophic factor (BDNF) (Du and Dreyfus 2002). Thus, the proper function of oligodendrocytes is essential for brain health.

Endothelial function plays an important role in the support of OPC (Rajani & Williams 2017). Endothelial cells can secrete factors, such as fibroblast growth factor and BDNF, that promote OPC proliferation (Leventhal *et al.* 1999). There are studies linking endothelial cell dysfunction with SVD. For example, increased levels of systemic endothelial activation markers, such as intercellular adhesion molecule 1, tissue factor pathway inhibitor, and thrombomodulin, are associated with cerebral SVD. Critically, these changes may be mediating the formation of WMH and lacunes (Hassan *et al.* 2003). Furthermore, the Austrian Stroke Prevention Study found an association between intercellular adhesion molecule levels and WMH progression at 3 and 6 years (Markus *et al.* 2005). Overall, these studies indicate that altered endothelial cell signaling might cause oligodendrocytes to be more vulnerable to damage, either by reducing their exposure to pro-survival factors or by reducing the ability of white matter to repair itself after injury (Rajani & Williams 2017).

In summary, endothelial dysfunction is a pathological hallmark of SVD (Poggesi *et al.* 2016). Immunohistological labeling shows evidence of vessel wall thickening and up-regulation of hypoxia-related markers within white matter lesions (Fernando *et al.* 2006). Endothelium NO signaling is an important factor in local CBF regulation and a large number of studies have found greater reductions in CBF in patients with more severe WMH (Markus *et al.* 2014) and within the WMH region compared with the surrounding normal-appearing white matter (van Dalen *et al.* 2016). In addition, the endothelium is linked to the health and function of oligodendrocytes and the brain's general regenerative capacities, further strengthening the association between WMH and vasculopathy (Hainsworth *et al.* 2015).

White matter hyperintensities in small vessel disease

Epidemiology and pathophysiology of white matter hyperintensities

Cerebral SVD is caused by chronic and diffuse ischemia and is associated with damage to cerebral white matter. Specifically, it manifests as WMH, lacunes, enlarged perivascular spaces, and microbleeds (Wardlaw *et al.* 2013b). White matter hyperintensities are the most common manifestation of SVD and are present on magnetic resonance imaging (MRI) in over 90% of older adults (Schmidt *et al.* 2011). Lacunes and microbleeds occur less commonly among older adults with frequencies ranging from 6 to 20% and 5 to 15%, respectively (Cavalieri *et al.* 2012). Epidemiological evidence consistently suggests that WMH are progressive in nature (Prins and Scheltens 2015). White matter hyperintensity progression was observed in 39% (of 668 participants) and 73.6% (of 394 participants) at 3 years' follow-up in the Rotterdam Scan Study (van Dijk *et al.* 2008) and the Leukoaraiosis and Disability Study (Schmidt *et al.* 2012), respectively. In the Austrian Stroke Prevention Study, participants with confluent lesions displayed a 2.7–9.3 cm^3 median increase, with a maximum increase of 21.0 cm^3 after 6 years (Schmidt *et al.* 2003). Generally, people with confluent lesions will experience greater progression over time (Schmidt *et al.* 2003; Schmidt *et al.* 2012) – the annual increase in WMH volume in those with early confluent lesions is 0.23 cm^3 and those with established confluent lesions is 1.60 cm^3 (Ovbiagele and Saver 2006).

White matter hyperintensities are typically imaged using MRI where lesions appear hyperintense on T2-weighted, proton density weighted, and fluid-attenuated inversion-recovery scans. They commonly occur in the periventricular or deep white matter regions. In the periventricular regions, WMH appear as 'caps' around the frontal horns of the lateral ventricles and as a pencil-thin lining or a smooth 'halo' along the side of the lateral ventricles. In the deep white matter, changes can occur as punctate or confluent lesions that have not cavitated (signal is different from cerebrospinal fluid) (Wardlaw *et al.* 2013a). As the disease progresses, WMH typically expand outward toward the subcortical white matter. Pathology studies suggest that several histologic processes are involved in these radiologic lesions. Subtle WMH are associated with microglial and endothelial activation. Punctate lesions are associated with dilated perivascular spaces and perivascular gliosis. Periventricular WMH are associated with discontinuous ependyma, gliosis, loosening of the white matter fibers, and myelin loss around tortuous venules in perivascular spaces. Caps are associated with myelin pallor, gliosis, and arteriosclerosis; and rims are associated with subependymal gliosis and loss of the ependymal lining. As periventricular WMH worsen, gliosis, demyelination, and fiber loss become more apparent. Generally, pathology reports have predominantly associated WMH with changes to oligodendrocytes resulting in demyelination and axonal loss (Chimowitz *et al.* 1992; Wardlaw *et al.* 2015).

White matter hyperintensities are associated with cognitive impairment

White matter hyperintensities are consistently associated with executive dysfunctions in SIVCI (Prins and Scheltens 2015). The term 'executive functions' refer to the ability to orchestrate different cognitive tasks to attain a specific goal. Executive functions are necessary if, for example, attentional resources have to be efficiently distributed among different sensory inputs or when predominant behavioral tendencies have to be inhibited (Perry and Hodges 1999). Thus, it includes the many stages necessary for goal-directed behavior. A deficit in executive functions result in an inability to participate in everyday activities and is a major component of cognitive disability within the context of SIVCI (Roman *et al.* 1993; Roman and Royall 1999).

Executive dysfunctions in SIVCI is supported by several large population studies (Debette and Markus 2010), including cross-sectional data from the Cardiovascular Health Study, Framingham Heart Study, Rotterdam Scan Study, and Leukoaraiosis and Disability Study (Longstreth *et al.* 1996; de Groot *et al.* 2000; Au *et al.* 2006; Verdelho *et al.* 2007; Poggesi *et al.* 2011). Specifically, increased WMH is correlated with poorer performance on tests of executive functions, processing speed, global cognition, and in some cases memory. Critically, the progression of WMH is associated with subsequent cognitive decline. The Cardiovascular Health Study (5-year follow-up) (Longstreth *et al.* 2005) and the Rotterdam Study (3-year follow-up) (van Dijk *et al.* 2008) reported an association between WMH progression with declines in global cognition (Longstreth *et al.* 2005; van Dijk *et al.* 2008) and information processing speed (van Dijk *et al.* 2008). A meta-analysis found that progression of WMH (1–1.5-year follow-up) was associated with greater declines in attention and executive functions

(Kloppenborg *et al.* 2014). Generally, the presence and progression of WMH is associated with cognitive decline.

In summary, SVD is associated with arteriolosclerosis and endothelial dysfunction causing chronic and diffuse ischemia. Ischemic damage predominantly results in WMH in the periventricular and deep white matter regions. Histopathology studies suggest that demyelination is a major component of the microstructural changes in SVD. White matter hyperintensities are associated with impairments in executive functions as well as global cognition. Critically, WMH are progressive in nature and result in worse cognitive outcomes over time. Thus, it is crucial that we develop strategies to combat SIVCI as it can interfere with the ability to function autonomously. Below we review the potential for exercise to mitigate SIVCI.

Role of exercise in mitigating SIVCI

Evidence suggests that regular exercise is a promising strategy to combat SIVCI. Exercise is a subcategory of physical activity that is planned, structured, and purposive to improve physical health (Bherer *et al.* 2013). Generally, there are two types of exercise: (i) aerobic training, which targets cardiovascular fitness (Myers 2003), and (ii) resistance training, which targets muscle mass and strength (Peterson *et al.* 2010). Below, we will review the role of exercise in reducing the risk for cognitive decline and promoting cerebral white matter health. Next, we will review the role of exercise in mitigating vascular injury in SIVCI.

Exercise reduces the risk for cognitive decline and promotes cerebral white matter health

Several longitudinal cohort studies have suggested that increased physical activity may slow the progression of cognitive decline (Rockwood and Middleton 2007; Middleton and Yaffe 2009; Geda *et al.* 2010). The Nurses' Health Study in women (follow-up of up to 15 years) (Weuve *et al.* 2004) and the Honolulu-Asia Aging Study in men (follow-up of over 30 years) (Abbott *et al.* 2004; Taaffe *et al.* 2008), found that higher levels of physical activity were associated with better cognitive performance and lower risk of cognitive decline. Similarly, the Monongahela Valley Independent Elders Survey project (Lytle *et al.* 2004) reported that higher exercise level (defined as aerobic exercise for ≥ 30 min performed ≥ 3 times per week) was associated with a reduced risk of cognitive decline. The Canadian Health and Aging Study reported that physical activity was associated with a 42% reduced risk of cognitive impairment–no dementia (Laurin *et al.* 2001). Overall, observational studies indicate that exercise may be beneficial for cognitive function.

Furthermore, several randomized controlled trials (RCT) support the efficacy of exercise in people with mild cognitive impairment (MCI). A study by Baker and colleagues (Baker *et al.* 2010) found that an aerobic training program improved executive functions in people with MCI, with more pronounced benefits for women than men despite comparable gains in cardiorespiratory fitness. In women with subjective cognitive complaints, Lautenschlager and colleagues (Lautenschlager *et al.* 2008) found that moderate intensity physical activity (predominantly involving aerobic activity) improved memory performance. In addition, an RCT conducted by Nagamatsu and colleagues (Nagamatsu *et al.* 2013) found that both aerobic and resistance training improved memory performance and executive functions in women with probable MCI. Another RCT in people with MCI found that progressive resistance training significantly improved global cognitive function, as measured by the Alzheimer's Disease Assessment Scale-cognitive subscale. Of note, participants maintained executive and global cognitive benefits for over 18 months (Fiatarone Singh *et al.* 2014). Conversely, other reports have indicated that exercise may not improve cognitive function in healthy older adults and people with MCI (Gates *et al.* 2013; Ohman *et al.* 2014; Young *et al.* 2015). A Cochrane Review found that aerobic exercise did not improve cognitive function in older adults without known cognitive impairment (Young *et al.* 2015). Furthermore, the Lifestyle Interventions and Independence for Elders (LIFE) randomized trial, the largest and longest RCT to assess the effect of exercise on cognitive function in sedentary older adults with no cognitive impairment, found that a 24-month moderate intensity exercise intervention did not result in better global or domain specific cognition compared with a health education program (Sink *et al.* 2015). However, the exercise intervention in the LIFE trial did not meet exercise prescription guidelines outlined by the American College of Sports Medicine for older adults; thus, the exercise prescription may have been insufficient to produce changes in cognitive function (Poulin *et al.* 2016). Similarly, a meta-analysis of RCT in people with MCI found that a majority of outcomes were non-significant providing no strong or consistent evidence that exercise improves cognitive function in MCI. However, these authors note that there were methodological problems in defining MCI, exercise prescription, blinding, inadequate sample sizes, and not reporting dropout rates or compliance (Gates *et al.* 2013). A systematic review of seven good or moderate quality RCT found that exercise was associated with positive outcomes in global cognition, executive functions, and attention in people with MCI (Ohman *et al.* 2014). Although more RCT are needed to ascertain the efficacy of exercise on cognitive function, there is evidence to suggest that regular exercise may be beneficial for cognitive performance in older adults with MCI.

Only one study has specifically assessed the impact of exercise in people with SIVCI (Liu-Ambrose *et al.* 2016). An RCT conducted by Liu-Ambrose and colleagues (Liu-Ambrose *et al.* 2016) demonstrated that 6 months of

aerobic training improved general cognitive function, as measured by the Alzheimer's Disease Assessment Scale-cognitive subscale, in people with mild SIVCI. Improved cognitive performance was associated with reduced diastolic blood pressure suggesting that reduced blood pressure may be a pathway by which aerobic exercise promotes cognitive health in SIVCI (Liu-Ambrose *et al.* 2016). Furthermore, a secondary analysis of neuroimaging data acquired from this trial found that participants in the aerobic training intervention group showed improvement in selective attention and conflict resolution, as measured by the flanker task. Improvement on the flanker task was associated with reduced task-related neural activation in the left lateral occipital cortex and right superior temporal gyrus, as measure by functional MRI (fMRI) (Hsu *et al.* 2017). Previous studies reported increased task-related neural activation, as a compensatory process, in people with SVD (Li *et al.* 2012) and older adults with higher cardiovascular risk (Chuang *et al.* 2014). This was supported by another study that reported an association between decreased white matter integrity and increased fMRI signal (i.e. less-wiring-more-firing) (Daselaar *et al.* 2015). Thus, it was postulated that aerobic training may maintain or increase neural efficiency among older adults with mild SIVCI by reducing the need for compensatory neural processes (Hsu *et al.* 2017).

Although not specific to people with SIVCI, other studies have assessed the impact of exercise on WMH in healthy older adults and people with MCI. A cross-sectional study found that moderate to vigorous levels of physical activity was associated with lower WMH volume in healthy older adults (Burzynska *et al.* 2014). An RCT in community dwelling older women reported that resistance training reduced WMH progression over 12 months (Bolandzadeh *et al.* 2015). These results are supported by the SMART Trial, an RCT conducted in people with MCI. This trial reported that high-intensity progressive resistance training resulted in a modest regression of WMH in periventricular and parietal zones while non-progressive resistance training groups displayed WMH progression; however, these results did not survive whole-brain correction (Suo *et al.* 2016). White matter hyperintensities are also associated with reduced white matter integrity in both projection and association fiber tracts (Chao *et al.* 2013). One study reported that light physical activity was associated with greater white matter integrity in parahippocampal regions in healthy older adults (Burzynska *et al.* 2014). In addition, another study found that greater aerobic fitness derived from a walking program was associated with increased white matter integrity in the frontal and temporal lobes, though there were no group differences in white matter integrity in this 1 year aerobic exercise intervention (Voss *et al.* 2013b). Together, these studies suggest that exercise, both aerobic and resistance training and of various intensities, are important for maintaining white matter health.

Despite the mounting literature showing that physical activity has favorable effects on cognition in older adults, the underlying mechanisms remain unknown (Colcombe and Kramer 2003). Animal models suggest that exercise enhances brain health, and thus cognitive health, by increasing the availability of several growth factors in the neurotrophin family including BDNF, IGF-1, and VEGF. Exercise can increase the bioavailability of BDNF directly in the brain and in the periphery. Animal studies found that voluntary wheel running increased levels of BDNF gene expression in the hippocampus, an area important for learning and memory. Brain-derived neurotropic factor may modulate exercise-induced synaptic plasticity mechanisms that underlie learning and memory, such as long-term potentiation (Cotman *et al.* 2007). Exercise facilitated long-term potentiation in the dentate gyrus, a subregion of the hippocampus, was paralleled by increases to dendritic length, dendritic complexity, spine density, and neural progenitor proliferation (van Praag *et al.* 1999). Overall, BDNF plays an important role in neuronal survival, growth, and synaptic plasticity (Cotman and Berchtold 2002; Cotman *et al.* 2007; Erickson *et al.* 2012).

Peripheral changes in BDNF expression and quantity have been observed in neurodegenerative and metabolic diseases. For example, in MCI, decreases in peripheral concentrations of BDNF are associated with age-related hippocampal dysfunction and memory impairment (Coelho *et al.* 2013). In type-2 diabetes, changes in glucose metabolism and insulin resistance are associated with decreased BDNF concentrations (Krabbe *et al.* 2007; Fujinami *et al.* 2008). Critically, several studies have reported that exercise, specifically aerobic training, increases peripheral concentrations of BDNF in healthy older adults and in people with MCI. Specifically, a study by Baker and colleagues (Baker *et al.* 2010) found that high-intensity exercises (75–85% of heart rate reserve) increased peripheral concentrations of BDNF in older men and maintained concentrations of BDNF in older women with MCI. It is known that BDNF is modulated by estrogen, such that BDNF expression is increased with increased estrogen levels (Singh *et al.* 1995). Thus, the decline in estrogen levels in women after menopause may result in a lower expression of BDNF (Simpkins *et al.* 1997). Furthermore, Erickson and colleagues (Erickson *et al.* 2011) found that increased serum BDNF levels mediated increased hippocampal volume after a 1-year aerobic exercise training program. Overall, there is evidence to suggest that aerobic exercise may improve cognitive function by increasing the bioavailability of BDNF.

Data from animal studies also suggest that both IGF-1 and VEGF can increase neurogenesis and angiogenesis (Cotman *et al.* 2007). Blocking IGF-1 or VEGF from crossing the blood–brain barrier can prevent exercise-induced neurogenesis in the hippocampus (Trejo *et al.* 2001; Fabel *et al.* 2003). Blocking IGF-1 signaling can also prevent the expression of hippocampal BDNF in response to exercise

(Ding *et al.* 2006). Furthermore, IGF-1 is involved in vascular maintenance and remodeling (Lopez-Lopez *et al.* 2004) as age-related reductions in IGF-1 are associated with decreased cerebral vascular density and blood flow (Sonntag *et al.* 1997). Studies in rodents found that aerobic exercise training prevents and protects the brain from ischemic injury and impedes progression of ongoing neurodegeneration through increased uptake of circulating IGF-1 by the brain (Carro *et al.* 2001). Although animal studies implicate VEGF and IGF-1 as key mediators in exercise-induced brain responses, evidence from human studies remain equivocal. Both a 1-year (Voss *et al.* 2013a) and 3-month (Maass *et al.* 2016) aerobic exercise intervention in healthy older adults did not reveal significant effects on serum levels of VEGF or IGF-1 compared to a control intervention involving muscle stretching. However, a systematic review suggested that aerobic exercise (as opposed to resistance training) would be the most efficacious method for increasing VEGF concentrations in older adults though the authors note that the limited number of studies and different populations analyzed make it difficult to reach a definitive conclusion (Vital *et al.* 2014). In contrast, resistance training is more efficacious in up-regulating IGF-1 levels. A study in young adults found that both low and high intensity resistance exercise increases levels of IGF-1, though low exercise intensity is sufficient to achieve the potential IGF-1-related benefits on brain neuroplasticity (Rojas Vega *et al.* 2010). Compared with a study conducted by Schwarz and colleagues (Schwarz *et al.* 1996) the rate of IGF-1 increase was modest with 7% for low-intensity aerobic exercise compared with 28% for low-intensity resistance exercise. To our knowledge, no studies have assessed the efficacy of aerobic or resistance training on VEGF or IGF-1 concentrations in people with SIVCI. However, the available literature suggests that different forms of exercise may initiate different pathways, such that aerobic training may up-regulate BDNF and VEGF and resistance training may increase IGF-1 concentrations.

There is mounting evidence suggesting that exercise, both aerobic and resistance training, can reduce the risk of cognitive decline and improve cognitive function. Currently, animal studies suggest that exercise training may improve cognitive function via growth factors such as BDNF, IGF-1, and VEGF that induce neuroplastic, neurotrophic, and neuroprotective factors (Cotman and Berchtold 2002). However, more studies in humans are needed to fully understand the interaction between exercise, neurotrophins, and cognitive function.

Exercise may mitigate vascular injury in subcortical ischemic vascular cognitive impairment

Exercise training may combat SIVCI by controlling vascular risk factors such as diabetes, hypercholesterolemia, and hypertension (Lakka and Laaksonen 2007; Fleg 2012; Phillips *et al.* 2015). For example, in a 4.1-year average follow-up Finnish study people who spent at least 2.5 h/week walking for exercise were 63-69% less likely to develop type 2 diabetes compared with those who walked < 1 h/week (Laaksonen *et al.* 2005). In addition, a meta-analysis of aerobic training trials in older adults found significant increases in high density lipoprotein (HDL – 'good' cholesterol) and reduced total cholesterol/HDL cholesterol ratio, independent of changes in body composition (Kelley *et al.* 2005). Regular physical activity can also have favorable effects on elevated blood pressure. A meta-analysis of 54 RCTs found that aerobic training decreased both systolic and diastolic blood pressure in normotensive and hypertensive adults (Whelton *et al.* 2002). Much evidence points to the benefits of regular physical activity in the prevention and control of type 2 diabetes, hypercholesterolemia, hypertension, and cardiovascular disease (Warburton *et al.* 2006).

Reducing vascular risk factors may have a direct impact on WMH progression. One longitudinal population based study of non-demented older adults found that people with untreated hypertension had significantly more WMH progression than people with treated hypertension over a 5-year period, after adjusting for age, sex, cardiovascular risk factors, and baseline WMH volume (Verhaaren *et al.* 2013). In another longitudinal study, subjects taking antihypertensive drugs and who had controlled blood pressure had less severe WMH compared with those who had high blood pressure at 4-year follow-up (Dufouil *et al.* 2001). Results from RCTs also suggested that controlling hypertension might reduce the risk of WMH progression. The Evaluation of Vascular Care in Alzheimer's Disease (EVA) trial assessed the impact of intensive vascular care compared with standard care in patients with AD who exhibited concomitant cerebrovascular lesions on MRI, and found that people receiving vascular care showed less WMH progression. However, the two groups were similar in the number of new lacunes (Richard *et al.* 2010) and no differences were observed in clinical function between the intervention and control group (Richard *et al.* 2009). In the PROGRESS MRI substudy of patients with symptomatic stroke, patients treated for high blood pressure were less likely to have new WMH at a mean 3-year follow-up (Dufouil *et al.* 2005). Overall, data from both observational studies and RCT indicate that reducing blood pressure may directly reduce the incidence and progression of WMH (Smith *et al.* 2017). For statin treatments, trials have provided conflicting evidence as to whether statin treatment reduces WMH progression (ten Dam *et al.* 2005; Mok *et al.* 2009; Xiong *et al.* 2014; Smith *et al.* 2017). In people with type 2 diabetes mellitus, glucose-lowering therapy did not reduce WMH progression (Launer *et al.* 2011), though the association between type 2 diabetes and WMH remains unclear – most studies have found no association or only a weak association between diabetes and WMH (Prins and Scheltens 2015). These results suggest that

hypercholesterolemia and diabetes may cause cognitive impairment through other mechanisms.

Vascular risk factors for SIVCI are associated with impaired endothelial-dependent vasodilation that is detectable before any morphological changes could be observed in the vessel wall. Increased aerobic activity may reduce vascular risk factors through NO-mediated vasodilation (DeSouza *et al.* 2000; Tanaka *et al.* 2000). Many factors can regulate the release of NO, including shear stress. Exercise training dramatically increases eNOS expression in endothelial cells, likely because of the increased shear stress caused by high cardiac output in sustained exercise. Direct shear-stress-mediated effects on the vascular endothelium may therefore be a possible mechanism by which exercise can mitigate SVD (Bolduc *et al.* 2013; Lucas *et al.* 2015).

Animal studies investigating both peripheral and coronary vasculature suggest that aerobic training enhances eNOS, and NO production and bioactivity (Green *et al.* 2004). For example, short-term exercise training in rats increased endothelial NO synthesis in skeletal muscle and muscle arterioles and increased vasodilator responses (Sun *et al.* 1994). In large conduit vessels, improved endothelium-dependent vasodilation was observed after 7 days of aerobic exercise in pigs (McAllister and Laughlin 1997). In cerebral arterioles, aerobic training was associated with increased NOS-dependent vasodilation in female rats (Arrick *et al.* 2016). In contrast, in human studies exercise training of healthy subjects with normal endothelial function does not seem to induce NO-vasodilation. In a study of young males, 4 weeks of handgrip training reduced minimum vascular resistance following an ischemic stimulus in the trained limb but forearm blood flow response to endothelium-dependent vasodilators was not altered in response to training (Green *et al.* 1994). A randomized cross-over study of combined aerobic and resistance training in healthy middle-aged men found that training did not significantly affect endothelium-dependent function. However, these results may be related to exercise intensity (Maiorana *et al.* 2001b). A study by Goto and colleagues (Goto *et al.* 2003) found changes in endothelium-dependent forearm vasodilation in the moderate intensity exercise group (50% of VO_2 max) but not in the low (25% of VO_2 max) and high (75% of VO_2 max) intensity groups. In the high-intensity group, there was evidence of increased oxidative stress, which may have abrogated any improvements in vascular function. The authors also postulated that low-intensity training may fall below a given threshold for improvement in endothelial function (Goto *et al.* 2003).

In contrast to healthy adults, the majority of studies performed in people with impaired endothelial function have reported improvements after exercise (Green *et al.* 2004). Studies in people with chronic heart failure (Maiorana *et al.* 2000) and type 2 diabetes (Maiorana *et al.* 2001a) suggest that depressed endothelial function is more capable of augmentation by exercise training compared with well-preserved vascular function in healthy subjects (Green *et al.* 2004). In subjects with chronic heart failure, combined aerobic and resistance training improved endothelium-dependent and -independent vascular function. These effects on the vasculature were evident in a vascular bed not directly involved in the exercise stimulus suggesting that exercise effects on the vasculature are generalized (Maiorana *et al.* 2000). In people with type 2 diabetes, a similar exercise program reported improved resistance and conduit vessel vasodilator function, potentially because of endothelium-dependent mechanisms (Maiorana *et al.* 2001a). Data from animal and human studies suggest that exercise training increases NO-dependent vascular function, including up-regulation of constitutive eNOS expression, particularly in people with compromised endothelial function. This suggests that people with impaired endothelial function may be more amenable to improvements in NO function as a result of exercise training (Green *et al.* 2004). This is particularly pertinent for people with SVD because increased NO bioavailability is considered a key factor in the maintenance of cerebrovascular function and for optimal regulation of CBF (Padilla *et al.* 2011).

Exercise mediated increases in NO and CBF may guard against vascular ischemic injury. In mice with mild brain ischemia, Gertz and colleagues (Gertz *et al.* 2006) reported that voluntary exercise training increased resting CBF in the ischemic lesion as well as better functional and cognitive outcomes. Importantly, the protective effects of physical activity were not present in animals that were either treated with an NOS inhibitor or in animals lacking eNOS gene expression ($eNOS^{-/-}$) (Gertz *et al.* 2006). Similarly, Endres and colleagues (Endres *et al.* 2003) demonstrated that 3 weeks of exercise training led to an increase in resting CBF and a reduction in cerebral infarct size in wild-type, but not $eNOS^{-/-}$ mice. Furthermore, Arrick and colleagues (Arrick *et al.* 2012) studied the effects of exercise training on ischemic damage in the brain of diabetic rats and found that the total infarct volume in cortical and subcortical regions were reduced in rats enrolled in a treadmill pre-training protocol of 6–8 weeks. The authors suggested that aerobic exercise training has beneficial effects on cerebral circulation and may have significant therapeutic potential for mitigating ischemic brain injury (Arrick *et al.* 2012). It is hypothesized that exercise training protects the cerebrovasculature by: (i) inducing endothelial cerebrovascular shear stress (shear stress increases NO bioavailability) required to match local CBF with neuronal activity associated with exercise (awareness, balance, concentration, etc.); (ii) increasing sympathetic activity to coordinate blood delivery and energy supply, and thus stimulating endothelial function and increasing NO bioavailability, and; (iii) delaying age-related stiffening of large arteries that may cause downstream problems for cerebral artery endothelial function and maintenance of cerebral perfusion (Bolduc *et al.* 2013).

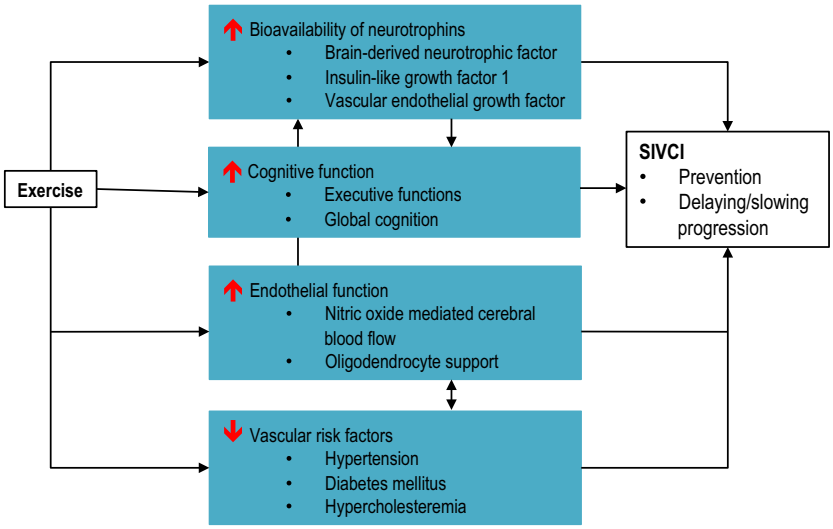

Fig. 1 There are several pathways by which exercise may mitigate the effects of subcortical ischemic vascular cognitive impairment (SIVCI): (i) Exercise increases the bioavailability of neurotrophins to prevent and protect the brain from ischemic injury, increase angiogenesis, and enhance neuronal function (and thus, cognitive function) (Cotman and Berchtold 2002); (ii) Both aerobic (Ohman *et al.* 2014) and resistance training (Fiatarone Singh *et al.* 2014) improves cognitive function and may reduce white matter hyperintensity progression (Bolandzadeh *et al.* 2015; Suo *et al.* 2016) and increase white matter intergrity (Voss *et al.* 2013b); (iii) Exercise may protect the cerebrovasculature by inducing the shear stress required to increase cerebral blood flow by increasing the bioavailability of nitric oxide and delaying arterial stiffening (Bolduc *et al.* 2013). Proper endothelial function is also important for the health of oligodendrocytes and the regenerative capacity of cerebral white matter (Rajani and Williams 2017) and; (iv) Vascular risk factors such as hypertension, diabetes mellitus, and hypercholesteremia are associated with SIVCI and endothelial dysfunction. Exercise is an effective strategy to reduce key vascular risk factors associated with SIVCI (Phillips *et al.* 2015).

Several findings suggest that the increase in flow is regional to the cortical activity reflective of the exercising extremity (Ogoh and Ainslie 2009). However, a study by Delp and colleagues (Delp *et al.* 2001) found that aerobic exercise in miniature swine resulted in local increases in CBF in several subcortical areas involved in: locomotion and integration of sensory inputs and motor outputs (anterior and dorsal cerebellar vermis), maintenance of equilibrium (vestibular nuclei), cardiorespiratory control (medulla and pons), and vision (dorsal occipital cortex, superior colliculi, and lateral geniculate body). In human subjects, fMRI data reported greater task-related activity in brain regions that control attention (i.e. middle frontal gyrus, superior frontal gyrus, superior parietal lobule) and reduced activity in the anterior cingulate cortex, a region associated with behavioral conflict and adaption of attentional control processes in older adults, after 6 months of aerobic exercise training (Colcombe *et al.* 2004).

There are several limitations associated with studies assessing the effect of exercise on endothelial function. First, most of these studies are in large vessels and it remains unclear whether these same mechanisms exist in small vessels. Second, each vascular bed has tissue-specific morphology, physiology, biochemistry, pathology, and pharmacology. There are major differences between endothelial cells lining large conduit arteries, small resistant arteries, and microvessels, which further increase the complexity of molecular mechanisms activated in the presence of vascular risk factors. Third, research on endothelial function in the cerebral vasculature is currently not possible in humans; as such, studies are reliant on animal models of hypertension or stroke (Katusic and Austin 2014). Notwithstanding these limitations, current knowledge indicates that damage to the endothelium is a major component of SVD. Thus, improving endothelial function is an important therapeutic target for the prevention and treatment of SIVCI.

Conclusion

In the past several decades there have been great scientific strides in understanding the pathophysiology of dementia; yet, no pharmacological treatment is available to halt or reverse the effects of dementia. Thus, risk reduction is currently a fundamental strategy in combating cognitive decline. Epidemiological studies have identified several potential modifiable risk and protective factors that could be targeted in dementia prevention. For example, factors that may increase the risk for cognitive decline include: history of depression, sleep disturbances, smoking, traumatic brain injury, mid-life obesity, hyperlipidemia, diabetes, and

hypertension. Factors that may reduce the risk of cognitive decline include: increasing years of formal education, social engagement, cognitive training, Mediterranean diet, and physical activity (Baumgart *et al.* 2015). In this review, we focus on the potential efficacy of aerobic and resistance exercise in combating SIVCI. However, we note that this is a targeted review of the literature and a systematic scope of the available information is not provided. Here, we propose that exercise may be an effective strategy for reducing the risk of cognitive decline, promoting brain health by increasing the bioavailability of neurotrophins, reducing vessel damage by targeting endothelial function, and controlling vascular risk factors (Fig. 1). Although more evidence from RCT are needed to ascertain the role of physical activity and exercise in combating SIVCI, there is support from scientific literature to suggest that regular physical activity and management of cardiovascular risk factors (diabetes, obesity, smoking, and hypertension) can reduce the risk or slow the progression of cognitive decline and dementia (Baumgart *et al.* 2015). Epidemiological research from large population studies in western Europe suggests that the prevention and treatment of vascular disease and chronic conditions may play an important role in the reduced or stable occurrence of dementia over the past 20–30 years (Wu *et al.* 2016). These findings highlight the importance of regular physical activity in the prevention of SIVCI.

Acknowledgments and conflict of interest disclosure

This work was supported by funding from the Heart and Stroke Foundation of Canada and the Jack Brown and Family Alzheimer Research Foundation Society. TLA is a Canada Research Chair (Tier II) in Physical Activity, Mobility and Cognitive Neuroscience. The authors declare that they have no conflicts of interest.

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