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# Resisting decline: the neuroprotective role of resistance exercise in supporting cerebrovascular function and brain health in aging

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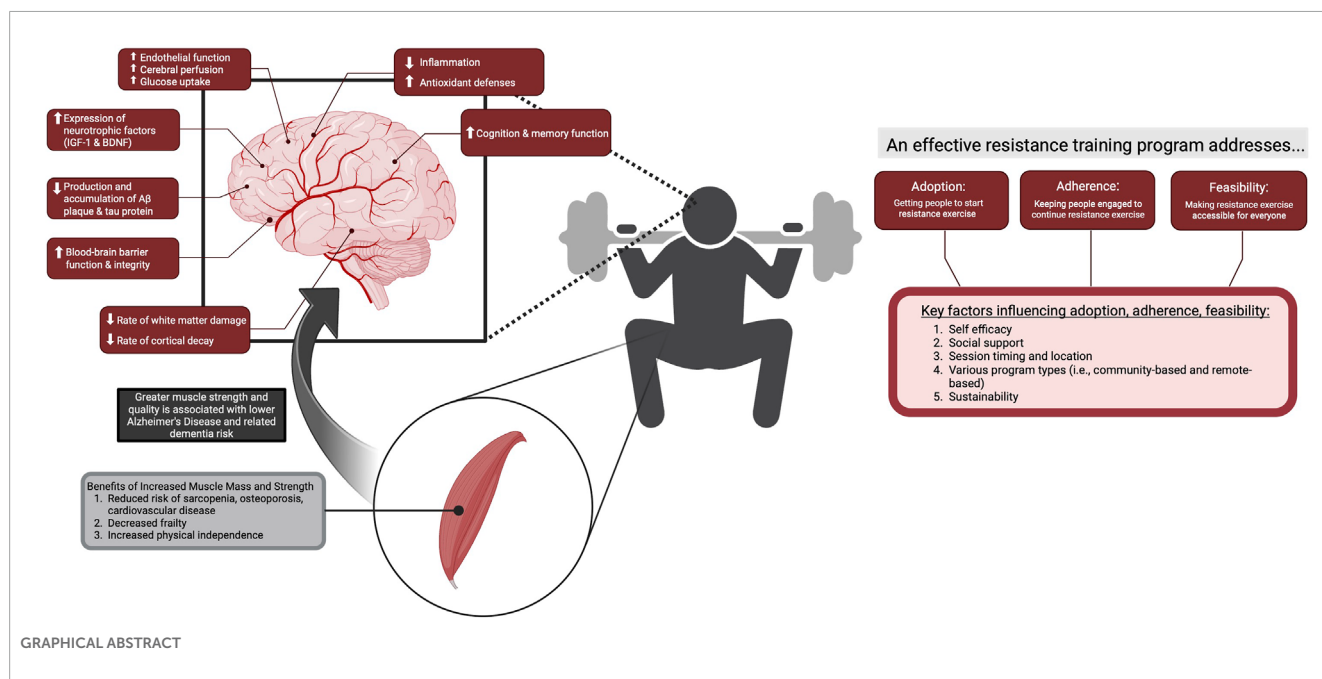
Reduced cerebral blood flow (CBF) and cerebrovascular function are critical early-stage biomarkers preceding changes in brain function and structure observed in normal aging and during the onset and progression of Alzheimer's Disease and related dementias (ADRD). Though several interventions attempt to curb the effects of aging and brain neurodegeneration, exercise and lifestyle habits remain one of the most impactful and easily modifiable factors for preserving brain health. Although the effects of aerobic exercise on cerebrovascular function and brain health are well established, resistance training (RT) is rapidly increasing in popularity across all age demographics due to its numerous health benefits. Despite the clear physiological benefits of resistance exercise, its potential efficacy for preserving or improving cerebrovascular and overall brain health remains understudied to date. The aim of this review is to examine the literature pertaining to ways in which resistance exercise may reduce the risk of ADRD and slow age-related decline of brain structures and functions. Additionally, this review seeks to highlight key considerations and challenges regarding the feasibility, adoption, and adherence to resistance exercise in the context of normal aging, mild cognitive impairment, and ADRD.

## KEYWORDS

resistance exercise, cerebral blood flow (CBF), Alzheimer's disease related dementias, brain health, cerebrovascular, neurodegeneration, aging, resistance training (RT)

## Introduction

As the global population ages, neurodegenerative conditions like Alzheimer's disease and related dementias (ADRD) are becoming increasingly prevalent (Rajan et al., 2021). These conditions involve a progressive decline of cognitive function, significant deterioration of neural structures, and widespread metabolic dysfunction throughout the brain (Hoyer et al., 1988; O'Brien J et al., 2020; Zhang B. et al., 2021). Pathological processes such as inflammation, oxidative stress, and cerebrovascular dysfunction emerge in early stages of disease



progression (Kinney et al., 2018; Huang et al., 2016; Nelson et al., 2016), long before clinical symptoms like memory loss appear, presenting a significant challenge for the timing and efficacy of targeted pharmaceutical interventions (Iturria-Medina et al., 2016).

Physical inactivity is an important modifiable risk factor for cognitive decline and progression of ADRD. Aerobic exercise is associated with beneficial effects on brain health such that increased physical activity is associated with attenuated rate of age-related cortical atrophy (Colcombe et al., 2003), hippocampal growth (Erickson et al., 2011; ten Brinke et al., 2015), and improved cognitive function (Nagamatsu et al., 2013). Much of the available literature has focused on the protective effects of aerobic exercise and cardiorespiratory fitness in reducing the onset and progression of ADRD (Colcombe et al., 2003; Erickson and Kramer, 2009; Baker et al., 2010; Alty et al., 2020). These neuroprotective and cerebrovascular benefits of aerobic exercise may be partly explained by its ability to reduced systemic inflammation (Gleeson et al., 2011), improved antioxidant defense systems (de Sousa et al., 2017), and improved vascular health and function (Bliss et al., 2021). Converging evidence suggests that reductions in cerebral blood flow (CBF) and cerebrovascular dysfunction may precede structural and functional deficits associated with neurodegeneration, representing one of the earliest indicators of ADRD risk (Jack et al., 2010), and therefore, cerebrovascular dysfunction may serve as an ideal early-stage biomarker that is receptive to aerobic exercise interventions (Kleinloog et al., 2019; Tomoto et al., 2022; Thomas et al., 2020).

Improved skeletal muscle strength is another exercise-induced effect associated with improvements in cognitive function (Van Dam et al., 2018; Frith and Loprinzi, 2018), maintenance of brain structure (Lu et al., 2024; Moon et al., 2019), and reduced risk for onset and progression of ADRD (Boyle et al., 2009; Esteban-Cornejo et al., 2022). Resistance training (RT) has gained popularity, particularly among those prescribing exercise to the elderly, due to its positive effects on muscle strength, metabolism,

bone density, and mobility, as well as its potential to reduce the risk and progression of osteoporosis, sarcopenia, frailty, and cardiovascular disease (Westcott, 2012). Likely due to the high magnitude and rapid oscillatory blood pressure responses associated with resistance exercise, the effects of RT on peripheral vascular and cerebrovascular function appear to be distinct from those of aerobic exercise (Thomas et al., 2021). Despite the numerous physiological benefits of RT, its impact on brain health in older adults, particularly those at risk for or living with ADRD, requires further exploration.

Thus, the purpose of this paper is to synthesize the current literature related to the effects of RT on brain health with a specific focus on cerebrovascular function, brain structure, and cognition. This review will first highlight the pathophysiological mechanisms underlying the onset and progression of ADRD. We will also explore mechanisms related to cerebrovascular and neurological adaptations to RT, and their interactions with age- and disease-related changes in cerebrovascular function and brain health. Additionally, this review will identify research gaps and propose future directions throughout for the study of RT and its effects on brain health and ADRD risk and progression. Finally, this review will summarize challenges of prescribing RT interventions (i.e., feasibility, adoption, adherence) in healthy and older adults at risk for ADRD and provide recommendations to overcome these challenges.

## Methods

### Inclusion and exclusion criteria

The population of interest for this review included humans (both male and female) described as middle- or older-aged in the studies, of any health status. We also included mechanistic evidence

from young healthy adults and animal studies to help support and interpret findings from human studies when available and appropriate. Studies of any study design were included in this review if they examined the effects of RT. Throughout the manuscript studies involving training interventions refer to the exercise stimulus as RT, whereas acute exercise is referred to as resistance exercise. Acute resistance exercise responses were considered to provide mechanistic background for longer-term adaptations to chronic RT. No limitations related to resistance exercise program design were placed, including factors of intensity, volume, frequency, duration, type of muscular contractions (i.e., concentric, eccentric, isometric), or type of resistance exercise performed. Outcomes of interest for this review included cellular factors such as neurotrophins (i.e., brain derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1)) and inflammatory markers, hemodynamic and functional measures for any cerebral conduit arteries (e.g., neck artery compliance/stiffness, blood flow, reactivity) and cerebral arteries (e.g., cerebral hemodynamics, blood flow, reactivity, autoregulation), brain structure (regional grey matter integrity, white matter lesions, diffusion tensor images, blood-brain barrier (BBB) integrity), clinical neurodegenerative measures (amyloid deposition, tau neurofibrillary tangles, inflammatory markers), functional connectivity (functional magnetic resonance imaging (fMRI) indices), and cognitive function. Studies were excluded from this review if they did not examine effects of resistance training on any outcomes mentioned above. Additional studies from outside our search including review papers and findings from animal studies are cited for interpretation and speculation of mechanisms underlying effects of resistance exercise on the above-mentioned outcomes.

## Search strategy and screening

Though this review is not a systematic review, we aimed to conduct best research practices and facilitate reproducibility in our search strategy. Our literature search was conducted in 3 databases: MEDLINE, EMBASE, and Web of Science with no date restrictions up to October 2024 (range of publication date for studies: 1985–2024). The search strategy was developed with assistance from a research librarian. For our search we used keywords related to cerebrovascular structure and function, resistance exercise and training, cerebral hemodynamics, cognitive function, brain structure, neurodegeneration, and dementia subtypes. Following the database search, authors (EYA, AMB, AR) screened papers for inclusion eligibility based on the inclusion and exclusion criteria mentioned above. Our search across three databases yielded  $N = 7275$  papers. After screening titles and abstracts for eligibility, there were  $N = 313$  papers for full-text screening. After completion of full-text screening, we had a final pool of  $N = 172$  papers. Because this is not a systematic review, not all 172 of these papers were reviewed comprehensively. Instead, we have used this pool of 172 papers as well as supplementing with articles from outside our search to narratively summarize and review overall trends, relationships, and underlying mechanisms behind the potential efficacy of RT and brain health in older adults and those vulnerable for the onset and progression of vascular dementia and Alzheimer's disease.

## Metabolic and vascular contributions to ADRD

It is important to recognize that the etiology of ADRD is multifactorial and heterogeneous (Iturria-Medina et al., 2016; Jack et al., 2010; Wang et al., 2017; Habes et al., 2020). In any given case, the onset and progression of ADRD may be driven by one or several interacting mechanisms discussed below, including inflammation and oxidative stress, alterations in cerebral metabolism, cerebral perfusion, systemic and cerebrovascular structure and function, and blood-brain barrier integrity. Moreover, this list is not exhaustive, and ongoing research continues to uncover additional contributors to neurodegeneration, emphasizing the complexity of ADRD pathophysiology and the need for specific prevention and intervention strategies.

### Cerebral metabolism

The brain has limited energy stores and a near exclusive reliance on glucose to support cerebral metabolism that is required to support its extensive energy requirements (Sims-Robinson et al., 2015). Normal aging is accompanied by a decline in cerebral metabolism, driven by impaired mitochondrial ATP production, increased reactive oxygen species (ROS), and decreased antioxidant defenses (Maldonado et al., 2023), and these deficits are amplified in ADRD compared to cognitively normal older adults (Patro et al., 2021; Ionescu-Tucker and Cotman, 2021). Mitochondrial dysfunction, oxidative stress, inflammation, and impaired ATP production occur in a feedforward cycle, serving as both consequences and causes of the marked reduction in glucose metabolism in the brain across the spectrum of ADRD development (Wang et al., 2017). Disrupted glucose metabolism in ADRD is closely linked with an inflammatory and neurotoxic milieu, as increased presence of ROS and pro-inflammatory cytokines reduce expression of glucose transporters, disrupt insulin signalling, and reduce mitochondrial efficiency and function, resulting in impaired transport, uptake, and metabolism of glucose (Rojas-Gutierrez et al., 2017; Yin et al., 2016). Indeed, glucose hypometabolism is present in both early and advanced stages of ADRD with greater impairments in metabolism coinciding with worsening neurodegeneration (Desgranges et al., 1998; Herholz et al., 2002). Furthermore, impaired cerebral metabolism appears to be an early-stage biomarker for ADRD, as several studies have shown reduced glucose metabolism in the hippocampus and posterior cingulate prior to observation of overt clinical symptoms (i.e., cognitive impairment) (Kumar et al., 2022; Protas et al., 2013; Ferrari et al., 2019; Chen et al., 2021).

### Cerebral perfusion

Converging evidence strongly supports the notion that changes in CBF precede structural and functional deficits associated with neurodegeneration, and may be amongst the earliest indicators of ADRD risk (Jack et al., 2010). In healthy individuals, CBF is tightly coupled to the metabolic demands of neurons (Claassen et al., 2021), however, it is unclear whether reduced CBF in ADRD is a cause

or consequence of cerebral hypometabolism. It remains unclear whether the observed cerebral hypoperfusion in those at risk for development of ADRD is primarily a consequence of impairments in systemic vascular health or a result of reductions in cerebral metabolism. Nonetheless, evidence supports the marked reductions in global CBF in early stages of MCI compared to age-matched controls with normal cognition, and further reduction in CBF as individuals progress from MCI into ADRD (Zhang H. et al., 2021). In people with MCI, the pattern of brain regions with reduced CBF aligns with regions impacted early in the ADRD pathophysiological cascade (posterior cingulate, parietal, temporal, and hippocampal regions (Zhang H. et al., 2021), supporting a role for cerebral hypoperfusion in the MCI-ADRD progression.

Cardiovascular disease is also associated with development of neurodegenerative conditions, driven by both cardiac insufficiency-related hypoperfusion as well as damage to cerebral microvasculature, similarly reducing blood flow to cerebral tissues (Newman et al., 2005; Stefanidis et al., 2018; KNOPMAN, 2007). The consequences of the cardiovascular disease-related reductions in CBF include accelerated reduction in frontal, parietal, and temporal grey matter volumes (Anazodo et al., 2013), greater white matter hyperintensity burden (Moroni et al., 2018), cognitive deficits (Jiang et al., 2023), and increased risk of ADRD (Brain et al., 2023). Given the role of CBF in supporting neuronal function, cardiovascular disease appears to exacerbate the feed-forward processes in neurodegeneration by contributing to chronic hypoperfusion and metabolic stress in these vulnerable regions. In the context of ADRD risk, cerebral hypoperfusion also appears to precede Amyloid- $\beta$  (A $\beta$ ) and hyperphosphorylated tau accumulation in the ADRD pathophysiological cascade (Iturria-Medina et al., 2016), particularly in regions vulnerable to early pathology (entorhinal cortex, hippocampus, inferior parietal cortex, inferior temporal cortex) (Mattsson et al., 2014). Increased A $\beta$  and neurofibrillary tangle deposition in the brain subsequently promote further cerebrovascular dysfunction via increased ROS production and inflammation (Alavi Naini and Soussi-Yanicostas, 2015; Cheignon et al., 2018). Thus, the literature related to the chronology of ADRD pathophysiology implicates CBF as a critical early-stage target for attenuating neurodegenerative cascades prior to symptomatic changes in brain function.

## Systemic vascular structure and function

Though it remains unclear whether reductions in CBF or cerebral metabolism occurs first in the ADRD cascade, mechanical factors such as systemic and cerebral arterial stiffening are additional early stage vascular markers implicated in cerebral hypoperfusion in older adulthood beyond the typical effects of aging (Mitchell, 2011; Jefferson et al., 2018; Muhire et al., 2019). The processes leading to increased arterial stiffness are related to structural remodelling such as increased collagen and decreased elastin in the vessel wall, as well as higher resting vascular tone, endothelial dysfunction, and reduced nitric oxide bioavailability (Lyle and Raaz, 2017). Other cellular factors such as oxidative stress and inflammation can also negatively impact systemic and cerebral endothelial function by damaging endothelial cells (Shaito et al., 2022) and reducing nitric oxide bioavailability (Gryglewski et al., 1986). Long-term

consequences of arterial stiffening include negative impacts on brain function, BBB breakdown (Krizbai et al., 2005), reduced CBF, and blunted cerebrovascular reactivity (Lourenço et al., 2017). Increased arterial stiffness in cerebral conduit arteries impairs their ability to dampen blood flow ejected from the heart, leading to transmission of high pressure and pulsatile blood flow to the cerebral microvasculature and neuronal tissue. This increased transmission of pulsatile and high-pressure blood flow into the cerebral circulation is associated with cerebral microvascular damage, which contributes to chronic reductions in CBF seen with aging and disease (Suri et al., 2020). Cerebrovascular pulsatility is elevated in ADRD compared to healthy controls (Chung et al., 2017; Roher et al., 2011). Previous work from our group supports the importance of arterial stiffness as an early-stage biomarker for future decrements in brain structure by showing that high levels of arterial stiffness in midlife, but not age-related arterial stiffening, are predictive of lower grey matter volume and greater white matter hyperintensity burden in a 10-year follow-up (Allison and Al-Khazraji, 2024a). Bown et al. similarly showed strong predictive effects of baseline arterial stiffness on occipital and hippocampal volume and temporal lobe white matter hyperintensity volume in a 5-year follow up (Bown et al., 2021), all of which are brain regions that are highly vulnerable to neurodegeneration (Fjell et al., 2014). These findings emphasize the importance of systemic vascular function and mechanics on long term brain health, likely mediated by damage and mechanical stress on cerebral microvasculature.

## Cerebrovascular function

Optimal function of cerebral conduit arteries is another critical factor in ensuring CBF matches the metabolic demands for brain function and maintain long-term brain health. Several techniques can be used to assess cerebral arterial function, including measures of perfusion (middle cerebral artery blood velocity; MCAv, CBF), cerebrovascular reactivity, cerebrovascular conductance, cerebrovascular resistance, cerebrovascular pulsatility, cerebral autoregulation, and neurovascular coupling (Ozturk and Tan, 2018). MCAv begins to decrease in early midlife (Alwatban et al., 2021), aligning with the reductions in global CBF observed with aging (Chen et al., 2011). Compared to healthy older adults, MCAv is lower in age-matched individuals with MCI and ADRD, worsening along the neurodegenerative spectrum (Zhang H. et al., 2021; Sabayan et al., 2012). Cerebrovascular resistance can also provide information on cerebrovascular function in ADRD. Greater cerebrovascular resistance is indicative of constricted downstream vessels (higher vascular tone) in the cerebral circulation, restricting perfusion into cerebral tissues (Claassen et al., 2021). Compared to cognitively normal older adults, cerebrovascular resistance is higher in individuals with MCI and ADRD, and has been associated with greater A $\beta$  burden, cortical atrophy, and risk of progression to ADRD (Yew and Nation, 2017). Additionally, increased cerebrovascular resistance has been suggested to precede observable reductions in regional CBF (Yew and Nation, 2017). Higher resting cerebrovascular tone may occur due to endothelial dysfunction (Bolduc et al., 2013) or chronic overactivity of the sympathetic nervous system (Willie et al., 2014), as seen in cardiovascular disease (Jay Widmer and Lerman, 2014; Malpas,

2010) and diabetes (Calles-Escandon and Cipolla, 2001; Esler et al., 2001), conditions which contribute to ADRD risk.

Cerebrovascular resistance serves as the foundational basis other indices of cerebrovascular function and health. Cerebrovascular reactivity is a frequently used measure to provide insight into the health and function of the cerebral vasculature, and is dictated by changes in cerebral vascular tone in response to a given stimuli (Claassen et al., 2021). Assessing changes in either large cerebral artery cross-sectional area and CBF (MRI) or cerebral hemodynamics (MCAv) in response to a vasoactive stimuli, such as carbon dioxide (CO<sub>2</sub>), forms the basis of cerebrovascular reactivity (Wang et al., 2023). CO<sub>2</sub> is a potent regulator of CBF, as elevated CO<sub>2</sub> and the accompanying pH change causes healthy cerebral arterioles to dilate, subsequently increasing conductance and CBF (Hoiland et al., 2019). Crucially, individuals in ADRD demonstrate marked impairments in cerebrovascular reactivity to CO<sub>2</sub> compared to controls (Glodzik et al., 2013; Alwatban et al., 2019; Gao et al., 2013; Vicenzini et al., 2007). Based on these associations, cerebrovascular reactivity may relate to early cerebrovascular dysfunction associated with neurodegenerative diseases like ADRD. Another key regulator of CBF is neuronal activity, mediated through the process of neurovascular coupling (Phillips et al., 2016). Briefly, neurovascular coupling describes the change in cerebral oxygen extraction or blood flow delivery to meet the metabolic demands of active neurons (Phillips et al., 2016). Similar to cerebrovascular reactivity, impaired neurovascular coupling is attenuated with advanced age (Peng et al., 2018), MCI and ADRD (Phillips et al., 2016; Peng et al., 2018; Nicolakakis and Hamel, 2011). Factors associated with impaired cerebrovascular reactivity and neurovascular coupling include cerebral microvascular dysfunction, insulin-like growth factor 1 (IGF-1) deficiency, and oxidative stress-related inhibition of neuronal and astrocytic vasodilators (Phillips et al., 2016; Zlokovic, 2005). The importance of these cerebrovascular functional measures are supported by the graded relationship between impairment in cerebrovascular reactivity to CO<sub>2</sub> (Kim et al., 2021; Silvestrini et al., 2006) and neurovascular coupling responses and severity of cognitive impairment in individuals with MCI and ADRD (van Dijk et al., 2024). Overall, these findings emphasize the importance of cerebral vasoreactivity as a marker of cerebrovascular and overall brain health.

## Cerebral autoregulation

The responsiveness of cerebral vasculature to stimuli also underlies cerebral autoregulation. The concept of cerebral autoregulation describes the ability of the cerebral vasculature to regulate CBF during oscillations in cerebral perfusion pressure (Claassen et al., 2021). Currently the data suggests that autoregulatory function remains intact in individuals across the spectrum of ADRD progression (Claassen et al., 2021; Claassen and Zhang, 2011; de Heus et al., 2018; de Jong et al., 2019). Increased resting cerebrovascular tone in individuals along the ADRD progression spectrum (Yew and Nation, 2017) is likely to restrict transient increases in blood pressure into the cerebral circulation. Thus, an absence of a change in CBF during increases in blood pressure due to increased resting cerebrovascular resistance in neurodegenerative models may mask differences in autoregulatory

function. Whether blood pressure oscillation direction (increases vs. decreases) affects interpretation of data pertaining to autoregulatory function in cognitive decline, vascular dementia, and ADRD remains unclear.

## Blood-brain barrier (BBB)

The structural and functional integrity of the BBB is emerging as another early-stage biomarker for neurodegenerative conditions. A critical neuroprotective structure, the BBB's primary role is regulating the transport of compounds into (influx) and out of (efflux) the parenchyma (Moyaert et al., 2023). A key characteristic of the BBB compared to peripheral vasculature is the arrangement of endothelial cells, which include tightly sealed cell-to-cell contacts called tight junctions (Moyaert et al., 2023). The BBB, similar to the peripheral vasculature, is susceptible to degradation and dysfunction of endothelial cells through oxidative stress, inflammation, and mechanical hemodynamic stress (i.e., high systolic pressures and pulsatility) (Moyaert et al., 2023; de Montgolfier et al., 2019). Damage to the tight endothelial junctions results in increased BBB permeability, leading to the entry of immune cells and inflammatory cytokines into the parenchyma, as well as impaired clearance of metabolic waste and neurotoxic compounds (Zlokovic, 2004; De Boer and Gaillard, 2006). One of the most vulnerable brain regions to normal age-related and disease related alterations in BBB permeability is the hippocampus (Sweeney et al., 2018a; Sweeney et al., 2018b). The disruption in BBB in the hippocampus is accelerated with MCI and ADRD progression compared to normal aging (Sweeney et al., 2018b). BBB dysregulation precedes A $\beta$  and tau protein deposition, cognitive decline, and structural changes in brain tissue (Iturria-Medina et al., 2016). The role of the BBB in the progression of ADRD is further supported by evidence showing that disrupted BBB function impairs efflux of A $\beta$  from the parenchyma (Wang et al., 2017; Zlokovic, 2004; Sweeney et al., 2018b). However, with continued accumulation of A $\beta$  plaques, the inflammatory and neurotoxic parenchymal environment can progress to further damage the BBB (Erickson and Banks, 2013). This cycle of A $\beta$  accumulation causing BBB damage, leading to further impairments in A $\beta$  efflux and thus greater accumulation is a major process underlying the severe and rapid loss of function in AD. Thus, the BBB may represent a viable therapeutic target to prevent or attenuate progression of ADRD prior to histopathological, structural, or functional changes in the brain.

## Why resistance exercise?

### Muscle strength as a risk factor for ADRD

Muscle weakness and the associated frailty are associated with MCI and ADRD severity (Moon et al., 2019; Boyle et al., 2009; Filardi et al., 2022; Dost et al., 2023). Sarcopenia and the accompanying loss in muscle strength and balance leads to frailty, decreased independence, lower rates of physical activity, and increased sedentary time (Loprinzi, 2016). Importantly, patterns of age-related muscle loss appear to be different between sexes, with

men demonstrating a greater rate of relative loss in muscle mass with age and females having a greater prevalence for sarcopenia—likely due to males having a higher muscular reserve compared to females (de Jong et al., 2023). The relationship between sex and prevalence of sarcopenia may partially be explained by longer life expectancy in females—as it is primarily an aging related disorder. Nonetheless, the greater likelihood of sarcopenia in females aligns with epidemiological studies that point to females comprising two thirds of all ADRD diagnoses (Mielke, 2018; Alzheimer's Association, 2019). Improving skeletal muscle mass and quality via RT may therefore be a critical non-pharmacological approach to attenuate systemic inflammation and ROS production associated with sarcopenia sedentarism (Meng and Yu, 2010; Dalle et al., 2017; Pan et al., 2021; Laufs et al., 2005; Gratas-Delamarche et al., 2014), and slow the rate of age and disease-related neurodegeneration. Given its beneficial effects on muscle size and quality (Westcott, 2012), and improved metabolic function (i.e., improved glucose metabolism, insulin sensitivity) (Zhou et al., 2022), partaking in regular RT is a promising behaviour to attenuate cellular and behavioural risk factors for neurodegenerative processes.

## Resistance exercise and sleep

Sleep duration and quality are important factors in the development and progression of ADRD (Himali et al., 2023). The glymphatic system, most active during slow-wave or restorative sleep, is essential for facilitating clearance of metabolic waste (Reddy and van der Werf, 2020; Xie et al., 2013). This process of glymphatic clearance during sleep includes the efflux of A $\beta$  and tau proteins out of the parenchyma (Xie et al., 2013; Holth et al., 2019; Kang et al., 2009). Beyond the two primary proteins of focus in ADRD progression, glymphatic clearance also helps support removal of inflammatory markers to maintain the parenchymal environment and reduce neurotoxic load on neurons (Mogensen et al., 2021). Meta-analyses have shown that habitual participation in RT is associated with improved sleep quality (Kovacevic et al., 2018). Further, in older sarcopenic adults, a 12-week RT program (3 times per week of full body RT at 75% 1RM) was shown to reduce sleep latency (shorter time necessary to fall asleep) as well as increase time spent in slow-wave sleep, when a large proportion of glymphatic drainage and restorative processes occur (De Sá Souza et al., 2022). While more work is needed to determine the optimal parameters of RT programs for improving sleep, it is nonetheless important to recognize the role of RT, and exercise in general, as a non-pharmacological strategy to support brain health. RT may help improve sleep, which could mitigate the accumulation of metabolic waste, inflammatory markers, and neurotoxic proteins, ultimately lowering the risk for the onset and progression of ADRD.

## Resistance exercise as a unique hemodynamic stressor

From a vascular perspective, the hemodynamic stimulus associated with resistance exercise, particularly at high intensities

is unique, characterized by high magnitude and rapid oscillations in blood pressure (Perry and Lucas, 2021). These oscillations in blood pressure involve a transition between hyper- and hypotension (corresponding to concentric and eccentric muscular contractions) within each repetition cycle (Perry and Lucas, 2021). While more research is necessary, repeated exposure to oscillatory hemodynamic stress and the associated patterns of shear stress on the endothelium may prime the vasculature to better handle both surges and sudden drops in systemic blood pressure, potentially leading to better maintenance and regulation of CBF during pressure challenges. Improved regulation of CBF in response to both transient hyper- and hypotension subsequently protects cerebral microvasculature from hyperperfusion injury and damage as well as ensuring cerebral perfusion is able to match metabolic demand during periods of reduced driving pressures (i.e., orthostatic stress) (Claassen et al., 2021). Indeed, recent cross-sectional evidence supports enhanced pressure regulation in the brain in resistance-trained individuals (Korad et al., 2024; Roy et al., 2022). Thus, the rationale for RT interventions to mitigate neurodegenerative processes is strengthened by the distinct vascular and cerebrovascular adaptations (Allison and Al-Khazraji, 2024b; Zhang Y. et al., 2021), as well as the apparent neuroanatomical and cognitive benefits that will be discussed in subsequent sections of this review.

## Resistance exercise as a cognitive stimulus

Resistance exercise involves multiple aspects that require attention and focus. These aspects include neuronal adaptations centered around synchronized recruitment of motor neurons in several different muscle groups, matching muscle fibre recruitment to exercise intensity, learning new motor patterns involving multiple muscle groups or muscles in isolation (Carroll et al., 2001; Gabriel et al., 2006), keeping track of repetitions and sets completed, and use of intentional breathing techniques such as the Valsalva Maneuver (Forte et al., 2013; Lepley and Hatzel, 2010). Indeed, motor task complexity has been linked to neuroplasticity (Carey et al., 2005). Thus, while significantly more research is necessary, the novelty and complexity of resistance exercises may be an important factor underlying its pro-cognitive effects and efficacy in driving neuroplasticity. Nonetheless, resistance exercise is a unique model, likely eliciting different neuronal and physiological adaptations related to improved brain health and function compared to other forms of exercise. The mechanisms underlying protective effects of RT on the brain and its role in reducing risk of neurodegeneration are discussed herein.

An important concept to define prior to synthesis of literature is progressive RT. Briefly, progressive RT relies on a fundamental principle of resistance exercise prescription—progressive overload in which intensities, reps, or sets may start lower but increase gradually over the duration of the intervention (Kraemer et al., 2002). The fundamental principles of progressive overload are rooted in facilitating continued strength gains; however, given the relationship between muscular strength and overall brain health, there may be potential application of these principles in improving brain health. Progressive overload is applied in

both human and animal research and will be referred to as progressive RT herein.

## Effects of resistance training on brain-related outcomes

The issue of maintaining and promoting brain health is highly complex. However, multiple factors, including inflammation (Ahmad et al., 2022) and cerebral perfusion (Wolters et al., 2017) have been supported as early-stage biomarkers for neurodegenerative processes that are receptive to intervention prior to onset of clinically relevant loss in brain function. Additionally, neurotrophic factors such as IGF-1 and BDNF are critical targets for facilitating slower rates of structural and functional decline in the brain with advancing age—as both promote neurogenesis (Park and Poo, 2013; Anderson et al., 2002), as well as neuronal plasticity (Zagrebelsky and Korte, 2014) and survival (Park and Poo, 2013; Nieto-Bona et al., 1997). While the factors underlying brain health and longevity discussed below are not exhaustive, they represent what appear to be the most quantifiable and targetable factors underlying neurodegenerative processes along the MCI-ADRD continuum. Below we discuss the effects of resistance exercise on both humans and in animal models. Though findings from animal models provide an important basis for future research in humans, the findings from studies using animal models need to be interpreted with caution and as hypothesis generating, rather than definitive evidence of the neuroprotective effects of RT. Nonetheless, for completeness and interpretive purposes, studies using animal models are included in this review and are explicitly described as such herein.

## Effects of resistance exercise training on oxidative stress and inflammation

Chronically elevated oxidative stress and diminished antioxidant defenses causes neuronal damage and mitochondrial dysfunction, which play key roles in neurodegenerative pathologies (Guo et al., 2013). The brain is particularly susceptible to oxidative stress given its limited antioxidant enzymatic capacity to counteract reactive oxygen species production (Ferreira et al., 2015). Despite a well-established relationship between acute resistance exercise and increased oxidative stress (Fisher-Wellman and Bloomer, 2009), habitual RT has been associated with a reduction in markers of oxidative stress at rest, with the bulk of evidence coming from animal models. 6 weeks of progressive ladder-climbing RT (8 climbs, progression from 50% to 100% maximal carrying load (MCL), 3 times per week) mitigates the rise in reactive oxygen species production, as represented by lipid peroxidation/malondialdehyde levels in the brain tissue of an AD rodent model (Özbeyli et al., 2017). The RT intervention also improved antioxidant defence capabilities, as represented by glutathione levels (Özbeyli et al., 2017). Interestingly, the same results were not observed in healthy age-matched mice, as 6 weeks of progressive ladder-climbing RT (3 climbs, progression from 50% to 100% MCL, 5 times per week) decreased lipid peroxidation in the cerebral cortex but increased lipid peroxidation in the hippocampus (Feter et al., 2019). It is

possible that RT in healthy mice may initially act on antioxidant defence capacity, rather than mitigating reactive oxygen species production directly. The benefits of RT on oxidative stress in rodent models of AD do appear to persist beyond 6 weeks, as another trial found that 8 weeks of ladder-climbing RT (8 climbs, 2 repetitions at 50%, 75%, 90%, and 100% MCL, 3 times per week) prevented a rise in lipid peroxidation (Schmidt et al., 2019). This evidence suggests that RT may be more effective at reducing oxidative stress in situations where ROS and antioxidant balance is compromised, as observed along the continuum of neurodegenerative disease progression or with aging. Indeed, 24 weeks of moderate intensity RT (3 sets of 8–12 reps with progression to 12–16 reps at 65%–75% 1RM, 2 times per week) in combination with cognitive stimulation and aerobic exercise in older adults with MCI reduced plasma markers of lipid peroxidation (Rondão et al., 2022). Similarly, 6 months of resistance training improved numerous blood indices of oxidative stress including reduced oxidative damage, ameliorated antioxidant defence and DNA stability in older adults (Franzke et al., 2018). Thus, current evidence suggests that RT protocols are beneficial for mitigating rises in oxidative stress that occur along the development of neurodegenerative diseases and aging. Future work is required to determine if this training modality can bolster antioxidant defenses and mitigate excess oxidative stress in healthy human populations.

Inflammation and oxidative stress are closely interconnected, as the cellular damage imposed by increases in oxidative stress prompts immune inflammatory responses which contribute to the development and severity of neurodegeneration (Heneka et al., 2015). Despite acute physical exercise transiently increasing inflammatory responses, longer-term RT lowers circulating levels and cellular concentrations of anti-inflammatory cytokines. Acute long duration resistance exercise (180 min of bilateral knee extensions at 55% 1RM) in elderly populations is typically accompanied by an acute inflammatory immune response characterized by the release of interleukin-6 (IL-6) into the circulation (Steensberg et al., 2002). Whereas, 4 weeks of progressive ladder-climbing RT (2 climbs per session at 75%, 90%, and 100% MCL) 5 times per week in a mouse model of AD lowered circulating IL-6 to levels comparable to healthy controls (Hashiguchi et al., 2020). Similarly, 12 weeks of progressive full body RT 3 times per week (3 sets of 10 reps, progression from 50%–80% 1RM), in older humans lowers basal IL-6 levels, which may represent an adaptation to the exercise (Forti et al., 2014). Though IL-6 has pro-inflammatory functions, it can also stimulate the release of IL-10 (Ostrowski et al., 1999) which in turn inhibits the production of inflammatory cytokines such as IL-1 $\beta$ , and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) (Cassatella et al., 1993). Indeed, progressive RT (15 climbs, progression from 15%–75% of MCL over 4 weeks) performed on alternating days attenuated neuroinflammation in the frontal cortex and hippocampus of mice by reducing mRNA expression of TNF- $\alpha$  and protein concentrations of IL-1 $\beta$  (Liu et al., 2020). In contrast to these findings, 8 weeks of progressive RT (3 sets of 8–12 climbs, 50%–100% of MCL) on alternating days in aging rats observed increased hippocampal protein expression of TNF- $\alpha$  and IL-1 $\beta$  (Vilela et al., 2017). However, given that this study did not measure IL-6 or IL-10, it is unclear where there was also a

concomitant increase in anti-inflammatory molecular factors to counteract this response. Overall, current research presents substantial evidence for the therapeutic potential of RT to mitigate oxidative stress and inflammation, which are crucial pathophysiological factors underlying neurodegenerative disease pathogenesis (Vints et al., 2024).

## Effects of resistance exercise training on ADRD biomarkers

For the last 2 decades, the discourse related to the underlying mechanism for development of AD specifically has largely focused on the amyloid hypothesis, attributing the transition from MCI to AD to the accelerated rate of A $\beta$  plaque deposition and subsequent neurofibrillary tangle formation (Hardy and Higgins, 1992). ROS production and inflammation are the assumed to be the primary drivers of accelerated A $\beta$  plaque deposition and neurofibrillary tangle formation (Huang et al., 2016; Ionescu-Tucker and Cotman, 2021; Cheignon et al., 2018). Several animal studies have shown proof-of-concept for alleviation of amyloid burden with RT interventions. In AD animal models, 3 days of progressive ladder-climbing RT (6–11 climbs progressing from 75%–100% MCL) on alternating days for 4 weeks resulted in significant reductions in A $\beta$  levels and significant reductions in IL-1, IL-4, IL-6, and no differences in IL-10 between exercising and AD non-exercising controls (Hashiguchi et al., 2020). The mechanisms for reduced A $\beta$  are hypothesized to be related to restoration of the BBB, facilitating efflux of A $\beta$  from the parenchyma (Zlokovic, 2004). A separate study from the same research group, using the same exercise protocol similarly showed significant reductions in A $\beta$  levels and increased microglia in the hippocampus in AD mice (Campos et al., 2023). These findings are supported by work from Liu et al who similarly observed increased expression of synaptic signalling proteins in the hippocampus, and reductions in A $\beta$  and tau burden in the frontal cortex and hippocampus of AD mice with 4-week progressive ladder-climbing RT (15 climbs, progression from 15%–75% MCL) (Liu et al., 2020).

Özbeyli et al showed that 3 days of progressive ladder-climbing RT (50%–100% MCL) per week for 6 weeks significantly reduced amyloid burden in AD mice compared to sedentary and aerobic trained AD mice (Özbeyli et al., 2017). In animal models of AD, RT has shown efficacy for mitigating accumulation of A $\beta$  plaques, with fewer studies showing positive effects on neurofibrillary tangles. Exercise related attenuations in A $\beta$  production is a critical consideration as well. Work from Marko et al demonstrated that treatment of human neuronal cells with post-exercise serum, albeit aerobic, was associated with decreased expression of amyloid processing enzyme  $\beta$ -secretase linked to production of A $\beta$  and increased expression of non-amyloidogenic enzyme  $\alpha$ -secretase, producing the soluble amyloid proteins that have not been implicated in neurodegeneration (Marko et al., 2022). The implications of the work from Marko et al should not be understated, as it provides critical insight into the effectiveness of even a single bout of exercise on reducing A $\beta$  production and plaque accumulation. Future studies should aim to extend these results to determine whether RT would have similar anti-amyloidogenic

effects on the amyloid precursor protein processing. In addition to acute effects, future studies should also aim to investigate the effects of RT interventions on biomarkers of ADRD in humans to continue to build understanding on how exercise can attenuate or potentially reverse ADRD pathology.

## Effects of resistance exercise training on circulating neurotrophins

Acute and chronic changes in circulating neurotrophic growth factors following RT have been extensively studied as potential mechanisms that contribute to the structural and functional improvements in brain health with RT. Although RT increases several circulating growth factors that are important for brain health, this review will primarily focus on BDNF and IGF-1, given their prominent role in modulating brain plasticity. BDNF is a member of the neurotrophin family that contributes to a myriad of functions including synaptic plasticity (Zagrebelsky and Korte, 2014), neuronal growth, survival, and repair (Park and Poo, 2013), and is essential for facilitating learning and memory (Cirulli et al., 2004; Lu et al., 2014). In particular, BDNF has been identified as a prominent contributor to exercise-induced changes in brain health. Evidence from murine models demonstrate that hippocampal and cortical BDNF mRNA expression remains elevated for up to 24 h post-exercise, supporting the role of BDNF in facilitating changes in brain function well beyond the cessation of exercise (Rasmussen et al., 2009). Further research has also provided evidence of increased hippocampal BDNF following both acute resistance exercise in insulin-resistant rats (Berbert-Gomes et al., 2024) and increases in basal BDNF concentrations following 8 weeks of progressive ladder-climbing RT (8 climbs, 2 repetitions for each load of 50%, 75%, 90%, and 100% MCL, 3 times per week) in a rodent model of AD (Jafarzadeh et al., 2021). Collectively, this evidence suggests that BDNF concentrations are rapidly increased following acute resistance exercise and performing repeated bouts of resistance exercise (i.e., RT) may lead to sustained increases in resting BDNF over time.

Given that blood BDNF concentrations decline with aging (Lommatzsch et al., 2005; Ziegenhorn et al., 2007), extensive research has aimed to assess whether RT is an effective lifestyle intervention to help mitigate these reductions in humans. Research assessing exercise-induced BDNF responses in humans are limited to only measuring peripheral concentrations of blood BDNF, unlike in animal models where brain BDNF expression and/or concentrations can be directly measured. As a result, it is difficult to precisely localize potential changes in brain function arising from exercise-induced increases in BDNF. Nonetheless, there is evidence to suggest that peripheral BDNF may cross the BBB into the brain parenchyma (Pan et al., 1998) and circulating concentrations closely mirror BDNF content in the brain (Klein et al., 2011; Sartorius et al., 2009), suggesting that peripheral BDNF concentrations may be a viable surrogate for brain BDNF concentrations. Numerous research groups have shown that acute resistance exercise robustly increases circulating BDNF in humans, albeit transiently (Yarrow et al., 2010; Walsh et al., 2015; Marston et al., 2017; Church et al., 2016), while other studies have demonstrated no such change in circulating BDNF following acute resistance exercise (Correia et al., 2010;

Goekint et al., 2010). Though the circulating BDNF response to acute resistance exercise is transient, Walsh et al demonstrated that post-exercise BDNF release persists, but did not increase as a result of 8 weeks of RT (3 exercises, 4 sets, 8–12 repetitions, progression from 60%–80% 1RM, 3 times per week (Walsh et al., 2015). In contrast, Church et al, who found that independent of training structure (high volume-low intensity [10–12 reps; 70% 1RM] vs. high intensity-low volume [3–5 reps; 90% 1RM], 4 days per week for 8 weeks) the magnitude of post-exercise BDNF release was increased compared to pre-training levels (Church et al., 2016), suggesting that each bout of resistance exercise session independent of training status provides a “dose” of BDNF to the brain, and the release of BDNF can be increased with habitual RT. These acute increases in circulating BDNF from resistance exercise may be an important stimulus for longer-term adaptations to brain health, given the plethora of evidence supporting the beneficial effects of RT on cognitive function, especially executive function (Liu-Ambrose et al., 2010; Landrigan et al., 2020). The neurocognitive effects of repeated acute BDNF doses via RT requires further research, as much of the current evidence aside from the work conducted by Church et al suggests that RT does not increase basal blood BDNF levels. Progressive RT interventions in middle-aged to older adults for 8 weeks (Walsh et al., 2015; Ruiz et al., 2015), 12 weeks (Forti et al., 2014), and as long as 9 months in individuals with type 2 diabetes (Swift et al., 2012) have not been shown to change basal serum BDNF. Previous work has also demonstrated that 8 weeks of combined aerobic and RT (full body RT; 3 sets of 8–15 reps to failure, 3 times per week) does not change basal plasma BDNF levels in individuals with Type 2 Diabetes (Silveira-Rodrigues et al., 2023) and 24 weeks of multicomponent exercise decreases basal plasma BDNF in older adults with MCI (Rondão et al., 2022). Contrarily, other work has shown that 10 weeks of RT (1–3 sets of 8 repetitions at 75% 1RM, 3 times per week) (Coelho et al., 2012; Pereira et al., 2013) and 16 weeks of a multicomponent exercise paradigm (2 sets of 6–8 repetitions, 2 times per week) (Vaughan et al., 2014) were both sufficient to increase basal plasma BDNF in otherwise healthy elderly adults. In summary, a single bout of resistance exercise likely leads to robust and transient increases in circulating BDNF, which may be leveraged in chronic RT interventions with repeated bouts to improve and/or protect brain health with aging. Furthermore, the literature related to the effects of RT on basal BDNF remain mixed and requires further investigation to clarify this relationship, with an emphasis on delineating these findings based on populations (i.e., young vs. older adults, healthy vs. chronic health conditions such as diabetes, ADRD) and exercise parameters (i.e., multicomponent vs. RT alone, intensity, frequency, duration of training).

Liver-derived IGF-1 is another neurotrophic growth factor implicated in long-term brain health. Similar to BDNF, IGF-1 modulates exercise-induced neurogenesis (Anderson et al., 2002), synaptic density and plasticity (Nieto-Bona et al., 1997), and hippocampal expression of BDNF (Ding et al., 2006). Furthermore, IGF-1 may regulate A $\beta$  plaque concentrations, as lower circulating IGF-1 have been associated with A $\beta$  plaque accumulation in the rodent brain (Carro et al., 2002). IGF-1 deficiencies are also implicated in the development of neurodegenerative diseases such as AD (Westwood et al., 2014), while excess levels of IGF-1 are associated with aberrant cellular growth (i.e., cancers) (Qian and Huo, 2020). The focus of this section is to review evidence related

the impacts of RT-induced IGF-1 on brain health and not to imply that more circulating IGF-1 is better. Indeed, in normal physiological circumstances, basal circulating IGF-1 is tightly regulated by the cerebral spinal fluid (CSF) and any changes in circulating IGF-1 due to a single bout of resistance exercise are transient. Limited evidence of basal changes in IGF-1 following a period of RT training are likely due to corrections of a deficit, rather than an increase in IGF-1 per se. Evidence from animal models suggest that improvements in spatial memory following an acute bout of resistance exercise may be mediated via IGF-1, however the relationship between IGF-1 and short term cognitive performance in humans remains unclear (Cassilhas et al., 2012). Findings from human trials showed that a single bout of isometric knee extension resistance exercise (40% and 110% of maximal effort) (Vega et al., 2010) elicits an increase in circulating serum IGF-1 in young adults, similar to both moderate (50% 1RM) and high-intensity (80% 1RM) resistance exercise (Tsai et al., 2014). The improvement in serum IGF-1 with resistance exercise (two sets of 10 repetitions at 75% 1RM) is also present in older adults with MCI, though these changes in IGF-1 were not associated with improvements in cognition (Tsai et al., 2018). The vast majority of IGF-1 is secreted by the liver (Laron, 2001) with tissues like skeletal muscle also contributing to IGF-1 release during resistance exercise (Perrone et al., 1995). Despite the exercise-induced increase in IGF-1, this increase has not been shown to be associated improvements in executive function in young (Tsai et al., 2014) or older adults with MCI (Tsai et al., 2018). The absence of a relationship between increases in IGF-1 and improvements in cognition following resistance exercise may be attributed to the transient nature of the circulating IGF-1 response, as levels remain elevated for only ~20 min (Tsai et al., 2014). IGF-1 is tonically regulated and in excess quantities is taken up by CSF. Therefore, a potential reason for the rapid return to baseline of IGF-1 post-exercise could be uptake into the brain via CSF (Pulford and Ishii, 2001). Despite the transient nature of resistance exercise-induced IGF-1 release, there is some evidence suggesting RT interventions may influence basal levels of IGF-1. The same work by Özbeyli et al mentioned in previous sections also demonstrated that 6 weeks of ladder-climbing RT improved basal serum IGF-1 levels in a rodent model of Alzheimer's disease (Özbeyli et al., 2017). In humans, 2 years of progressive RT (full body RT; 2 sets of 2–8 repetitions with progression from 30%–55% 1RM, 2 times per week) increased basal levels of plasma IGF-1 in older women, with changes in IGF-1 concentration being associated with improvements in global cognition (Molina-Sotomayor et al., 2020). In contrast, 8 weeks of lower-limb RT (Walsh et al; exercise parameters highlighted in BDNF section) did not change basal serum IGF-1 (Walsh et al., 2015). Thus, it is possible that longer-term interventions are needed to elicit a change in basal serum IGF-1 concentrations in humans. Collectively, there is limited evidence to demonstrate that chronic RT may be improving cognitive function and protecting brain health through augmenting circulating IGF-1. The inconsistent results regarding IGF-1 responses to RT further suggests that the relationship between exercise and molecular factors underlying the neurocognitive benefits of exercise are complex and extend beyond IGF-1 and BDNF alone. Additional research is needed to clarify our current understanding, especially considering circulating IGF-1 responses to acute resistance exercise and RT have been understudied relative to BDNF.

## Effects of resistance exercise training on cerebrovascular health and function

Our group has previously reviewed the effects of habitual RT on cerebrovascular function across the lifespan (Allison and Al-Khazraji, 2024b). Habitual RT is associated with improved endothelial function (Silva et al., 2021), nitric oxide bioavailability (Güzel et al., 2007), resting arterial diameter (Zoeller et al., 2009), improved cerebral autoregulatory function (Roy et al., 2022), and importantly improved global (Xu et al., 2014) and regional CBF (Macaulay et al., 2022). Despite the clear associations between habitual participation in RT and improved vascular and cerebrovascular function, the mechanisms as they relate to neurodegenerative disease such as ADRD have not been discussed. Increased oxidative stress and inflammation ultimately disrupts proper endothelial function (Gryglewski et al., 1986), leading to impaired BBB integrity and cerebrovascular dysfunction (Krizbai et al., 2005), neurovascular coupling (Lourenço et al., 2017), and cerebrovascular reactivity (Mayhan et al., 2008). There are limited data related to effects of RT on cerebrovascular function in the elderly or in neurodegenerative conditions. Despite the paucity of data in older adults, findings from young healthy individuals may provide a fundamental backdrop for future study considerations. RT and its effects on arterial stiffness remain a topic of debate (Miyachi, 2013). Meta-analyses suggest that RT interventions increase aortic and carotid artery stiffness in healthy young men in an intensity dependent manner—such that higher intensities (75%–80% of 1RM) yield greater increases in central arterial stiffness (Kawano et al., 2006; Miyachi et al., 2004; Okamoto et al., 2009; Okamoto et al., 2006), but no such evidence has been observed in healthy young women (Morgan et al., 2023; Rossow et al., 2014), or older adults (Rossow et al., 2014; Cortez-Cooper et al., 2008; Ramírez-Vélez et al., 2020; Jefferson, 2014). Acutely, high intensity resistance exercise (80%–100% 1RM) has been reported to increase carotid artery stiffness for up to 30 min post-exercise (Lefferts et al., 2014), MCAv for at least 1-min post exercise, and MCA pulsatility index in the immediate (~30s) post-exercise period (Koch et al., 2005). The increase in MCAv and MCA pulsatility index is likely a compensatory response to counter the drop in blood pressure following resistance exercise and maintain adequate cerebral perfusion (Lefferts et al., 2014; Koch et al., 2005). Indeed, the magnitude of post-exercise hypotension is commensurate with the pressure challenge during exercise (Chen and Bonham, 2010). On the surface, increased arterial stiffness in young men with habitual RT may raise concern due to its associations with hypertension (Safar, 2018), cardiovascular diseases (Mitchell et al., 2010), and cerebral microvascular damage (Badji et al., 2019; Tsao et al., 2013; Singer et al., 2014; Mitchell, 1985). However, the relationship between RT and arterial stiffness may need recontextualization and in our opinion should not be interpreted in the same lense as disease related arterial stiffening. There is evidence of chronic RT-induced adaptations supporting improved pulsatile dampening in the cerebral vasculature—in turn reducing pulsatile burden on the cerebral microvasculature in trained individuals (Nakamura et al., 2021). Perhaps the structural remodelling of arteries with RT is a compensatory adaptation to reduce arterial distension during high-grade resistance exercise-induced oscillations in blood pressure. Additional work is necessary

to understand the broader cerebrovascular and neurological implications of RT-related arterial stiffening. Nonetheless, there is currently no evidence that RT is associated with negative effects on the cerebral vasculature despite the theoretical link between RT-induced arterial stiffness and microvascular damage.

Cross-sectionally, young healthy resistance-trained individuals (>6 months) have elevated cerebrovascular resistance and reduced cerebrovascular pulsatility during high intensity exercise. The cerebrovascular adaptations to RT are supported by work from Thomas et al, who conducted 12 weeks of progressive RT (progression from 60%–90% 1RM with repetitions lowering as intensity increases, 3 times per week) in healthy young adults and similarly observed increased cerebrovascular resistance and decreased pulsatility at rest. These findings are unique to RT, as Thomas et al observed no such changes in the age-matched aerobically trained group (Thomas et al., 2021). Further research is required to better understand cerebrovascular adaptations to RT, as increased resting cerebrovascular resistance is typically a sign of negative alterations in cerebrovascular function (Yew and Nation, 2017). As mentioned previously, increased cerebrovascular resistance at rest, whether it be related to aging or disease, is typically a negative change in cerebrovascular function and is a sign of greater flow impedance—ultimately leading to reductions in CBF (Claassen et al., 2021). In the work from Thomas et al, they observed a significant but relatively minor increase in resting mean arterial pressure (~3 mmHg) and a reduction in resting MCAv (~3 cm/s) after 12 weeks of RT. This is an important finding related to cerebrovascular function, as cerebrovascular resistance is an index measure calculated as mean arterial pressure divided by MCAv (Thomas et al., 2021). Therefore, even slight increases in resting mean arterial pressure alongside reductions in MCAv would lead to significant increases in cerebrovascular resistance. Elevated mean arterial pressure with RT reported in this study is of note due to the more frequently reported blood pressure lowering effects of RT reported across the literature, particularly in hypertensive individuals (Correia et al., 2023). Considering the positive effects of RT on blood pressure in older and hypertensive adults, it is unlikely that the ~3 mmHg rise in resting blood pressure observed by Thomas et al is of clinical concern. Importantly, the authors of this work similarly did not interpret their findings related to cerebrovascular resistance as negative adaptations to RT, but instead consider the increase to be a protective response to reduce the effects of increased mean arterial pressure on the cerebral circulation - where hyperperfusion can damage the microvasculature (Thomas et al., 2021). Indeed, despite the increase in cerebrovascular resistance with 12 weeks of RT, the authors also observed a significant reduction in MCA pulsatility index—suggestive of improved pulsatile damping despite the increase in mean arterial pressure. Thus, in alignment with the interpretation from Thomas et al, perhaps changes in cerebrovascular resistance observed in RT are to be separated from vascular pathology and recontextualized as a favourable adaptation, as increased resistance may suppress transmission of pulsatile blood flow into the cerebral circulation during- and post-resistance exercise (Koch et al., 2005). Reduced cerebrovascular pulsatility with RT could also be interpreted as improved capacity for cerebral arteries to dampen pressure waves ejected from the heart. Nonetheless, more work is necessary to better understand the

effects of RT on cerebrovascular structure and function, particularly in elderly and diseased populations.

As it relates to cerebral autoregulatory function, Koch et al demonstrated that acute resistance exercise (low load ~20 repetitions at 50%–60% 1RM; high load ~8 repetitions at 80%–90% 1RM) has been shown to significantly impair the cerebral autoregulation immediately post-exercise, demonstrating a stark increase in MCAv relative to blood pressure (autoregulatory gain) (Koch et al., 2005). Impaired cerebral autoregulation and the other metrics of cerebral hemodynamics reported by Koch et al (rapid rise in MCA pulsatility, drop in cerebrovascular resistance index) in the immediate post-exercise period align well with the phenomenon of *weightlifter's blackout*—in which individuals may experience syncope or pre-syncope immediately following high intensity resistance exercise, particularly when in the upright standing position due to the sudden pressure drop upon release of the external load (Compton et al., 1973). However, the work from Koch et al is suggestive of a compensatory response to the sudden drop in blood pressure. Given that blood pressure drops dramatically following resistance exercise, an increase in pulsatility, a drop in resistance, and an overall increase in MCAv (and likely cerebral perfusion) are indicative of an emergency protective response to avoid pre-syncope and syncope (Koch et al., 2005). Thus, while metrics of cerebral autoregulation appear to be impaired immediately following resistance exercise, increased autoregulatory gain (change in MCAv relative to change in blood pressure) should not be misinterpreted as damaging but instead as oppositional to *weightlifter's blackout*.

In untrained individuals, the cerebral circulation exhibits greater sensitivity to reductions (than increases) in mean arterial pressure, demonstrating a greater change in MCAv (and assumingly CBF) during a hypotensive stimulus compared to a hypertensive stimulus (Roy et al., 2022; Allison and Al-Khazraji, 2024b). Interestingly, based on cross-sectional studies, it appears that sensitivity to reductions and increases in mean arterial pressure are handled similarly by the cerebral vasculature in resistance-trained adults (Roy et al., 2022). Furthermore, recent work from Korad et al. suggests improved pressure-buffering capacity of the cerebral circulation in resistance-trained adults, in which trained participants exhibited a similar change in MCAv to controls during unilateral knee extension resistance exercise despite a greater systemic blood pressure response (Korad et al., 2024). While they did not investigate the directional sensitivity of the cerebral circulation in this study, their findings do support adaptation in the inherent directional sensitivity of the cerebral pressure-flow relationship. While longer-term interventional work is necessary to understand how RT directly influences directional sensitivity of the cerebral pressure-flow relationship, the findings from Korad et al and Roy et al do indeed suggest that frequent exposure to oscillatory pressure challenges via resistance exercise may habituate the arteries to better handle both elevations and drops in mean arterial pressure and avoid hyperperfusion and pre-syncope and syncope responses, respectively (Korad et al., 2024; Roy et al., 2022).

In cross-sectional work from Xu et al, higher global CBF was observed in older individuals who frequently participating in RT (Xu et al., 2014). One of the few training studies in older adults from Macaulay et al, reported increased regional CBF in the hippocampus, anterior cingulate, posterior cingulate, putamen,

insula, occipital lobe, and temporal lobe following high-intensity (70%–85% 1RM) RT 3 times per week for 12 weeks (Macaulay et al., 2022). Though the effect size was small (attributed to short duration of the exercise intervention by authors), the ~4% increase in temporal lobe CBF is of clinical interest due to the region's relationship with memory and AD. Furthermore, Macaulay et al also observed significant increases in the fMRI-derived fraction of low frequency fluctuations in the cerebellum, right middle temporal gyrus, and bilateral inferior parietal lobes, representing greater functional neuronal integrity and connectivity between brain regions (Macaulay et al., 2022). Reduced fraction of low frequency fluctuations has been reported in MCI and AD (Yang et al., 2018), suggesting that RT may support regional neuronal activity and functional integrity. Considering the critical importance of CBF delivery in maintaining neuronal health and function, these findings alone warrant further interventional investigations on how long-term RT affects cerebrovascular function in older adults across the cognitive and neurodegenerative spectrum.

Many of the positive vascular and cerebrovascular adaptations to RT can be linked back to reduced ROS production, improved antioxidant defenses, and reduced inflammation. These adaptations underlie the improvements in endothelial function via habitual RT which are well established (Silva et al., 2021) and likely driving the beneficial effects on CBF and improved regulation of CBF with changes in arterial blood pressure that have been observed to date. However, the implications of these improvements on BBB permeability and function are an emerging area of study. Recent work from Cho et al in women aged 65–84 showed improvements in BBB integrity with 12 weeks of 3 times per week moderate intensity (10–14/20 RPE) resistance band-based RT. Importantly, alongside the observed improvement in BBB function was an enhancement of antioxidant capacity, increased vascular endothelial growth factor and BDNF signalling (Cho and Roh, 2022). The neurotrophic responses to RT alongside upregulation of endothelial growth factors, improved endothelial function, and reduced inflammation and oxidative damage together implicate a role of RT in restoration of BBB function. However, additional research is needed to establish protective effects of RT on the BBB.

## Effects of resistance exercise training on brain structure

Given the importance of brain structure as a predictive biomarker for neurological health (Ten Kate et al., 2018; Planche et al., 2019; Fein et al., 2000; Dicks et al., 2020), and its chronology in the neurodegenerative cascade (preceded by inflammation, oxidative stress, vascular dysregulation, and A $\beta$  deposition) (Iturria-Medina et al., 2016), measures of brain structure can provide tangible insight into whether exercise as a therapeutic intervention is efficacious for slowing the rate of atrophy with age and neurodegenerative disease.

Most literature reports overall positive effects of RT on regional grey matter brain structure, but effects of RT on global brain structure are less clear. One study from Liu-Ambrose et al observed significant reductions in global brain volume following 1 year of high-intensity progressive RT (2 sets of 6–8 repetitions at 70%–85% of 1RM, either once or twice weekly) in older women free from

MCI (Liu-Ambrose et al., 2010). Despite a reduction in whole brain volume with RT, there was a clear improvement in cognitive function following the RT intervention. The reduction in brain volume with RT has been observed in pharmaceutical trials for AD, and is hypothesized to be related to reduction in A $\beta$  load (Fox et al., 2005). The authors use this rationale cautiously to reconcile the mismatch between improved cognition and reduced brain volume, stating A $\beta$  clearance and subsequent shifts in cerebrospinal fluid may therefore have also partially explained their findings. Improvements in BBB function (in particular efflux of metabolic waste), and reduced A $\beta$  burden have been reported with RT in animal models (Hashiguchi et al., 2020).

More research is necessary to elucidate underlying causes for reductions in brain volume in response to exercise in older adults, including specific measurement of A $\beta$  and neurofibrillary tangles. In work from Best et al, there was no evidence of attenuated global grey matter atrophy with 1 year of high-intensity progressive RT (2 sets of 6–8 repetitions at 70%–85% of 1RM, either once or twice weekly) in 155 older women (Best et al., 2015). Though Best et al reported no change in grey matter atrophy rates, they did observe clear improvements in memory (Best et al., 2015). These findings suggest that positive effects of RT on brain function may occur without changes in total brain volume and grey matter volume.

Increases in global brain volume in response to exercise is not well supported; however, there is support that while exercise may not reverse age-related cortical decline, it does appear to reduce the rate of cortical decline compared to normal aging (Colcombe et al., 2003). Additionally, while the changes in global brain structure may be negligible, evidence does suggest that certain brain regions are particularly responsive to exercise effects. In cardiac rehab settings, 3 days per week of moderate-intensity aerobic exercise for a total of 6 months was associated with improved regional grey matter volume in the superior frontal gyrus, superior temporal gyrus, posterior cerebellum, and supplementary motor area (Anazodo et al., 2013). While these findings were in response to aerobic exercise training, they support the notion that not all regions of the brain are structurally responsive to the benefits of exercise. As it relates to RT interventions, importantly, the hippocampus and related subfields appear to be highly responsive to RT interventions (Broadhouse et al., 2020; Peter et al., 2018). Broadhouse et al demonstrated a clear protection of the left hippocampus with 6 months of high-intensity RT (3 sets of 8 repetitions at 80% 1RM, two or three times per week) compared to sham—an effect that persisted 1-year post-intervention in the 200 older adults studied (Broadhouse et al., 2020). In particular, there was a clear neuroprotective effect on the left CA1, dentate gyrus, and subiculum regions of the hippocampus, all showing a reduced atrophy rate compared to sham controls (Broadhouse et al., 2020). The CA1, dentate gyrus, and subiculum regions are of particular interest in the context of AD, as they are associated with autobiographical memory (Bartsch et al., 2011), encoding and retrieval of episodic memories (Hainmueller and Bartos, 2020), and hippocampal synaptic relay (Baset and Fengwen, 2024), respectively. Protection of these hippocampal subfields is critical in maintaining memory function with advanced age.

The benefits of RT on hippocampal subfields are further supported by recent work from Vints et al, demonstrating that even 12 weeks of progressive RT peaking at 85% of 1RM was

sufficient in improving CA1, CA4, subiculum, and dentate gyrus volume in 70 older men and women (Vints et al., 2024). In contrast, a study investigating the effects of 6-month of either high intensity aerobic training or lower limb progressive RT (3 sets of 6–10 repetitions with intensity progression from 70%–85% 1RM, 2 times per week) on hippocampal volumes in 29 older women with probable MCI demonstrated a 5.6% and 2.5% increase in the left and right hippocampus, respectively, in response to aerobic exercise training—but observed no such positive effects of RT on hippocampal volumes (ten Brinke et al., 2015). Considering the small sample size in the RT group (N = 8), further study is necessary to determine the effects of RT on hippocampal volumes. The responsiveness of the hippocampus and its subfields to exercise are well supported by molecular mechanisms—as these brain regions exhibit elevated levels of neurotrophic factors (IGF-1; BDNF expression) with RT (Berbert-Gomes et al., 2024). Taken alongside the reported increases in regional CBF discussed previously, increased expression of neurotrophic factors in response to RT may facilitate neurogenesis and synaptic plasticity in the hippocampus and its subfields.

The improved brain structure in older adults after RT may also be related to increased cerebral glucose metabolism. Hippocampal atrophy has been shown to be strongly linked to cerebral glucose hypometabolism in older adults with AD (Yamaguchi et al., 1997). Though there are limited studies investigating the effects of RT on cerebral glucose metabolism, studies looking at the effects of 16 weeks of combined exercise interventions (aerobic and RT) reported significant improvements in glucose metabolism in the sensorimotor cortex in 172 elderly adults (Shah et al., 2014). 12 weeks of moderate-intensity RT (3 sets of 10–13 repetitions at 45%–65% 1RM, 3 times per week) has also been shown to improve systemic glucose metabolism in older adults with metabolic syndrome (Zhou et al., 2022). Indeed, decreased insulin sensitivity and impaired glucose metabolism systemically are linked to the progression of neurodegenerative diseases (Faroqui et al., 2012). Though the direct effects of RT on cerebral glucose metabolism across the cognitive spectrum remain unclear, the mechanistic rationale is sufficient to warrant future investigations on mechanisms underlying improved brain structure with habitual RT.

RT interventions have also been demonstrated to improve measures of white matter integrity. One year of high-intensity RT (2 sets of 6–8 repetitions at 70%–85% of 1RM) twice per week in 54 older women (65–75 years) reduced white matter hyperintensity progression compared to balance and toning controls. However there was no difference between controls and individuals who did the RT protocol only once per week—indicating a training frequency threshold of 2 times per week on neuroprotective effects, in line with current physical activity guidelines (Bolandzadeh et al., 2015). In a separate research article from the same cohort and intervention, 1 year of RT was associated with reductions in white matter hyperintensity related disruptions in the sensorimotor network, and dorsal and ventral attention networks (Crockett et al., 2022). Similarly, 4-month of thrice-weekly RT (3 sets of 8–15 repetitions at 50%–80% of 1RM) improved white matter density in 37 frail older women (Bucci et al., 2023). The observed effects in this study were also observed with physical phenotype, as frail women who were born to lean and normal-weight mothers conferred greater RT-related white matter benefits compared to those born

to obese mothers. The underlying cause of these observations are likely to be multi-factorial, receiving contributions from metabolic, inflammatory, and vascular factors. In a previously mentioned study primarily investigating regional changes in CBF in response to RT, a reversal of the progression of white matter lesion volume - indicative of improved white matter perfusion - was also reported following 12 weeks of RT (Macaulay et al., 2022). Best et al similarly reported positive effects of RT on white matter structure, demonstrating a reduced rate of white matter atrophy in individuals in the RT group compared to controls after the 1-year training intervention as well as 1 year post-intervention (Best et al., 2015). These findings also align well with the work from Broadhouse et al, in which improvements in brain structure are maintained up to 1-year after cessation of training (Broadhouse et al., 2020). It is unclear whether these benefits in the RT groups compared to controls are related to residual physiological effects of training or whether they are a result of habit-forming related to the 1-year exercise intervention. Future works should consider collecting questionnaire or physical fitness data to determine the underlying cause of the long-term benefits of RT.

## Effects of resistance exercise training on cognitive function

The effects of acute and habitual exercise of any type on cognitive function are well established, with multiple quality reviews highlighting the effectiveness of resistance exercise on improved cognition across multiple domains (Landrigan et al., 2020; Chang et al., 2012; Herold et al., 2019; Cheng et al., 2022; Coelho-Junior et al., 2022). Acutely, it appears that low-to-moderate resistance exercise is effective in improving global cognition, as well as multiple aspects of executive function, cognitive flexibility, and processing speed, with inconsistent findings as it relates to memory function (Loprinzi et al., 2018). For the purposes of this review, memory will be the primary domain of interest due to its intimate relationship with MCI and ADRD. Cognitive performance in subdomains of memory also track well with brain regions most vulnerable to age- and disease-related atrophy (Fjell et al., 2014). In contrast to the equivocal effects of resistance exercise, other studies show strong associations between acute bouts of aerobic exercise and improved memory performance (Cantelon and Giles, 2021). It is unclear whether the discrepant impacts of resistance versus aerobic exercise on memory-related tasks in humans results from activation of different physiological pathways, individual differences in response to exercise, or different cognitive testing approaches used across studies.

The literature widely reports benefits of RT on global cognition (Suo et al., 2016; Coelho-Junior et al., 2020; Fiatarone Singh et al., 2014; Chupel et al., 2017; Mavros et al., 2017) and executive function (Nouchi et al., 2014; de Oliveira Silva et al., 2019; Helmes and Harris, 2017) in older adults across the neurocognitive spectrum (cognitively normal and MCI) but free from diagnosed ADRD. Though acute effects of resistance exercise on memory function are contentious at best, it is reasonable to assume habitual RT would be more efficacious in improving memory given the associations between muscular strength and both memory (Shaughnessy et al., 2020; Liao et al., 2024; Cai et al., 2023) and hippocampal volume

(Kim YS. et al., 2017; Firth et al., 2020; Meysami et al., 2023). Greater muscle strength in older adults is inversely related to the development of sarcopenia and frailty (Veen et al., 2021). Maintaining muscle strength and mass is critical for promoting higher functional capacity and physical independence with aging (dos Santos et al., 2017). The positive adaptations observed in both global and regional measures of perfusion and brain structure to RT detailed in the sections above also support reported benefits of RT on memory function. A study investigating the effects of thrice-weekly moderate intensity resistance-band RT with self-directed intensity progression in over 200 community dwelling older adults demonstrated marked improvements in working memory (Lachman et al., 2006). Furthermore, the magnitude of cognitive benefits of RT were associated with the strength gains made over 6 months—suggesting a dose-response relationship between increased muscular strength and memory function (Lachman et al., 2006). A study from Mavros et al reported that muscle gains via RT (3 sets of 8 repetitions at 80%–90% 1RM, 2–3 times per week), but not improvements in aerobic fitness over 6-month were related to improved memory performance in 100 community dwelling adults diagnosed with MCI (Mavros et al., 2017). Additionally, a 1-year training study in 155 older women demonstrated that not only was a single day of high intensity RT (2 sets of 6–8 repetitions at 70%–85% of 1RM) per week sufficient to improve memory at the cessation of the study compared to pre-training, but these cognitive benefits persisted for 1 year after training compared to balance-and-toning controls (Best et al., 2015). The relationship between exercise intensity and neurocognitive effects of RT is supported by work from Feter et al, who showed improvements in cognition over 12-week of high velocity RT (1–3 sets of 8–10 repetitions at 40%–60% 1RM, 2 times per week) were statistically mediated by the improvements in lower body strength, power, and muscle thickness (Feter et al., 2023), though they did not find any effects of the RT intervention on memory-related domains. The null findings on memory reported by Feter et al may be related to exercise intensity—as increases in muscle mass are not necessarily intensity dependent (McLeod et al., 2024), but evidence does support that intensity mediates exercise-related neurogenesis and neuroplasticity in interval and aerobic exercise models (Marko et al., 2022; Freitas et al., 2018; Hoffmann et al., 2016; Kovacevic et al., 2020; Murawska-Ciałowicz et al., 2021). Another large-scale trial (N = 1335) similarly found no clear benefits of low-to-moderate intensity RT (2 sets of 15 repetitions at 60% 1RM, 5 times per week) on memory function in 2 years of training, further suggesting the importance of intensity in maximizing pro-cognitive effects of RT (Komulainen et al., 2010). It is important to note that in an investigation from Cassilhas et al directly comparing the effects of different intensities of RT (2 sets of 8 repetitions at 50% 1RM vs. 80% 1RM, both conducted 3 times per week), there appeared to be no differences in cognitive benefits (Cassilhas et al., 2007). The underlying factors for absence of differences in the work from Cassilhas et al despite clear mechanistic rationale and evidence for intensity-mediated neurocognitive benefits of RT remains unclear and warrants further study. Nonetheless, the literature does suggest that moderate-to-high intensities of RT is associated with significant improvements on memory function (Best et al., 2015; Coelho-Junior and Uchida, 2021; Marston et al., 2019).

The cognitive benefits of RT may also be related to the inherent complexity of resistance exercise itself. As mentioned

previously, resistance exercise requires individuals to remember exercises, machine settings, and training protocols, synchronize movements between several muscle different groups, and recruit the appropriate amount of muscle fibres to meet exercise demands. Thus, resistance exercise may act as a cognitive stimulus in and of itself (Forte et al., 2013). Furthermore, dual-task exercises that combine RT with simultaneous cognitive tasks may provide additional challenges, potentially enhancing cognitive outcomes. This idea is supported by Baek et al, who reported improved cognitive performance in older adults with cognitive impairment that completed 6-week of dual-task resistance band-based RT (3 sets of 10 repetitions, 3 times per week), which involved cognitively stimulating tasks simultaneously during RT (Baek et al., 2024). Several studies have demonstrated that resistance exercise, across varying intensities, improves psychological wellbeing without measurable changes in neurocognitive performance from pre to post-intervention (Tsutsumi et al., 1997; Peig-Chiello et al., 1998). The absence of improvements in neurocognitive performance may be due to limitations in study duration or the specific cognitive domains assessed. However, qualitative analyses of participants' experiences in RT programs highlight perceived improvements in psychological wellbeing, which suggest enhanced self-efficacy—a critical factor for long-term adherence (Dionigi, 2007).

## Practical considerations for resistance training in older adults at risk of ADRD

### Adherence, adoption, and feasibility of resistance training interventions

Adherence to exercise programs, particularly RT, is a multifactorial challenge influenced by biopsychosocial factors. Barriers to adherence can be broadly categorized under the concept of self-efficacy, which refers to an individual's confidence in their ability to succeed in specific tasks, including both physical and psychological aspects. Additionally, social support plays a critical role in overcoming these barriers (Dionigi, 2007). Effective programs must address both the initial adoption of exercise and the sustained maintenance of participation over time. A study by Furlano and Nagamatsu demonstrated that longer-term RT (2 sets of 6-8 repetitions at 70%–85% of 1RM, 3 times per week for 26 weeks) is generally feasible for older adults at risk of type 2 diabetes, a population often experiencing deficits in cognitive functioning and at elevated risk for AD (Furlano and Nagamatsu, 2021). Although recruitment posed challenges, the study achieved high retention (100%) and adherence (85.5%) rates within the RT group. Notably, 90% of participants reported enjoying the program, with many citing social interaction and increased feelings of strength, mobility, and fitness as their favorite aspects. Key factors influencing adherence included program characteristics such as session timing and location, social connectivity, enjoyment, perceived safety, and delivery by trained healthcare professionals (Furlano and Nagamatsu, 2021). These findings underscore the critical role of socialization and perceived physical benefits in driving adherence, suggesting that similar strategies could be applied across diverse populations with chronic health conditions. However, recruitment challenges highlight potential barriers to

scaling similar interventions, particularly in populations with varying degrees of health or cognitive impairment. These studies highlight the importance of self-efficacy, social interaction, and program characteristics in promoting adherence, aligning with biopsychosocial models of adherence that emphasize the interplay between individual motivations, environmental factors, and perceived outcomes (Dionigi, 2007).

Personalized exercise prescriptions that cater to the unique needs of older adults are essential. Individualized program design, including adjustments to intensity and duration, is crucial for optimizing outcomes. RT programs can be adapted to various settings, including community centers, homes, and online platforms, increasing accessibility for a diverse population. For example, online RT programs demonstrate increased accessibility with high adherence levels and improved psychological wellbeing. In addition to being accessible and feasible, RT is cost-effective compared to balance and toning exercises, offering significant health and cognitive benefits. For instance, Davis et al found that 6 months of RT (2 sets of 6-8 repetitions at 70%–85% of 1RM, 2 times per week) in older adults with MCI led to greater cognitive improvements compared to the balance and toning group (Davis et al., 2013). Moreover, resistance training classes were more cost-effective for achieving each unit of Stroop test performance compared to balance and toning classes. These findings suggest that RT is a feasible, affordable, and effective option for individuals of varying health statuses, potentially promoting greater adherence after initial adoption. It is important to consider the role of total training load on exercise adherence in older adults, as training overload in older adults may lead to dropout. This is of particular concern in interventions using a multimodal approach of both aerobic and resistance exercise. Current recommendations suggest ~150 min of moderate intensity aerobic exercise per week alongside moderate intensity RT at least twice per week (Nelson et al., 2007). While multimodal exercise has potential to negatively influence adherence by increasing total training volume, studies have demonstrated that multimodal or circuit-based exercise protocols are not only feasible but well-tolerated in older adults. A single session each of aerobic and resistance exercise per week (two total exercise sessions) was shown to elicit significant improvements in muscular strength and aerobic fitness similar in magnitude to twice and thrice weekly over the course of the 16-week intervention—though this study did not include cognitive or brain related measures (Fisher et al., 2013). Furthermore, all three groups (1 aerobic/week, 1 RT/week; 2 aerobic/week, 2 RT/week; 3 aerobic/week, 3 RT/week) had adherence rates of >88% over the duration of the 16-week protocol (Fisher et al., 2013). These findings suggest that combination exercise, particularly in older adults may be effective without necessarily needing to increase exercise frequency. Indeed, other work has demonstrated that RT twice weekly has been shown to improve cognitive performance (Bolandzadeh et al., 2015), and taken alongside low-moderate intensity aerobic exercise such as walking (Lee et al., 2025), is likely to be well received by older adults - particularly if there is a social element integrated into the program (Dionigi, 2007). Despite the numerous factors mentioned above, further research is still needed to explore long-term adherence and its determinants. Strategies to improve adherence include clear communication, addressing motivation and self-efficacy, and fostering social interactions while balancing exercise load and

physical fatigue (Dionigi, 2007; Furlano and Nagamatsu, 2021). A biopsychosocial approach to program design can better address diverse health statuses and contribute to sustained engagement to ensure that participating individuals experience the psychological and physiological benefits of RT.

## Additional considerations in resistance training approaches

The combined effects of protein supplementation and resistance training on muscle mass, strength, and cognition in older adults remain a complex and debated area of research. RT is a well-established intervention for mitigating age-related muscle loss and weakness, and as discussed earlier, has demonstrated potential for improving cognitive functioning. However, the additional benefits of protein supplementation are less definitive, with studies reporting mixed outcomes (Griffen et al., 2024; Amasene et al., 2019). Some research suggests a synergistic relationship between protein intake and resistance exercise, noting that protein ingestion close to the time of exercise may enhance specific domains of cognitive functioning, like executive function, processing speed, memory, and reaction time (Griffen et al., 2024). However, many studies involving older adults have failed to demonstrate consistent added benefits of protein supplementation, potentially due to variations in the protein dosage and RT protocol itself. Amasene et al. found that 12 weeks of RT (2 sets of individualized repetitions, progression of intensity from 50%–75% 1RM, 2 times per week) alone increased physical function, with no additional benefit from leucine-enriched whey protein supplementation (Amasene et al., 2019). In this study, authors noted that the dosage of protein after RT sessions may have been inadequate and suggested that participants may have required higher supplementation levels. Griffen et al. aimed to address insufficient protein supplementation by examining how increasing protein intake, in isolation and with RT, in older adults would impact cognitive outcomes (Griffen et al., 2024). Their study found that whey protein supplementation at approximately 1.6 g/kg/day resulted in statistically significant improvements in executive function compared to the control group and the RT-only group. However, this improvement appeared domain-specific, as no significant differences were observed in working memory. Interestingly, RT (3 sets of 8–12 repetitions progressing from 50%–80% 1RM, 2 times per week) alone did not improve cognitive function in this study, nor did it exhibit synergistic effects with protein supplementation (Griffen et al., 2024). In addition to an underpowered analysis for the synergistic effects of protein and RT, Griffen et al. noted that after final progressions to 80% 1RM, their RT protocol involved a ~10% higher intensity than those examined in previous studies, potentially influencing the cognitive outcomes (Griffen et al., 2024). These discrepancies underscore the mixed results regarding the effects of protein supplementation and its interaction with RT. Future research should aim to disentangle these inconsistencies by carefully examining the specific health outcomes being measured (e.g., physical function versus cognitive function), the type and dosage of protein used, individual differences in protein intake, characteristics of the target population, and the design of RT protocols. A more nuanced understanding of these variables will help clarify the

potential benefits of combining protein supplementation with RT in older adults.

Innovative approaches are essential for enhancing RT programs for older adults by addressing diverse needs and barriers. Various modalities of RT such as elastic bands (Yoon et al., 2017) and isometric exercise training (Hess and Smart, 2017), as well as different RT set structures, have shown efficacy in improving levels of critical neuronal growth factors, cognitive and physical function, and vascular and mental health. Other RT prescription structures, such as drop-set RT (several sets to failure with descending loads with each consecutive set), have also shown significant improvements in BDNF and nerve growth factor levels in middle-aged Korean women with obesity (Bang, 2023). This highlights the potential of drop-set RT for targeting populations with specific metabolic or health challenges, though its high intensity and tempo may limit broader applicability. Compared to RT alone, which was shown to improve psychological wellbeing and physical functioning in older adults with cognitive impairment, dual-task exercises (exercise plus cognitive stimulation) were shown to also improve cognitive functioning (Baek et al., 2024). This suggests that a dual-task exercise, which requires both cognitive and physical effort, may be a more potent stimulus that allows older adults to maximize the benefits from RT.

Blood flow restriction exercise is also a promising avenue for improving functional capacity in older adults where exercise with high external loads may not be well tolerated (Törpel et al., 2018). RT with blood flow restriction is an ideal alternative to RT alone for older adults facing physical barriers as it is a safer and more efficient approach to elicit improvements in muscle strength and hypertrophy while minimizing the risk of injury (Ramos-Campo et al., 2018). Importantly, acute blood flow restriction exercise using an occlusive cuff in the upper or lower limbs has been shown to elicit similar improvements in cognitive flexibility compared to traditional RT despite working with significantly lower loads (30% of 1RM in blood flow restricted RT vs. 70% of 1RM in traditional RT) (Batman et al., 2024). In addition to its muscle and strength building qualities despite a lower relative load, blood flow restriction exercise with low loads has been shown to have no adverse effects on vascular function or blood flow in older adults (Lopes et al., 2022; Kim J. et al., 2017). Furthermore, recent meta-analyses of 12 randomized control trials demonstrated that blood flow restriction exercise is associated with improved arterial endothelial function (as assessed via brachial artery flow mediated dilation test) (Zhang et al., 2022). As mentioned in previous sections, strength gains have been associated with cognitive improvements in response to exercise interventions (Mavros et al., 2017; Lachman et al., 2006; Feter et al., 2023). While the direct neuroprotective effects of blood flow restriction exercise remain unclear (Törpel et al., 2018), exercise of any form are suggested to have positive effects on brain function. Blood flow restriction both increases the efficiency of RT (from a strength and hypertrophy perspective) while simultaneously lowering the barrier to entry, thus making it an exciting focus for future research with implications on exercise prescription in older adults with physical limitations.

Alternative approaches leveraging technology—such as online platforms, mobile apps, and wearable devices—can improve adherence and streamline program delivery (Coletta et al., 2024; Lee et al., 2024). However, accessibility issues, such as technological

literacy and cost, may limit their reach in underserved populations. One solution could be community-based programs, which combine cognitive and physical training with health education lectures. Indeed, these programs have been shown to improve both physical and cognitive function among community-dwelling older adults (Nose et al., 2023). Emerging approaches like Electrical Muscle Stimulation (EMS) combined with RT may also offer additive benefits. Thapa et al demonstrated that EMS combined with RT enhanced strength, physical performance, and cognitive outcomes in middle-aged and older women compared to RT alone. While these findings highlight the potential of EMS as a complementary strategy, future research could explore its application in clinical populations with limited physical capacity, where traditional RT may be less feasible (Thapa et al., 2023). These innovations underscore the importance of tailoring RT programs to individual needs through holistic approaches that address physical, psychological, and social factors (Iuliano et al., 2015). Future research should investigate long-term outcomes, cost-effectiveness, and the comparative benefits of these methods relative to traditional RT. Additionally, exploring how these approaches can be integrated with other interventions, such as dietary strategies, may further optimize overall health outcomes (Iuliano et al., 2015).

## Safety of resistance training in older adults and clinical populations

Despite the benefits of RT on multiple physiological systems, particularly related to muscle mass and reducing the risk of frailty and loss of independence, as of 2018 only 19% of older adults report participating in muscle strengthening activities of any kind (Hyde et al., 2021). The hesitancy for participation in RT in older adults can be largely attributed to safety concerns—a topic that has been debated in recent years (Fragala et al., 2019). These concerns are a valid barrier to entry, as RT-naïve older adults may very well incur injury without proper program design (i.e., exercise intensity, volume), technique, and supervision (Fragala et al., 2019). Additionally, resistance exercise has traditionally been considered hazardous (Sagiv, 2009) for individuals with cardiovascular dysfunction due to exaggerated blood pressure responses. However, with appropriate exercise prescription beginning at lower intensities and coupled with incremental progression, these effects are of less concern (Fragala et al., 2019). Importantly older adults participating in RT should be coached on proper breathing techniques, specifically to avoid the Valsalva maneuver during exercise to reduce the likelihood of problematic increases in blood pressure. With coached breathing and appropriate supervision, RT at low-to-moderate intensities are unlikely to elicit Valsalva maneuver related spikes in blood pressure, as the Valsalva maneuver is only involuntary at intensities >80% of 1RM (MacDougall et al., 1992). To further ensure safety during RT in older adults, prescribing machine-based exercise early on in programming as opposed to free-weights is an ideal alternative that typically will protect the lower back by avoiding spinal loading and compensatory movements through the back, and allow for greater control and balance during exercise with external load (Feigenbaum and Pollock, 1999). Thus, for promotion of participation in RT in older adults, lower intensity, machine-based exercise led by qualified exercise

professionals is critical for safe implementation of RT (Fragala et al., 2019). Ultimately, while safety concerns related to participation in RT are valid, when exercise is prescribed and monitored appropriately, the benefits of RT outweigh the risks and have potential to dramatically improve quality of life and independence in older adults (Levinger et al., 2007).

Similar to otherwise healthy older adults, individuals living with chronic health conditions stand to greatly benefit from participation in RT. The positive effects of RT are well-documented, improving glycemic control in healthy adults (Ashton et al., 2020) and type-2 diabetics (Ishiguro et al., 2016; Jansson et al., 2022), reducing resting and ambulatory blood pressure in individuals with hypertension (Correia et al., 2023), enhancing muscular strength and function in sarcopenia (Zhao et al., 2022) and osteoarthritis (Lim et al., 2024), and positively influencing vascular health in those with cardiovascular disease (Paluch et al., 2024; Fecchio et al., 2021). Despite its effectiveness, several key considerations must be addressed when prescribing RT to ensure safety, adherence, and efficacy.

Medical clearance from a physician and individualized risk assessment are essential by certified healthcare and exercise professionals (Liguori and American College of Sports Medicine, 2020). In individuals with diabetes, careful attention to glycemic control is necessary, including monitoring blood glucose levels before and after training sessions and timing exercise to avoid periods of peak insulin activity (KANALEY et al., 2022). In hypertensive individuals, while RT can lower resting blood pressure over time, acute hypertensive responses during high-intensity or isometric lifts warrant caution (Vermeer et al., 1997; de Souza Nery et al., 2010). Submaximal loads and avoidance of the Valsalva maneuver via controlled breathing are recommended (Williams et al., 2007). Indeed, while progressive overload remains foundational to resistance training, but initial intensities should typically be low to moderate (e.g., 40%–60% of 1RM) with gradual increases to minimize injury risk (Paluch et al., 2024). For individuals with cardiovascular disease or stroke, factors such as impaired autonomic regulation, cerebrovascular function, and potential motor or balance deficits need to be considered and monitored during exercise sessions (Billinger et al., 2014). As such, programming may need to begin with machine-based or seated exercises, with gradual progression as physical function improves. When tailored appropriately to the individual's clinical status, capacity, and goals, RT serves as an important element alongside aerobic exercise for management of chronic disease.

## Female-specific considerations in administration of resistance exercise

The feasibility and practical considerations discussed above apply to both males and females, but it is also important to acknowledge sex-specific barriers to RT—particularly as it pertains to older females. While in recent years the dogma of RT being inherently “masculine” has fallen out of favour, older adults may still possess pre-conceived notions about the concept of weightlifting. Though participation in RT has increased in females in recent years (Kraemer et al., 2025), many older females still report hesitancy,

citing a lack of education and beliefs that any heavy lifting should be avoided (Hurst et al., 2023). The pre-conceived notion that RT needs to be done with heavy external loads is damaging and plays into the stereotype that there is no clear access point for RT-naïve older adults, and older females in particular. A lack of education and resources, taken alongside a generally lower level of baseline strength in older females compared to males, may deter females from initiating participation in RT programs and further promote the age-related loss in muscle and physical independence that disproportionately affects older females (de Jong et al., 2023). Hurst et al. reported that although awareness and understanding of RT is low in older females, there is open mindedness towards resistance exercise as a modality so long as adequate peer and healthcare professional support is provided (Hurst et al., 2023). While participation in RT in older adulthood is key for females to combat age-related muscle loss, adoption of RT in females in midlife is of critical importance. Promotion of RT to maintain and build muscular strength in midlife greatly reduces the onset and progression of sarcopenia in older age (Vaishya et al., 2024). The primary barrier for participation in RT in midlife cited by females is related to time constraints and shifting life transitions, which include taking on primary caregiver roles to not only children but potentially aging parents as well (Stimson et al., 2024). Providing education on short duration resistance exercise provides an accessible and feasible approach to facilitate participation and adherence to RT and greatly reduces risk of frailty in older adulthood. In summary, addressing misconceptions, improving access to female-focused programming, and promoting time-efficient, low-barrier approaches to RT are critical to improving participation in older females.

## Summary

The neuroprotective effects of RT are multi-factorial and have direct effects on ADRD pathophysiological cascades. Initial benefits of RT primarily begin at the molecular level, as even an acute bout of resistance exercise reduces inflammation and increases antioxidant defenses (Özbeyli et al., 2017; Feter et al., 2019; Schimdt et al., 2019; Rondão et al., 2022; Franzke et al., 2018; Heneka et al., 2015; Steensberg et al., 2002; Hashiguchi et al., 2020; Forti et al., 2014; Ostrowski et al., 1999; Cassatella et al., 1993; Liu et al., 2020; Vilela et al., 2017; Vints et al., 2024), promotes expression of neurotrophic factors such as IGF-1 (Özbeyli et al., 2017; Cassilhas et al., 2012; Vega et al., 2010; Tsai et al., 2014; Molina-Sotomayor et al., 2020) and BDNF (Berbert-Gomes et al., 2024; Jafarzadeh et al., 2021; Yarrow et al., 2010; Walsh et al., 2015; Marston et al., 2017; Coelho et al., 2012; Pereira et al., 2013; Vaughan et al., 2014) in brain regions vulnerable to neurodegeneration (i.e., hippocampus). While reduction in inflammation and ROS production may not be sufficient to reverse A $\beta$  and neurofibrillary tangle deposition; there is reason to believe that the production and accumulation of neurotoxic compounds in the parenchyma is attenuated with habitual RT, potentially preventing further accumulation. Furthermore, habitual RT is associated with improvements in endothelial function (Silva et al., 2021), cerebral perfusion (Xu et al., 2014; Macaulay et al., 2022), and glucose uptake in the brain (Yamaguchi et al., 1997; Shah et al., 2014),

resulting in a better matching between neuronal metabolic supply and demand. The improved endothelial function reported with RT may also have implications on BBB function and integrity. In both animal and human studies, RT interventions have been shown to improve BBB structure and function (Hashiguchi et al., 2020; Cho and Roh, 2022), and likely underlie findings related to A $\beta$  clear-out with habitual RT. Given that neuronal atrophy is largely driven by cerebral hypoperfusion and hypometabolism, a restoration in CBF via exercise has been shown to reverse or attenuate the rate of white matter damage (Macaulay et al., 2022; Best et al., 2015; Broadhouse et al., 2020; Bolandzadeh et al., 2015; Crockett et al., 2022; Bucci et al., 2023) and improve or attenuate age-related reductions in grey matter volumes, particularly in the hippocampus and its related subfields (Vints et al., 2024; Broadhouse et al., 2020; Feter et al., 2018). Restoration of cerebral tissues, increased expression of neurotrophic factors promoting neuroplasticity and neurogenesis, and improved efflux of neurotoxic A $\beta$  with RT are likely to drive the subsequent improvements in cognition observed across the literature in several domains, particularly memory function (Gabriel et al., 2006; Best et al., 2015; Lachman et al., 2006; Coelho-Júnior and Uchida, 2021; Marston et al., 2019).

Ultimately, the neuroprotective cascade via habitual participation in resistance exercise hold promise for reducing risk of onset and reducing the rate of progression of ADRD. RT programs for older adults are most effective when they address adoption, adherence, and feasibility concerns, by integrating dietary strategies and innovative approaches to enhance outcomes (Dionigi, 2007; Davis et al., 2013; Griffen et al., 2024; Amasene et al., 2019; Lee et al., 2024). Employing methods such as dual-task training, community-based programs, and technology-based delivery, can improve cognitive and physical health while ensuring long-term engagement and accessibility (Baek et al., 2024; Coletta et al., 2024; Lee et al., 2024; Nose et al., 2023). Investigators should continue to prioritize conducting well-controlled randomized control trials to gain greater insight into the effects of multiple types of RT, multi-modal training, and community-based RT programs on brain health outcomes across the lifespan in both healthy and clinical populations. There should also be a priority to investigate whether RT has differential effects on males and females as it relates to cerebrovascular and brain health—as sexual dimorphism in exercise-related reduction in ADRD risk remains poorly understood. Future research should also consider personalized interventions, include measures of psychological and behavioral factors, and examine the combined effects of exercise and dietary interventions in a more nuanced manner, alongside the role of vascular health.

## Author contributions

EA: Writing – original draft, Visualization, Writing – review and editing, Methodology, Project administration, Conceptualization. AB: Writing – review and editing, Writing – original draft, Methodology. AR: Methodology, Writing – original draft, Writing – review and editing. VM: Visualization, Writing – review and editing. JW: Conceptualization, Methodology, Writing – original draft, Writing – review and editing. JH: Writing – original draft, Methodology, Conceptualization, Writing – review and editing.

BA-K: Writing – review and editing, Conceptualization, Funding acquisition, Supervision, Methodology, Writing – original draft.

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