Physical activity, sex, and obesity: the effects on aging brains

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Abstract

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During aging, vascular declines occur causing cerebral atrophy, and functional deteriorations. When this decline is faster than the expected age-related decline, a heightened risk of developing dementia can occur. Understanding what risk factors contribute most to cerebral health across the lifespan prior to the onset of vascular changes is of upmost importance. Potential mediators of the aging vascular system include non-modifiable outcomes such as sex, and modifiable factors like physical activity level (PA) and body mass index (BMI).

This thesis includes one systematic review and three original studies investigating the effectiveness of PA to enhance cerebral health. In manuscript one we conducted a systematic review of cognitive or exercise interventions in healthy older adults that collected magnetic resonance imaging (MRI) scans. We identified that cognitive training was associated with white matter microstructure improvements, exercise training with macrostructural enhancements, and both demonstrated changes to the blood oxygen level dependent signal, indicating changes to hemodynamics, neuronal resources, or efficiency. However, the underlying mechanisms for enhanced cerebral health were unclear given the heterogeneity of interventions, measurements, and samples in terms of age and health status. In manuscript two, we investigated very healthy older adults with no underlying comorbidities comprehend the relationship between cardiovascular fitness and cerebral hemodynamics. We revealed paradoxical findings of greater cardiovascular fitness associated with decreased cerebrovascular reactivity, but preserved structure. In a normal aging sample, the relationship between sex, BMI, PA, and structural outcomes was examined. Females with greater BMI had enhanced structural outcomes, and regardless of BMI, higher PA was beneficial to cerebral health. In contrast, overweight males had the greatest volumetrics and PA did not have much influence on these relationships. The final manuscript incorporated a larger age range of individuals, showing an overall beneficial effect of PA on cerebral blood flow (CBF), but males and females demonstrated unique

relationships with CBF, and the intensity of PA reported, which was further influenced by whether they were middle aged or older.

Therefore, our studies contribute to our understanding of the beneficial effects of PA on brain health, and how these effects are influenced by sex, age, and obesity.

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Contribution of authors

This thesis was authored and written by myself, under the co-supervision of my supervisors Drs Claudine Gauthier and Louis Bherer. Together, we created the study designs, developed methodologies employed here applicable, conducted analyses, interpreted all results, and wrote the manuscripts. The thesis consists of one systematic review and three original studies, the contributions of each of the co-authors is listed in detail below.

Chapter 1: Grand introduction

Writing: Brittany Intzandt

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Chapter 2: Comparing the effect of cognitive vs. exercise training on brain MRI outcomes in healthy older adults: a Systematic Review

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Chapter 3: Higher cardiovascular fitness level is associated with lower cerebrovascular reactivity and perfusion in healthy older adults

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Chapter 4: Sex-Specific relationships underly the interactions between obesity and physical activity on gray and white matter volume in a sample of cognitively unimpaired older adults.

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Writing: Brittany Intzandt

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Chapter 5: **Sex differences in the beneficial effects of physical activity on cerebral blood flow in aging**

In preparation for submission to NeuroImage

Authors: Brittany Intzandt*, Safa Sanami, Louis Bherer and Claudine Gauthier.

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Data analysis: Brittany Intzandt and Safa Sanami

Data interpretation: Brittany Intzandt, Louis Bherer and Claudine Gauthier

Writing: Brittany Intzandt

Editing: Brittany Intzandt, Louis Bherer and Claudine Gauthier

Chapter 6: Grand Introduction

Writing: Brittany Intzandt

Editing: Brittany Intzandt, Louis Bherer and Claudine Gauthier

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1 General Introduction

1.1 Executive Summary

By the year 2050, it is estimated that the number of individuals over the age of 65 will double globally (United Nations, 2020), and in Canada, over 25% of the population will be comprised of older adults by 2030 (Bohnert, Chagnon, Dion, & Statistics Canada, 2015). This will present a significant burden to health care systems, caregivers, and aged individuals alike given that aging is associated with an assortment of declines to cognitive (Levy & Aging-Associated Cognitive Decline Working Party:, 1994), functional (Hébert, 1997), and mental health (Han et al., 2019) for many individuals. In fact, more than 100 million deaths worldwide occur annually due to age-related disease, and in aging Canadians, cerebral diseases, stroke and dementia, account for two of the five leading causes of death (Canada, 2021). Moreover, almost 30% of those over the age of 65 years live the remainder of their life in an unhealthy state (Bushnik, Tjepkema, & Martel, 2018). This concept can be understood with the health adjusted life expectancy, which refers to the number of years that an individual can be expected to live given current mortality and morbidity conditions in the population (Berthelot, 2002). Normal aging is the biological aging process as experienced by the general population, which may be healthy or include common conditions (e.g., hypertension) and pathologies (e.g., dementia). In contrast, healthy aging, is the portion of the lifespan that is free of pathological conditions (Rowe & Kahn, 1987). The benefits of maximizing healthy aging are obvious, but the lifestyle components that most effectively contribute to it remain unclear. Yet, external factors like physical activity (PA), diet, psychosocial factors, and genetics, to name a few, are more likely to be the cause of many of the age-related conditions, rather than age itself. Though aging does come with an assortment of burdens, the primary outcome of interest for the purpose of this thesis will be the changes that occur in the brain, as it is the central organ associated with dementia.

It is well documented that alongside aging, age-related cognitive decline occurs (Levy & Aging-Associated Cognitive Decline Working Party, 1994), which can, in some cases, lead to dementia (Tucker-Drob, 2019). Cerebral decline, whether age-related or dementia-related, is associated with an assortment of cerebral changes that can lead to the behavioral manifestation of

cognitive decline. These cerebral deteriorations include but are not limited to, the atrophy of structural tissue, the expansion of ventricular and cerebral spinal fluid, reduction to cerebral blood flow and other vascular parameters, as well as the development of vascular lesions, loss of neuronal bodies and dendritic spines (Lindenberger, 2014; Raz & Rodrigue, 2006). Yet, the pattern of age-related cerebral decline is fairly distinct from the degeneration associated with dementia in terms of the regions that are most influenced in each (e.g., temporal versus frontal versus hippocampal regions), the components of cerebral health that are most affected (e.g., structural versus neurofibrillary tangles and plaques), and the rate of decline. However, the work in this thesis focuses on healthy older adults who are cognitively unimpaired at the time of data acquisitions and is aimed at understanding healthy and normal aging.

Notably, cerebral aging, even in the absence of dementia, is well documented to be heterogenous in nature, in terms of what occurs during aging across individuals (Tucker-Drob, 2019). These heterogeneities are driven by interindividual differences that can be non-modifiable outcomes like an individual's sex, as well as other factors, including modifiable risk factors, many of which were highlighted in a recent Lancet Commission paper (Livingston et al., 2020a). Here, it was identified that there are twelve important risk factors throughout the lifespan that can increase risk of cognitive decline. However, for the purposes of this thesis, the focus will be PA and obesity, as well as sex, given the well documented vascular association of each (Ji et al., 2022; Livingston et al., 2020a).

To date, the effects of sex, obesity, and PA on cerebral outcomes in healthy aging populations have yet to be fully elucidated. Given that they have been identified as crucial risk factors for the development of dementia, there is an urgent need to further explore these factors and their interactions on cerebral health. Thus, in this thesis, we aimed to address these key gaps in the literature by examining individuals with differing PA levels and in a range of common body mass indices [BMI] (indirect measure of obesity), while completing sex-disaggregated analyses in the latter chapters. Here, we also examined cerebral health by employing two unique magnetic resonance imaging (MRI) techniques that can measure common cerebral declines associated with aging. In particular, the use of white, and gray matter volume were investigated given the well documented atrophy that occurs across the lifespan. Moreover, as the key themes examined (i.e., sex, PA, and obesity) are heavily influenced by the state of one's vascular health,

cerebral blood flow was also investigated. Pseudo-continuous arterial spin labeling (pCASL) is capable of quantifying cerebral blood flow (CBF) through identifying the amount of blood reaching a specific cerebral tissue, per unit of time. When the pCASL sequence is paired with a vasodilatory stimulus, like carbon dioxide, a metric called cerebrovascular reactivity (CVR), a measure of vascular reserve, can also be quantified. Thus, these four-imaging metrics are the primary dependent variables of this thesis.

The body of this thesis is comprised of four manuscripts. The first of these manuscripts is a systematic review of the literature investigating two common lifestyle interventions, exercise and cognitive training, to further comprehend the components of cerebral health that can be influenced by these interventions during aging. This manuscript explores interventional studies that employ MRI before and after each intervention, regardless of the technique utilized. The second manuscript builds on key findings from manuscript one, where we investigate the relationship between cardiovascular fitness, volumetric outcomes, in particular gray matter volume, and cerebral hemodynamics as assessed with CBF and CVR in a very healthy aging sample. Manuscript three explores the sex-specific relationships between volumetric outcomes, BMI, PA, and their interaction. Finally, manuscript four examines the sex-specific relationships between PA and CBF across a wider age range, to understand whether the impact of PA differs in a middle and older age sample of both sexes.

1.2 Structural Outcomes in Aging

1.2.1 Grey Matter Volume and Decline with Aging

During aging, cerebral structural declines occur, including grey matter atrophy (Chen, Rosas, & Salat, 2011). Gray matter is composed of neuronal cell bodies and unmyelinated axons. The atrophy that occurs is due to a loss of these cell bodies and axons that result in tissue loss. (Morrison & Hof, 1997). In particular, the shrinkage of large neurons has been discovered as the most relevant component of atrophy (Terry, DeTeresa, & Hansen, 1987), as well as microvascular regression leading to neuronal loss (Riddle, Sonntag, & Lichtenwalner, 2003). Bulk gray matter volume (GMV) can be quantified by acquiring a T1-weighted scan using a Magnetic Resonance Imaging (MRI) machine, and then employing voxel-based morphometry (VBM) (Ashburner & Friston, 2000). Briefly, VBM is a neuroimaging technique that allows for

segmentation of the brain into GM, white matter (WM) and cerebrospinal fluid (CSF) based on statistical differences between an individual compared to the expected volume of a template tissue. Thus, this technique provides a statistical map for each voxel, and then classifies it into GM, WM, or CSF according to the highest tissue probability, allowing for a more standardized comparison between participants or individuals. Once in a common space, it is possible to identify regions of atrophy as lower GM or WM tissue probability as compared to the template, indicating a chance in contrast from a higher CSF contribution.

Much work over the past thirty years has consistently identified that both in cross-sectional life span work and in longitudinal studies, total brain volume and regional volumes significantly decline with advancing age. Early work by Raz and colleagues (Raz et al., 1997; Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998) identified a linear decline in GMV in a sample of individuals from 18 to 77, and that these reductions were most prominent in the prefrontal cortex but were also present in the inferior temporal and superior parietal cortices. In a larger, later study, it was identified that GMV does atrophy with age, but that changes before 50 were small, followed by a period of linear decline after 50 (DeCarli et al., 2005). Conversely, Chen and colleagues revealed that gray matter declines at a rate of 0.85% (of total intracranial volume) per year across the lifespan beginning in the twenties (2011) (Chen et al., 2011). Though many studies have reported a different rate of decline and *when* the decline occurs across the lifespan, depending on the study design and the specific location in the brain.

Early work by Resnick and colleagues demonstrated a pattern of regional decline where the frontal and parietal lobes atrophied the most over time compared to temporal and occipital regions (Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003). These findings were longitudinally replicated in a much larger sample, where Crivello and colleagues also identified that a higher rate of decline was present in the superior, middle, and inferior frontal gyri, the superior and inferior parietal gyri as well as the middle and superior occipital gyri as can be seen in figure 1 (Crivello, Tzourio-Mazoyer, Tzourio, & Mazoyer, 2014). Over their four-year investigation, it was identified that a loss of overall GMV occurred at a linear rate of 0.8% per year after the age of 65. In comparison, decline to hippocampal volume was accelerated with a 2.8% decline per year, 35 times the rate of the decline in global GMV. This suggests that the heterogeneity in global rates of decline and when the decline occurred could in part be explained

by differences in atrophy rate between regions. More evidence for regions of the brain to have different critical age windows of decline was eloquently demonstrated by Fjell and colleagues (Fjell et al., 2009). More specifically, they identified that a linear decline occurred with age in the amygdala, putamen, thalamus, and cerebellar cortex whereas the hippocampus demonstrated an initial weak age-correlation and then around mid-life, starting at 50, there were accelerated declines, which was then followed by a linear age-related decline stabilizing around 60 years old. Finally, total brain volume and the cerebral cortex demonstrated a stronger decline with age after the age of 60, compared to the preceding years (Fjell et al., 2009).

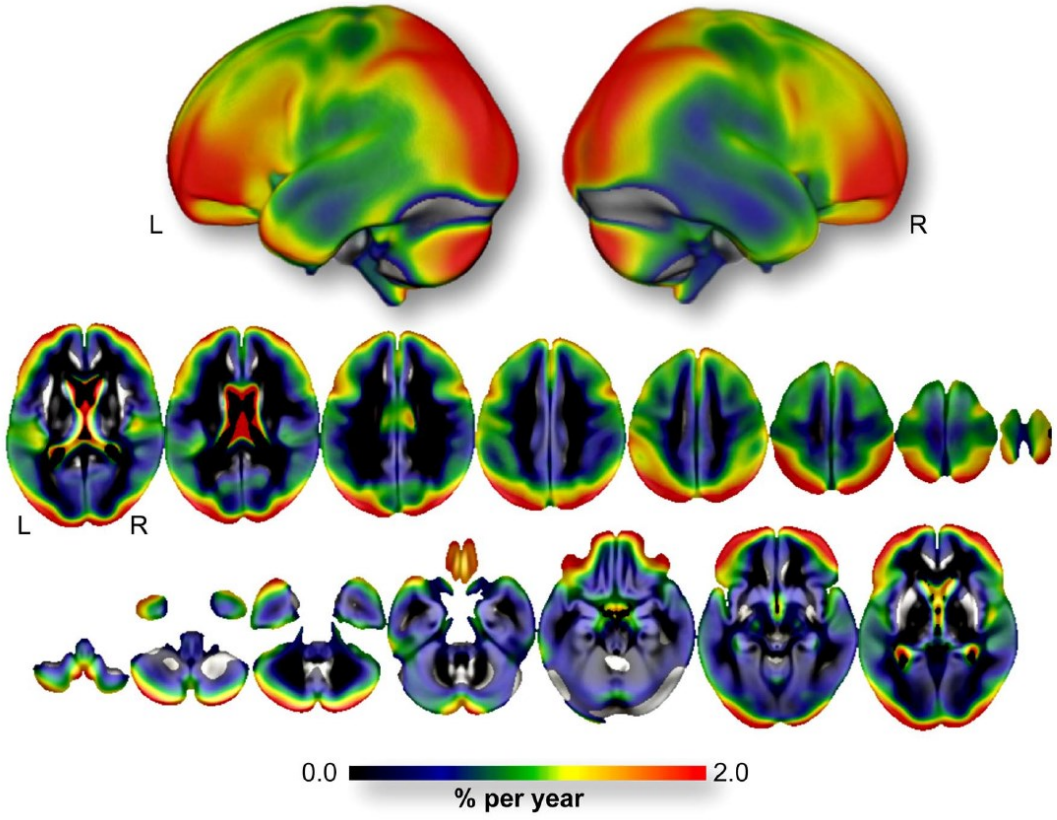

Figure 1—1: Figure taken from Crivello et al., 2014, demonstrating the heterogeneity in the annual GMV decline depending upon the region of interest.

Notably, these declines to GM have also been associated with reductions to cognitive health, where significant GM atrophy has been identified in the medial temporal lobe (Pelletier et al., 2017; Susanto, Pua, Zhou, & Alzheimer's Disease Neuroimaging Initiative, 2015; van de Mortel, Thomas, van Wingen, & Alzheimer's Disease Neuroimaging Initiative, 2021), hippocampus (Chen et al., 2021; van de Mortel et al., 2021), parietal (Susanto et al., 2015; Wu,

Peng, Hong, & Zhang, 2021), frontal (Wu et al., 2021), and cingulate cortices (Susanto et al., 2015; Wu et al., 2021) in those with dementia. These relationships between GM atrophy and cognition have been extended to healthy aging individuals as well, who demonstrate reductions GMV in the frontal and temporal lobes, which experience the greatest atrophy, followed by the hippocampus (Bourisly et al., 2015; Lemaitre et al., 2012). Notably, work in healthy older adults revealed that a decline to hippocampal volume was significantly associated with a reduction to memory performance over a four-year span (Kramer et al., 2007). Others found that when total GMV was reduced there was a significant decline to processing speed as well as episodic memory (Arvanitakis et al., 2016). Moreover, a meta-analysis revealed that those with greater prefrontal cortices volume had significantly better executive functions (Yuan & Raz, 2014). Taken together, these results implicate the relationship between structural and cognitive decline, revealing the importance of studying these structural outcomes in aging to further uncover the potential for future cognitive decline in these domains in aging.

Overall, the literature convincingly shows that global, as well as regional GM atrophy occurs in aging, though the mechanisms underlying this atrophy are not fully understood. There are likely an assortment of exogenous factors however, including lifestyle and modifiable factors. These lifestyle and modifiable factors can either accentuate, or attenuate the GM atrophy seen, including, but not limited to obesity, as well as physical activity. Both of which will be discussed in future sections (physical activity – section 1.7.1, and obesity – section 1.81).

1.2.2 White Matter Volume and Aging

Changes in WM have also been observed in aging, yet it does not occur until later life, generally observed above the age of 50 (Kemper, 1994) (See Figure 2 demonstrating the change in WM across the lifespan (Irimia, 2021)). It is hypothesized that WM atrophy occurs because of an increase in perivascular spaces and a reduction in myelinated fiber size (Meier-Ruge, Ulrich, Brühlmann, & Meier, 1992), causing WM fiber deterioration to occur. Thus, in aging, the length of myelinated axons and overall WMV are reduced (Fjell, Westlye, Amlien, & Walhovd, 2011).

WM has been found to remain quite consistent from adolescence (Salat, Kaye, & Janowsky, 1999; Walhovd et al., 2005) until around midlife, with a nonlinear decline above the age of 50 (see Figure 2 taken from (Irimia, 2021)) correlating with the expansion of CSF

(Jernigan et al., 1991). Though, it is worth noting that frontal regions continue to myelinate until around 30 years old, which could partially explain why WM atrophy appears later in life, as WM maturation plateaus later on in adulthood. It has been hypothesized that WM damage occurs due to oxidative stress (Weber, 1994) and in some cases, strokes (Kertesz et al., 1988). Early work by Salat and colleagues found that healthy young older adults (ages 64 to 76) have significantly greater WMV compared to their older adults (84 to 95 years old), particularly within the prefrontal cortex (Salat et al., 1999). Other follow up work confirmed that in fact the prefrontal WM, as well as the inferior parietal regions were most affected by aging (Raz et al., 2005). Other work has indicated that in addition to this frontal cortex vulnerability, the temporal (Bartzokis et al., 2001; Raz et al., 2005) and parietal cortices (Resnick et al., 2003) also exhibit atrophy, while the occipital cortex remains relatively spared (Raz et al., 2005). Interestingly, it has been observed that there is a disproportionately greater decline to WMV than GMV (as demonstrated by a larger gray to white matter ratio) in healthy older adults compared to healthy younger older adults (Salat et al., 1999). It was concluded that this was likely due to a decrease in WMV, rather than increasing GMV, as in aging, increasing neuronal density is not common (Morrison & Hof, 1997). This relationship between age and WMV decline across the lifespan can be visualized in figure 2 where WMV demonstrates a somewhat inverted U shape, suggesting the bulk volumetric declines in WM do not begin until the microstructure (as indicated by fractional anisotropy (FA) and mean diffusivity (MD) measured with diffusion MRI) has already significantly declined.

Nonetheless, there are still associations between WMV and cognitive decline in aging, particularly, declines to processing speed are associated with decreased WM volumetrics (Madden et al., 2004). Others have identified that greater WMV in each of the four cortical lobes was associated with significant improvement on task switching performance during the Stroop test (Hirsiger et al., 2017). Moreover, the relationship between prefrontal WM integrity on fluid intelligence (Persson et al., 2016), as well as parietal and frontal WMV on verbal memory (Leong et al., 2017) have been identified as well. Together, these studies reveal the importance of WMV integrity on cognitive outcomes in older adults and the globality that WMV seems to have on memory, executive function, and processing speed.

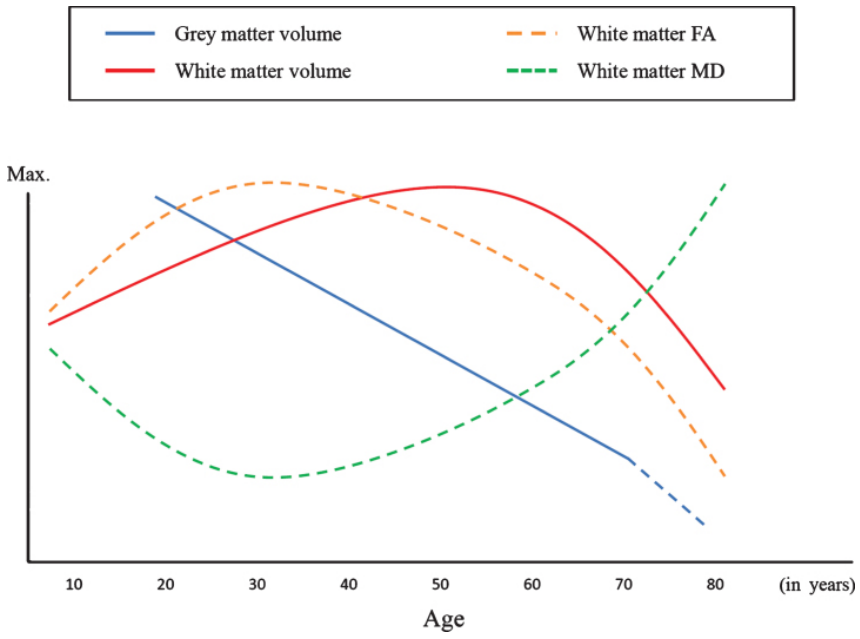

Figure 1—2: Structural decline across the lifespan differing by tissue type, taken from Irimia, 2021, demonstrating the unique decline in structural outcomes across the lifespan, where GMV declines earlier and at a faster rate than WMV, though it appears as though WMV declines quickly after the 5th decade.

1.2.3 White Matter Hyperintensities and Lesions in Aging

WM lesions (WML) and hyperintensities (WMH) are common, clinically silent abnormalities that show up as hyperintense signals on T2-weighted imaging and fluid attenuated inversion recovery (FLAIR) maps. They are located in WM and vary in size. It is hypothesized that WMH and lesions (WMHL) reflect demyelination, increased water content, microvascular disease, and reduction in vessel endothelium (Fazekas et al., 1993; Fernando et al., 2004; Oppenheimer et al., 1995; Smith, Snowdon, & Markesbery, 2000). WML and hyperintensities (WMHL) are thought to be due to vascular changes and ischemic events that occur during aging and continue to increase in prevalence with age. It is estimated that anywhere from 60 to 100% of individuals over the age of 65 have at least some WMHL, though volume and number vary greatly between individuals (de Leeuw et al., 2002; Wardlaw, Smith, & Dichgans, 2019). Much of the variability associated with WMH is due to the chronological age of the individuals included in the study (de Leeuw et al., 2002; Jernigan et al., 1991; Melazzini et al., 2021) and vascular risk factors that are associated with their presence, such as hypertension (de Leeuw et al., 2002; Firbank et al., 2007) and obesity (Han et al., 2021).

There are two types of WMHL, and these are categorized according to their location within the brain. Periventricular WMHL are those which are observed in the white matter adjacent to the ventricles. It is hypothesized that the periventricular space is particularly susceptible to WMH as this area is a blood supply watershed region (Rowbotham & Little, 1965), thus making it more sensitive to ischemic damage due to low perfusion. Conversely, deep WMHL appear first in the frontal lobes, and then progress within parietal and occipital lobes (Galluzzi, Lanni, Pantoni, Filippi, & Frisoni, 2008). Generally, the temporal lobe is spared from WMHL, though it has been observed to be affected in the most severe cases (Grueter & Schulz, 2012). A meta-analysis of prospective longitudinal studies found that WMHL was associated with a twofold increase in the risk of developing dementia, and three times the risk of experiencing a stroke (Debette & Markus, 2010). Other work has identified that WMHL are associated with longitudinal cortical thinning, particularly within the middle frontal cortex (Rizvi et al., 2021) and others have extended this to include greater WMHL independently predicting an atrophy rate per annum of 0.03% for the whole brain and 0.25% for hippocampal, regardless of cognitive status (Fiford et al., 2021).

Importantly, work has revealed that greater WMHL is associated with significant reductions to executive functions in healthy older adults, and over a four-year timeline, greater development of WMHL was associated with even further decline to executive functioning from baseline (Kramer et al., 2007). Others have linked greater burden of WMHL to declines in processing speed, immediate and delayed recall, and overall cognitive function (Alzheimer's Disease Neuroimaging Initiative et al., 2020; d'Arbeloff et al., 2019; Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009).

Given that WMHL can occur in the absence of symptoms early on, they are thought to be an early sign of aging-related structural changes. As such, it is crucial to understand their development, and whether they are partially reversible through lifestyle interventions.

1.3 Cerebral Hemodynamics

1.3.1 Cerebral Blood Flow: Physiological Underpinnings

Cerebral perfusion allows for the brain to receive glucose and oxygen to maintain adenosine triphosphate (ATP) production and to replenish ATP stores during neuronal activity. The brain has limited metabolic stores, and thus to meet its energy needs, which are 20% of oxygen consumption at rest (a significant proportion given that the brain is only about 2% of total body weight (Clarke & Sokoloff, 1999)) relies on consistent cerebral blood flow (CBF) (Williams & Leggett, 1989). Importantly, though the brain requires constant perfusion to maintain neuronal metabolism, it is unable to cope with large surges in volume of blood supply due to the sensitivity of the cerebral vasculature, thus making the vasculature particularly vulnerable to changes that occur in CBF. To achieve this, under normal physiological conditions CBF and neuronal activity are tightly coupled through neurovascular coupling. This ensures that when neuronal activity increases, the metabolic needs of the neurons are met through increased CBF via vasodilation (Lipecz et al., 2019; Tarantini, Tran, Gordon, Ungvari, & Csiszar, 2017). Neurovascular coupling occurs in a coordinated manner, ensuring that CBF is increasing in a region-specific manner, to meet local demand.

1.3.2 Cerebral Blood Flow Measurement Technique: Arterial Spin Labeling

CBF is the amount of blood flow that is delivered to the brain in units of ml/100g of tissue/minute, indicating the volume of flow per gram of brain tissue (generally GM) per unit of time. In order to quantify CBF, it is necessary to utilize some form of tracer that can diffuse from the vasculature to the parenchyma, prior to venous washout. There are multiple techniques to quantify CBF in this way, but only one method, arterial spin labeling (ASL), utilizes arterial water as an endogenous tracer (Alsop & Detre, 1996; Detre, Leigh, Williams, & Koretsky, 1992; Detre et al., 1994) and thus does not require the injection of exogenous tracers that could potentially be harmful (Borogovac & Asllani, 2012). As ASL is non-invasive, it is also safe for repeated use and therefore is a prime candidate to quantify CBF in longitudinal studies (Borogovac & Asllani, 2012). Other benefits of ASL include the fact that it provides an absolute quantification of CBF and can be expressed in physiologically meaningful units (ml/100g/min) rather than just a percent change. It is also preferable to transcranial Doppler (TCD), which is another non-invasive technique but measures flow velocity in large arteries rather than tissue perfusion, thereby affording limited local information unrelated to the microvascular health most likely to be affected by PA.

Generally speaking, ASL sequences take advantage of the magnetic properties of arterial blood water and are able to 'label' the oxygenated blood traveling into the brain via the carotids. The molecules then reach the capillaries and diffuse into tissue causing a change in signal. Since we are interested in measuring the labeled water once it is in tissue, there is thus a time delay that occurs between the labeling at the carotids and the time that the images are acquired in the brain. This time is referred to as the post labeling delay (PLD). A control image is also acquired, where no label has been applied at the carotids. Acquisition of these labeled and control images is repeated numerous times to obtain a time series of images. A pair-wise subtraction, or the difference between the control and labeled images is then completed, creating a perfusion-weighted image which represents the amount of CBF supplying each specific voxel (see figure 3). Perfusion maps are created through the application of a kinetic model to obtain values of flow in each voxel (Alsop et al., 2015; Chappell et al., 2013).

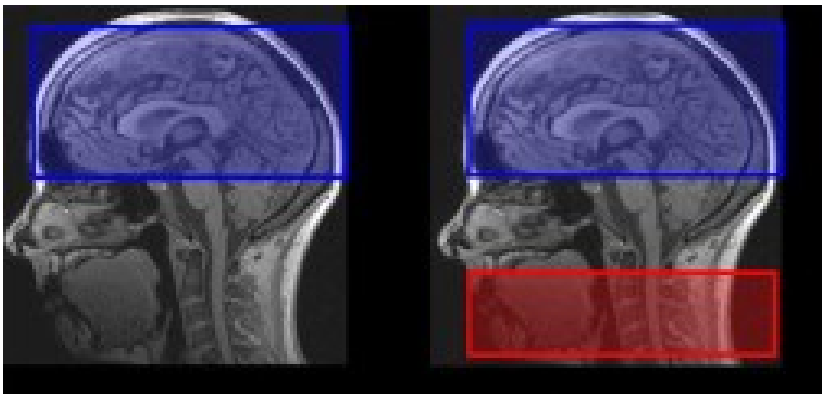

Figure 1—3: the image on the left depicts a control image being collected, the image on the right indicates the labeling plane, at the level of the carotids and again the image collected in the brain after the label has been applied. Image adapted from Ferré et al., 2013

Several implementations of ASL have been developed, which are categorized according to how the labeling is achieved (Dai, Garcia, de Bazelaire, & Alsop, 2008; Garcia, Duhamel, & Alsop, 2005; Wu, Fernández-Seara, Detre, Wehrli, & Wang, 2007). For the purposes of this thesis, we will focus on pseudo-continuous ASL since this is the recommended implementation (Alsop et al., 2015) and since this is the sequence used throughout all studies. Briefly, pseudo-continuous ASL (pCASL) causes the inflowing of blood to be continuously labeled, rather than labeled at a single time point as in pulsed ASL implementations. The PLD is an important parameter to be set, and consideration of the population being investigated is imperative to inform the choice of PLD. As PLD is the time between the blood being labeled at the carotid and

the time until the image is acquired in the parenchyma, the velocity at which the labeled blood reaches the parenchyma (referred to as the arterial transit time), should determine the PLD. This time will vary depending on the participant due to arterial transit time differences in aging and disease (Liu et al., 2012; MacIntosh et al., 2015). Thus, those who are older would require a longer PLD, as their arterial transit time would be longer compared to a younger adult, given the vascular changes that occur that can cause a reduction in the flow of blood, including arteriosclerosis, arterial thickening, and arterial inflammation (see (Zimmerman, Rypma, Gratton, & Fabiani, 2021) for a more in-depth review). Moreover, other factors may be at play, including presence of pathology and increased tortuosity of the carotids, causing blood to travel at a different rate, which will affect the arterial transit time, and thus the PLD chosen. However, since these factors are not typically known, a compromise PLD is usually chosen and used for all participants, based on prior studies in groups of similar ages or vascular health status.

This can lead to an onerous decision if a study is investigating individuals across the lifespan, or those with presence of disease compared to those without for example. Choosing the PLD is a balance between waiting a sufficiently long period of time so that the majority of the labeled blood flow is able to reach the parenchyma allowing for the greatest amount of signal to be measured (Buxton et al., 1998), but not so long that much of the labeled blood has already left that region of the imaged parenchyma. Therefore, the chosen PLD, when a single PLD sequence is employed, is of utmost importance as it can lead to an apparent over or under estimation of perfusion in those individuals due to differing arterial transit times.

The advent of multi-delay PLD pCASL, provided the ability to use multiple unique PLD durations in the same acquisition, therefore overcoming the restrictive nature of choosing a single compromise PLD. Multi-delay PLD sequences tend to be composed of PLDs ranging in length from short (~200 ms) to very long (~3000ms). All PLD's are then utilized to help quantify the arterial transit time and thus provide a more accurate quantification of CBF with a kinetic model fit. A pitfall of multi-PLD pCASL sequences is that they require a very specific sequence that is not available at many centres or on all scanners. Also, a sufficient number of label-control pairs must be acquired at each PLD, or the signal to noise ratio could be significantly reduced, preventing accurate quantification.

Taken together, pCASL quantification of CBF is a valuable tool for non-invasive assessment of cerebrovascular health. While some challenges exist, it represents the best available tool to investigate the effects of PA and obesity on cerebrovascular health and hemodynamics.

1.3.3 Cerebral Blood Flow and Aging

Across the lifespan, CBF has been consistently shown to decline, which is particularly evident in aging. This was documented as early as 1952 by Fazekas et al. (Fazekas, Alman, & Bessman, 1952) and followed up in 1956 by Kety (Kety, 1956). Since then, CBF has been consistently shown to increase throughout adolescence, and then plateau in adulthood until around middle age where the decline in cerebral perfusion begins (see Figure 4 from Zhang and colleagues 2017 for a visual representation (Zhang, Gordon, & Goldberg, 2017a). Indeed, CBF declines are hypothesized to occur earlier than structural declines (de la Torre, 2000; Farkas & Luiten, 2001), making it a promising early marker of cerebral aging. The reduction of CBF across the lifespan has been demonstrated to occur at differing annual rates and to date, the exact mechanisms related to this CBF reduction during aging are thought to be due to decreased elasticity of the vascular system, changes to the cerebral blood vessel density, fibrinogenesis, and degeneration of pericytes (Farkas & Luiten, 2001). The current working hypothesis for this decline to CBF within the aging years is in fact due to a lifetime of cellular damage (de la Torre, 2018), which is accentuated by vascular risk factors, like hypertension (Bangen et al., 2014; van Dalen et al., 2021), causing a vicious cycle of further reductions to perfusion (de la Torre, 2000).

Overall damage of the cerebrovasculature is reported to be caused by, but not limited to arterial inflammation, arterial stiffening, arterial weakening, reduced cerebrovascular reactivity, a leaky blood brain barrier, loss of the microvasculature and increased tortuosity of micro vessels (see (Zimmerman et al., 2021) for an in-depth review of these factors). Moreover, as can be seen in Figure 5, taken from Zimmerman and colleagues, the age of onset of each factor, the time course, as well as the likelihood of its prevention and reversibility are clearly indicated in the study. For example, the range of events begins around early adulthood with arterial inflammation and stiffening, which are reversible, followed by arterial weakening and decreased vascular reactivity which are occurring in mid-life, coinciding with the beginning of perfusion decline, and are not reversible or likely, respectively.

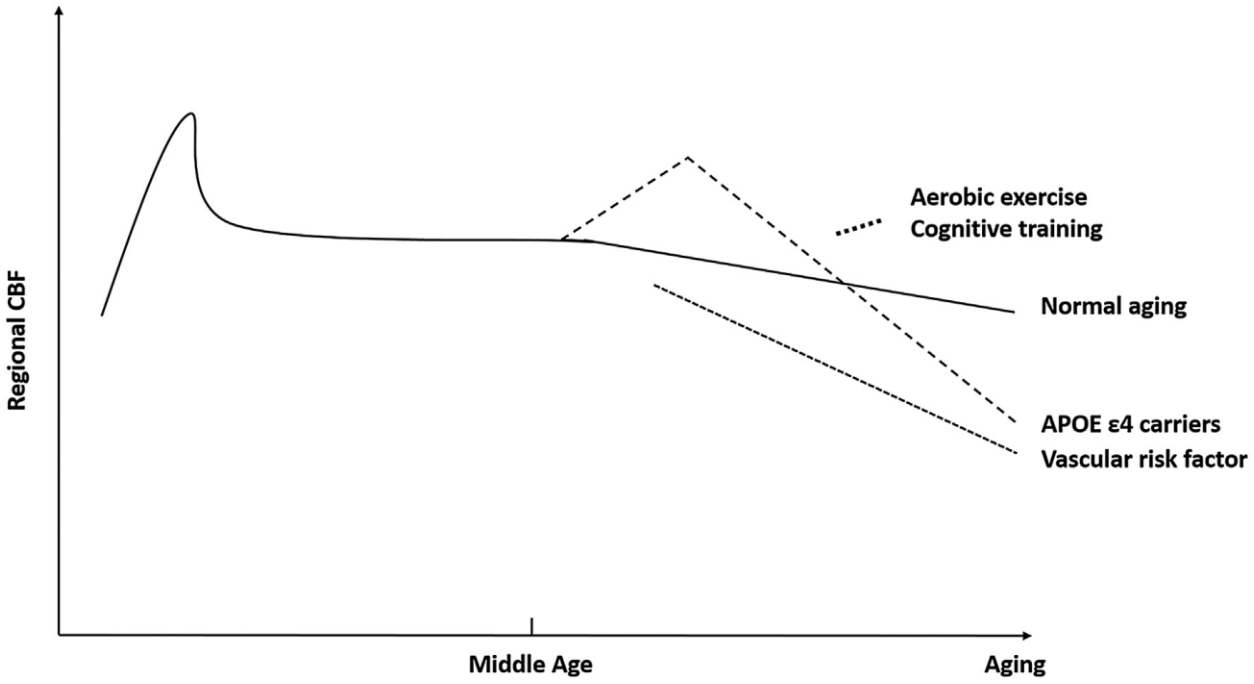

Figure 1—4 Decline of CBF across the lifespan where it begins an accelerated linear decline around middle age. Figure taken from Zhang and colleagues (2012).

Different rates of decline have been reported in the literature. For example, Chen and colleagues identified that CBF declines at a rate of 0.38% per year, which results in a reduction of almost 27% over a 70-year adult lifespan (Chen et al., 2011). Other work has identified that the decline is higher at 0.45% decline per year (Parkes, Rashid, Chard, & Tofts, 2004a). Regardless, it is apparent that the reduction in CBF due to aging is dependent on the region of interest (Chen et al., 2011; Claus et al., 1998; Leenders et al., 1990; Parkes et al., 2004a). These regional differences extend to what structure is being investigated. For example, WM perfusion appears to be more maintained with less than 0.3% decline per year, when accounting for the age-related volume decline. Moreover, the amount of perfusion that each tissue type receives is different, for example GM tissue receives more CBF, which on average a normal amount in young individuals is approximately 50 mL/100 g of gray matter tissue/ minute and in older adults is approximately 40 mL/100 gm of GM tissue/minute (De Vis et al., 2015), compared to WM, which only receives 20 mL/100 g of white matter tissue/minute (Gilkes & Whitfield, 2009). The physiological mechanism underpinning this significant difference in CBF between tissue types lies in the fact that GM is comprised of more blood vessels, whereas WM has significantly less

density of blood vessels (Gross, Sposito, Pettersen, & Fenstermacher, 1986; Kubíková, Kochová, Tomášek, Witter, & Tonar, 2018), and more diving arteries that are very long and thus lower perfusion pressure (Torkvik, 1984), and overall blood flow.

	Onset	Preventability	Reversibility	Time course
Arterial inflammation	~20	Partial	Yes	~Likely exponential
Arterial stiffening	~30	Partial	Yes, up to critical zone	~Likely exponential
Arterial weakening	~40	Partial	No	Not strongly related to age (in cerebral arteries)
Decreased vascular reactivity	~35–60	Likely	Likely	Possibly sigmoidal
Leaky blood–brain barrier	~40	Partial	Likely	Context dependent
Loss of microvasculature	~50	Likely	Likely	Microvascular density increases before decreasing to floor
Tortuosity of small vessels	~50	Unknown	Unknown	Unknown

Figure 1—5: A listing of underlying mechanisms leading to cerebrovascular damage that is present in aging, as well as indicating the age of onset in general for this occurrence, the preventability of this outcome from occurring, if this outcome is reversible and what is the time course of each component to manifest. Table adapted from Zimmerman et al., 2021.

Regionally specific declines to CBF during aging have been reported in numerous cross-sectional designs, where the frontal, parietal and temporal regions have all been identified to have significantly decreased CBF in older adults compared to younger adults (Chen et al., 2011; De Vis et al., 2015; Parkes et al., 2004a). More specifically, the inferior (Leoni, Oliveira, Pontes-Neto, Santos, & Leite, 2017), middle (Leoni et al., 2017; Parkes et al., 2004a; Zhang et al., 2017a) and superior frontal gyri (Leoni et al., 2017; Parkes et al., 2004a), middle temporal (Zhang et al., 2017a); superior temporal gyrus (Leoni et al., 2017; Zhang et al., 2017a), pre and post central gyri (Leoni et al., 2017; Parkes et al., 2004a), insula, putamen, inferior parietal gyrus (Leoni et al., 2017; Parkes et al., 2004a; Zhang et al., 2017a) and cingulate gyri (Leoni et al., 2017; Liu et al., 2012; Zhang et al., 2017a) have been reported to demonstrate significantly reduced perfusion pattern in healthy older adults compared to younger healthy adults. Other work has found that there is significant cerebral perfusion decline within the medial temporal lobes (Asllani, Habeck, et al., 2008), an area associated with atrophy in dementia (Woodworth et al., 2022). Though it is important to note that aging is not always associated with hypoperfusion. In fact, a few studies have identified patterns of hyperperfusion in older adults, compared to younger adults in the lateral and medial temporal lobes as well as the anterior cingulate cortices (Lee et al., 2009; Preibisch et al., 2011; Zhang et al., 2017a). These hyperperfused regions are

thought to be a compensatory mechanism in aging, whereby increased neuronal activity and recruitment is occurring in the face of other neurophysiological declines (Celone et al., 2006).

Notably, though cross-sectional studies have demonstrated both regions with hypoperfusion and those with hyperperfusion, only reductions to CBF have been found in longitudinal prospective studies within participants. Globally speaking, over a 2.1-year period it was found that there was a 1.9% reduction in CBF from age approximately 69 to age 71, and this was associated with the progression of WMH volume over the same time period (Han et al., n.d.). Others have found that there is a CBF reduction of 0.66 mL/100 g of GM tissue/min on a yearly basis in healthy older adults (Staffaroni et al., 2019), while in those with hypertension, this decline was accelerated to a rate of 1.6 mL/100g GM tissue/ min annually (van Dalen et al., 2021). Camargo and colleagues identified that over an approximate 2.5-year period, CBF was significantly declined, but specifically within the bilateral hippocampi and the left fusiform gyrus by almost 1 mL/100 g/min (Camargo, Wang, & Alzheimer's Disease Neuroimaging Initiative, 2021). Furthermore, there are indications that cross sectional studies under-estimate age-related perfusion decline and that longitudinal changes occur at a faster rate than what is described in the cross-sectional literature. This could be due to participant bias, whereby those older adults that are unusually healthy are included in these cross-sectional estimates (Han et al., 2021.).

CBF decline has been identified as a potential marker for the accelerated cognitive decline experienced in some, whereby baseline global CBF has predicted future cognitive impairment or decline (De Vis et al., 2018) in particular within the processing speed domains, reasoning as well as working and episodic memory 4 years later. Others have identified that there was no relationship between CBF and memory, but that a significant decline to CBF was associated with a reduction in attention (Catchlove, Macpherson, et al., 2018). This discrepancy in findings for CBF and memory could be driven in part, by the presence of amyloid beta accumulation, as Bangen and colleagues found that in their otherwise healthy older adults, those with presence of amyloid beta demonstrated a relationship between CBF and memory, yet those without amyloid beta, did not possess that relationship (Bangen et al., 2017). However, it is also likely that the lack of results in Catchlove et al., 2018 was driven by a lack of power and averaging of multiple memory domains into one memory composite score which could be missing subtle associations in more specific domains of memory like verbal or working

(Catchlove, Macpherson, et al., 2018). For example, a much larger study with over 2500 participants have recently confirmed that lower CBF is related to lower verbal memory, working memory and speed in a healthy aging population (Moonen et al., 2021).

1.3.4 Cerebrovascular Reactivity and Aging

Another promising biomarker of cerebral physiology in aging is cerebrovascular reactivity (CVR). CVR is a measure of the vasodilatory or constrictive reaction of the cerebral blood vessels in response to a stimulus. The more the vascular system is able to vasodilate, the more blood can be perfused through that tissue and the greater the hemodynamic response to the vasodilatory challenge will be. Thus, it is hypothesized that greater CVR is related to enhanced cerebrovascular health (Mandell et al., 2008). Vasodilatory challenges include the injection of acetazolamide (Inoue, Tanaka, Hata, & Hara, 2014a), an individual holding their breath for a specific time period, and hypercapnic gas manipulations, as carbon dioxide (CO_2) induces a dilation of blood vessels. For the purposes of this dissertation, the use of hypercapnia will be the focus of any discussion relating to CVR, unless otherwise specified.

The inhalation of CO_2 causes a rapid onset of vasodilation and is considered to be a purely vascular challenge, allowing for the measure of the vascular health, without theoretical contaminant signal from other neurophysiological outcomes, like oxidative metabolism. End-tidal CO_2 is measured at rest and during the hypercapnic manipulation which can be completed during a blood-oxygen level dependent (BOLD) signal acquisition, an arterial spin labeling scan, or both, depending upon the overall research question being investigated. A larger change in the end tidal CO_2 is representative of a greater challenge to the vascular system. In a normal, healthy vascular system, an increase in CO_2 leads to a progressive increase of blood flow in most areas of the brain (Battisti-Charbonney, Fisher, & Duffin, 2011; Sobczyk et al., 2014). Physiologically speaking, CO_2 is thought to act through the nitric oxide pathway, increasing arterial diameter (Iadecola, 2017; Pelligrino et al., 2000), and leading to an almost 25% increase to GM CBF for a 5mmHg CO_2 change (Gauthier & Hoge, 2012). Furthermore, GM has almost 3 times greater reactivity than WM (Liu et al., 2012; Rostrup et al., 2000), following the same trend as CBF due to the abundance of blood vessels within the GM.

In recent years, CVR has become more widely used and is thought to be a potentially vital clinical marker (Donahue et al., 2014). Indeed, it has been identified to be a more dynamic

measure of cerebral hemodynamics, as it is shown to decline earlier in the course of aging than even CBF (De Vis et al., 2015; Gauthier et al., 2013; Jefferson et al., 2018; Lu et al., 2011). It has been hypothesized that impaired CVR is related to microvascular dysfunction and has been implicated in many neurovascular disorders such as Alzheimer's disease (Sur et al., 2020; Yezhuvath et al., 2012), mild cognitive impairment (Kim et al., 2021; Sur et al., 2020) and stroke. During normal aging, CVR has been demonstrated by numerous groups to be significantly reduced compared to young adults (De Vis et al., 2015; Gauthier & Hoge, 2012; Gauthier et al., 2013,; Lu et al., 2011). The extensive decline in aging to CVR can be seen in Figure 6 and can also be visualized to show the more prominent decline to CVR across the lifespan compared to CBF (Lu et al., 2011). Furthermore, Gauthier and colleagues (2012) identified that within the left frontal lobe, younger adults had 0.24 % change in BOLD signal per mmHg increase of CO_2, whereas the older adults had a 0.18% change in BOLD signal per mmHg increase of CO_2 (Gauthier et al., 2013). These same trends were extended to the right frontal lobe, as well as the parietal, and global gray matter CVR (Gauthier et al., 2013). In another study, when age and CVR were entered into a linear model, it was found that *only* CVR in the temporal lobe was declined (Catchlove, Macpherson, et al., 2018) [the only region that was not significant in (Gauthier, Desjardins-Crépeau, Madjar, Bherer, & Hoge, 2012). However, when the sample was broken up into a younger age, those 21 to 44 and an older age range, 55 to 75, they found cohort specific declines in the older group to the cingulum, overall GM, and temporal regions. It's important to note that in Gauthier et al., the age range in the younger group was 18 to 30 years of age, thus it is possible that more regions were significantly different between young and old, because overall younger participants would theoretically have healthier vascular systems, and enhanced vasodilatory responses (Gauthier et al., 2013). In a sample more similar to Gauthier et al., 2013, with an age range of 20 to 33, it was revealed that CVR was also significantly declined in whole brain gray matter CVR, frontal lobes, temporal and occipital lobes, albeit not within the parietal lobe (De Vis et al., 2015). Notably, global CVR has also been shown to decrease in a 4-year longitudinal design by Peng and colleagues (Peng et al., 2018a). In this study, the annual rate of change to CVR was -0.0024 % change in BOLD signal/ mmHg increase in CO_2/ year. Thus, identifying the regionality and the rate of CVR declines in aging is imperative, as regions with low reactivity are thought to be the harbingers of lower perfusion, and could explain some of the age-related cognitive decline that is reported in aging. Reduced

CVR could be an early indication of regions that are unable to increase perfusion as easily in response to rising demand, eventually leading to long-term hypoperfusion and hypoxic damage.

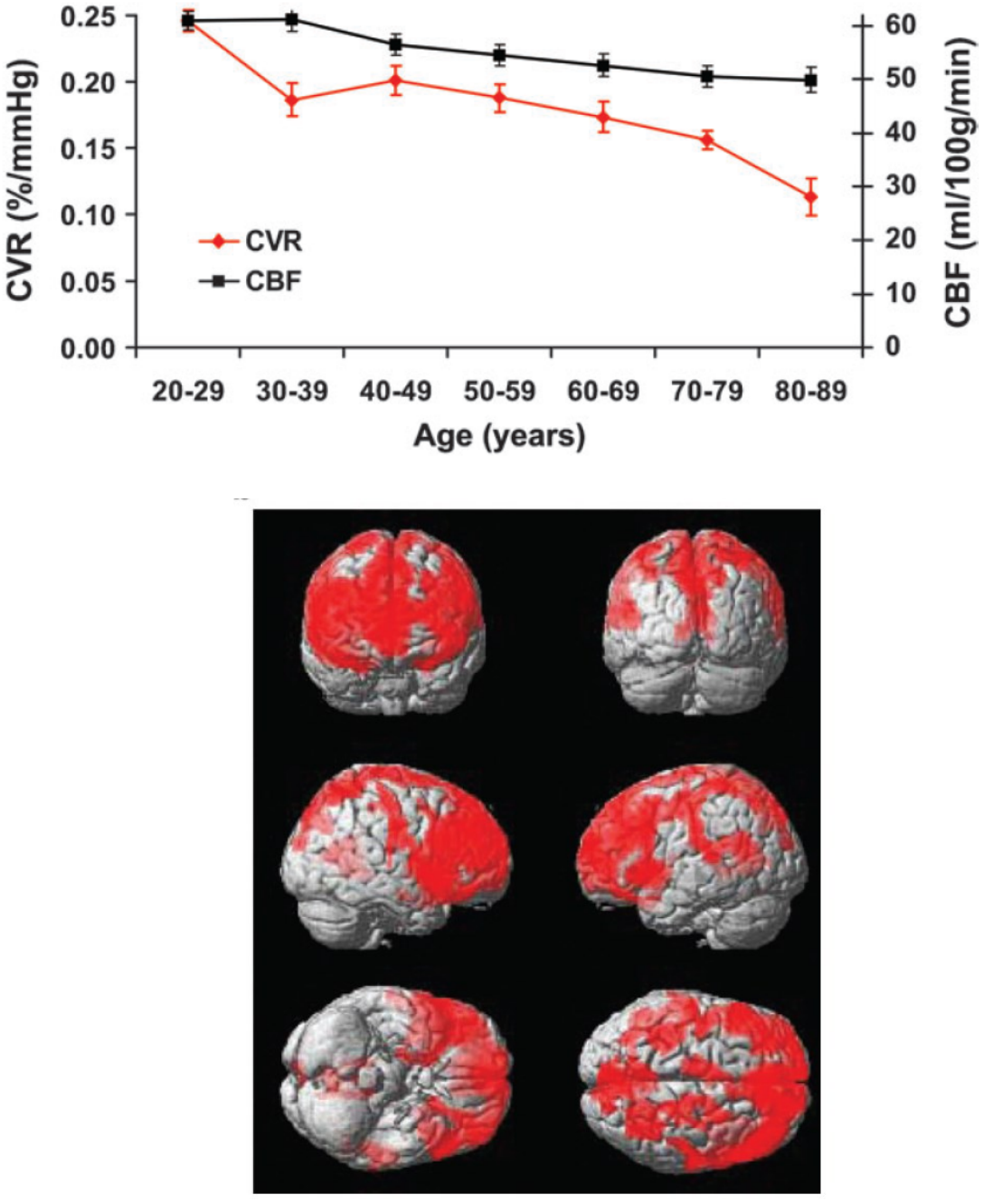

Figure 1—6: A) Decline of CBF and CVR in individuals from different age groups demonstrating the earlier and faster decline of CVR compared to CBF. B) Areas demonstrating CVR decline in aging. Taken from Lu and colleagues (2011)

Taken together, it is apparent that cerebral hemodynamic declines occur during aging, whether measured with CBF, CVR or a combination of both. Furthermore, the evidence seems to indicate that CVR is a more sensitive marker of cerebrovascular decline, though it can be a more difficult marker to collect as tolerance to CO_2 can be difficult in older adults.

1.4 Physical Activity and other essential exercise physiology background

1.4.1 Physical Activity

Physical activity (PA) can be defined as any bodily movement, recreational or for employment, produced by skeletal muscle, that results in the expenditure of energy (Caspersen, Powell, & Christenson, 1985). PA can be expressed as a rate, where the amount of energy, in kilocalories per unit of time, expended by an individual is a continuous variable ranging from low to high. Those activities that require a greater amount of muscle mass to complete a bodily movement require more energy. Also determining the amount of energy expended is the amount of time that each activity is completed for, the frequency of said activity and thus muscular contractions, as well as the intensity of said activity (Taylor, Buskirk, & Henschel, 1955)

1.4.1.1 Metabolic Equivalents

Another common unit of energy cost of PA is the metabolic equivalent (MET) which was created to allow for a practical and simple quantification of PA. More specifically, a MET is defined by a resting metabolic rate, which is the amount of oxygen that an individual consumes at rest, sitting quietly in a chair, corresponding to approximately 3.5 ml O_2/kg/min. Activities requiring more muscle mass will therefore require further oxygen to sustain said activity, and those with higher intensity will also require a greater amount of oxygen to successfully continue with that activity.

An expert fitness committee identified three major categories of intensity to be used (Bouchard et al., 1983). More specifically, light activities were defined as those that only caused a slight increase in breathing above normal and minimal perspiration, like light gardening, whereas moderate referred to those that result in obvious perspiration and breathing considered above normal, such as brisk walking, and finally, heavy activities are those that cause high level of perspiration and breathing, like those induced by running. These three categories were created

to allow for a more standardized explanation for individuals when inquiring about their PA, allowing clinicians and researchers to specify if a brisk walk would qualify as a light to heavy activity based on an individual's explanation of physical outcomes associated with the PA. A compendium of PA (Ainsworth et al., 2011), was developed listing all common household activities, recreational activities, and providing the METs for each activity at each category of intensity. METs are the continuous outcome that will be used to quantify PA for the remainder of this dissertation, unless otherwise indicated.

1.4.2 Other important definitions

1.4.2.1 Exercise and Cardiovascular Fitness

Although similar to PA, exercise and PA are not synonymous, though they tend to be grouped together (Caspersen et al., 1985; Taylor et al., 1955). Exercise is structured, planned, purposeful and repetitive participation in activities that enhance or maintain physical fitness as the primary objective. In this sense, exercise can be considered a subcomponent of PA. Conversely, physical fitness is a set of attributes that people genetically have or that can be achieved, generally by participating in exercise that continues to challenge the specific physiological system being trained (Pate, 1988). For example, there are multiple components of physical fitness, such as cardiovascular fitness, which refers to how well the muscular, circulatory, and respiratory systems are able to provide fuel during sustained exercise and to reduce or eliminate the products of exercise after supplying the energy necessary (Corbin, Pangrazi, & Franks, 2000; Corbin, Reimann, Walsh, & Krebs, 1970). There are also other components, such as muscular strength, muscular endurance, body composition and flexibility, which are all equally important components of physical fitness, but are beyond the scope of this dissertation. Thus, for the remainder of this dissertation, the focus of any physical fitness outcome will be that which is pertaining to cardiovascular fitness.

Cardiovascular fitness can be quantified through the employment graded exercise test that measures maximal oxygen uptake during this test, or VO_2max, which is considered to be the gold standard for measuring cardiovascular fitness. There are numerous protocols that can be utilized to measure an individual's VO_2max, depending upon age, comorbidities, purpose of the test, as well as physical abilities. For example, some protocols can involve the use of a cycle

ergometer and others utilize one that requires a treadmill. Generally speaking, in the aging literature, due to safety and balance issues, an upright cycle ergometer tends to be the method of choice. Protocols will generally differ in the amount of load that is present at the beginning of the test, how long a participant cycles at each specific work stage, the rate that they must cycle at (revolutions per minute), as well the amount of load increased each stage. During this time, a mask covering the participant's nose and mouth is also installed that is connected to a computer that measures breath by breath data. This is to specifically measure the amount of oxygen inhaled and the volume of carbon dioxide that is exhaled providing the ability to quantify the maximal oxygen utilization during the test in units of ml of oxygen per minute in absolute terms and can be corrected for body weight to allow for a more relative measure in ml of oxygen per kg of body weight per minute. The higher this number is, the more enhanced an individual's cardiovascular system is thought to be as they are able to utilize more oxygen at greater levels of cardiovascular stress. Typically, for a test to be considered maximal, there are numerous physiological criteria that must be met, including, but not limited to: plateau in the volume of oxygen consumed despite increasing workload (Taylor et al., 1955), respiratory exchange ratio (O_2/CO_2) > 1.15 (Howley, Bassett, & Welch, 1995), increased blood lactate levels (> 8.0 mMol/L), within 10 beats of heart rate max, and a rating of perceived exertion > 17 out of 20 (where higher numbers are associated with greater exertion). Given all these criteria, particularly the plateau in oxygen consumption despite increased workload, and the extreme fatigue required for a full maximal test, it has been identified that in older adults, a full maximal test may not be practically attainable (Huggett, Connelly, & Overend, 2005). In the place of a true maximal test that has specific physiological requirements that cannot always be met, a VO_2peak can be utilized. It is the highest volume of oxygen consumed throughout the test, and is not limited by a physiologically rigorous guideline, therefore making it more realistic to use in a sample of normal older adults, who generally do not have experience with pushing to their maximal cardiorespiratory levels.

1.5 Physical activity and Brain Health

In 2020, a Lancet dementia commission identified that an important risk factor for dementia and other late life diseases is physical *in*activity (Livingston et al., 2020a). More specifically, this committee recommended that policies that encourage PA across the life course should be developed, and that PA should be particularly maintained or initiated during midlife

and late life. In the seminal review by Colcombe and Kramer (Colcombe et al., 2004), it was identified that exercise enhances overall cerebral health and function, as well as cognition. Since this review, there has been an explosion of interest in investigating PA and exercise on cerebral health across the lifespan, with a focus on aging, given the well documented cerebral alterations and declines that occur in older adults. In fact, there has been a sufficient number of studies in humans since then to allow for a meta-analysis of longitudinal observational studies that ranged in length from 1 to 21 years showing that participating in exercise was associated with a reduction in the risk of developing dementia (Livingston et al., 2017). Others have found that moderate to vigorous intensity PA, and not just overall PA, was associated with a reduced risk of developing dementia over 25 years when completed at least weekly during midlife (Zotcheva et al., 2018). Furthermore, another study found that at least 2.5 hours of moderate to vigorous PA was associated with a reduced risk 10 years later of dementia diagnosis, though not at the 28 years follow up (Sabia et al., 2017). In fact, it has also been found that physical *in*activity has positive correlations with mortality rates in AD (Baranowski, Bott, & MacPherson, 2018; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001), demonstrating not only the importance of just participating in moderate to vigorous PA for reduction of risk of dementia/AD, but an effect of overall PA on mortality.

An assortment of physiological mechanisms has been identified that could be underlying the protective effects of PA, though specific mechanisms will be further discussed in the subsequent sections as they relate specifically to structural and hemodynamic changes since the proposed mechanisms for the benefits of PA seem to be slightly different for structural and hemodynamic outcomes. Nonetheless, it has been generally hypothesized that PA, and in particular exercise, is able to increase metabolites and myokines associated with muscular contraction, which are capable of crossing the blood brain barrier, and can modulate the function of neuronal and glial cells (Di Liegro, Schiera, Proia, & Di Liegro, 2019). Moreover, PA reduces inflammation not only peripherally, but also in the central nervous system, where exercise specifically, was able to reduce neuroinflammatory markers, decrease neuronal cell death and attenuate the production of microglia cytokines, alongside which a reduction in a beta and amyloid peptides.

1.5.1 Physical Activity and Cerebral Structure

1.5.1.1 Gray Matter Volume and Physical Activity in Aging

Much of the early work exploring PA, and exercise, on brain health was completed in cross sectional studies, investigating individuals with varying levels of cardiovascular fitness and GMV globally, as well as in relations to specific regions known to atrophy during cognitive aging, like the hippocampus. For example, seminal work by Kramer and colleagues indicated that aerobic exercise could improve executive control processes (Kramer et al., 1999). From here, it was found that those with higher cardiovascular fitness, compared to their lower fit counterparts, had significantly enhanced GMV within prefrontal and temporal regions (Burns et al., 2008; Colcombe et al., 2003) as well as larger hippocampal volume (Colcombe et al., 2003; Erickson et al., 2011). Moreover, in a study of Master Athletes (those individuals who have participated in lifelong exercise training and in sports competitively) it was revealed that compared to their inactive counterparts, Master Athletes had significant increased GMV in the right parietal lobe, occipital lobe and the cerebellum (Tseng, Uh, Rossetti, Cullum, Diaz-Arrastia, et al., 2013) They also found that a higher maximal oxygen uptake (VO_2max) was significantly related to increased GMV within the parietal lobe. Likely indicating that, as all the aged individuals in this study had significantly reduced parietal GMV compared to young adults, that higher cardiovascular fitness might attenuate some of the age-related decline in this area. Greater VO_2peak was identified to be associated with increased GMV within the superior temporal gyrus in a group of very healthy older adults, who were free of any chronic metabolic or vascular conditions and were not on any medications (Intzandt et al., 2020). Thus, even in a sample of older adults that would be considered to be those with enhanced cerebrovascular health, and thus structural integrity, greater cardiovascular fitness was associated with even further enhanced GMV.

Studies investigating the cross-sectional association between PA and GMV also identified that those that self-reported higher volumes of PA consistently demonstrated increased GMV within the frontal cortex (Flöel et al., 2010; McEwen et al., 2015; Rovio et al., 2010) and within the hippocampi (Brown et al., 2014; Demirakca et al., 2014; Killgore, Olson, & Weber, 2013). Other work extended these positive findings between PA and GMV to the inferior parietal lobe, inferior temporal region, caudate, and the putamen (Papenberg et al., 2016). In a study that PA measured by more objective outcomes, such as accelerometers which measures the actual amount of movement and the intensity of that movement (i.e., walking versus running) in a large

sample of the UK BioBank participants, greater amounts of PA were associated with increased global GMV, but only in those older than 60 years of age, not in those between 50 to 59 years of age (Hamer, Sharma, & Batty, 2018). Though it is unclear if there were any differences between these two age groups in terms of cardiovascular risk factors, sex, education, amount of time spent in PA, and the intensity of PA, as it was not reported. Particularly given that the Lancet Commission paper indicates the opposite should be the case, whereby, it should be those in midlife who benefit more from PA, rather than what was found by Hamer and colleagues. Thus, the underlying mechanism for these age group differences is unclear though conversely to the lancet commission paper again it has been reported that PA could be more beneficial or seemingly so, to those who are less healthy at baseline, and therefore have more room to gain. For example, the relationship with PA and GMV, particularly within the hippocampus, is stronger in those with mild cognitive impairment (Makizako et al., 2015) and early AD (Burns et al., 2008) compared to cognitively healthy older adults. Suggesting that PA might appear more influential on GM integrity once tissue loss has become discernible.

Studies focusing on the relationship between PA and GMV, but from a longitudinal perspective, have also found similar findings to the cross-sectional literature, albeit not necessarily as consistently. For example, it was identified that those individuals completing more than 72 blocks of walking in a one-week time span in their regular activity, had larger GMV in the frontal lobes, temporal lobes as well as the hippocampal regions at the 9 year follow up (Erickson et al., 2011). Boraxbekk and colleagues (2016) identified that baseline PA was associated with enhanced GM integrity within the bilateral posterior cingulate cortices at the 10 year follow up (Boraxbekk, Salami, Wåhlin, & Nyberg, 2016). Others have found that if PA is increased during a 4-to-6-year longitudinal assessment, it was associated with a larger increase in GMV within the left inferior orbital cortex and the precuneus (Raji et al., 2016). These results have also been extended to the hippocampus, wherein Fraser and colleagues identified that in middle aged individuals, for every increase in 10 METs per week, an increase of 0.33% for hippocampal volume was identified 12 years later (Fraser, Walsh, Shaw, Anstey, & Cherbuin, 2022). This result was also found in older adults, though, not to the same extent, where the benefits started as a 0.05% larger hippocampal volume, but this benefit was reduced by 0.005% per year. Others found that PA was not associated with GMV changes at a 2 or 9 year follow up (Binnewies et al., 2021), though importantly the age range for this study was 18 to 65 years old,

also suggesting that the effect that PA has on the GM is not evident until sufficient tissue loss has occurred, as is the case in aging. Another group identified that total energy expenditure was not associated with GMV in females in the frontal lobe 8 years after follow-up, but there was a relationship present for males. Yet for the temporal lobe, both males and females demonstrated no association between temporal GMV and energy expenditure (Yuki et al., 2012). Thus, indicating that results are likely heavily influenced by the age of participants and sex differences, which are likely influencing the association with PA and GMV in the long term.

More recent research has revealed that the reported PA intensity also influences GMV. For example, Northey and colleagues differentiated the METs associated with light, moderate and vigorous PA and observed that only moderate PA shared a positive relationship with GMV in the dorsolateral prefrontal cortex. A recent study also identified that after controlling for the amount of time spent in light intensity PA, the association between the total brain volume and moderate to vigorous PA was no longer significant (Spartano et al., 2019), indicating that in this sample there might not be further benefit from participating in higher amounts of physical activity. Though, a caveat to this interpretation is the fact that almost 50% of their sample met current guidelines, when in the general population this tends to be closer to 25% of the population. Thus, it is possible that these participants were already engaging in large amounts of activity, and it is likely that there is a ceiling effect, or a dose response effect of the amount of PA on brain health, in healthy aging populations.

The physiological mechanisms underlying these associations between PA and GMV have been investigated for decades, but the precise underlying mechanisms have yet to be fully elucidated. However, it is hypothesized that it is through a PA-mediated increase in brain-derived neurotrophic factor (BDNF) and CBF, as well as a reduction to oxidative stress and amyloid accumulation (see (Cabral et al., 2019; Chieffi et al., 2017; Lista & Sorrentino, 2010; Umegaki, Sakurai, & Arai, 2021) . Moreover, a well-established marker of neurodegeneration, neurofilament light chain, has very recently been identified to be significantly lower in the peripheral blood of physically active participants, indicating PA likely has a role in reducing neurodegeneration (Raffin et al., 2022). Figure 7 taken from Umegaki et al., provides a schematic outline of the overall hypothesized changes and cascades of effects throughout the cerebral system (Umegaki et al., 2021).

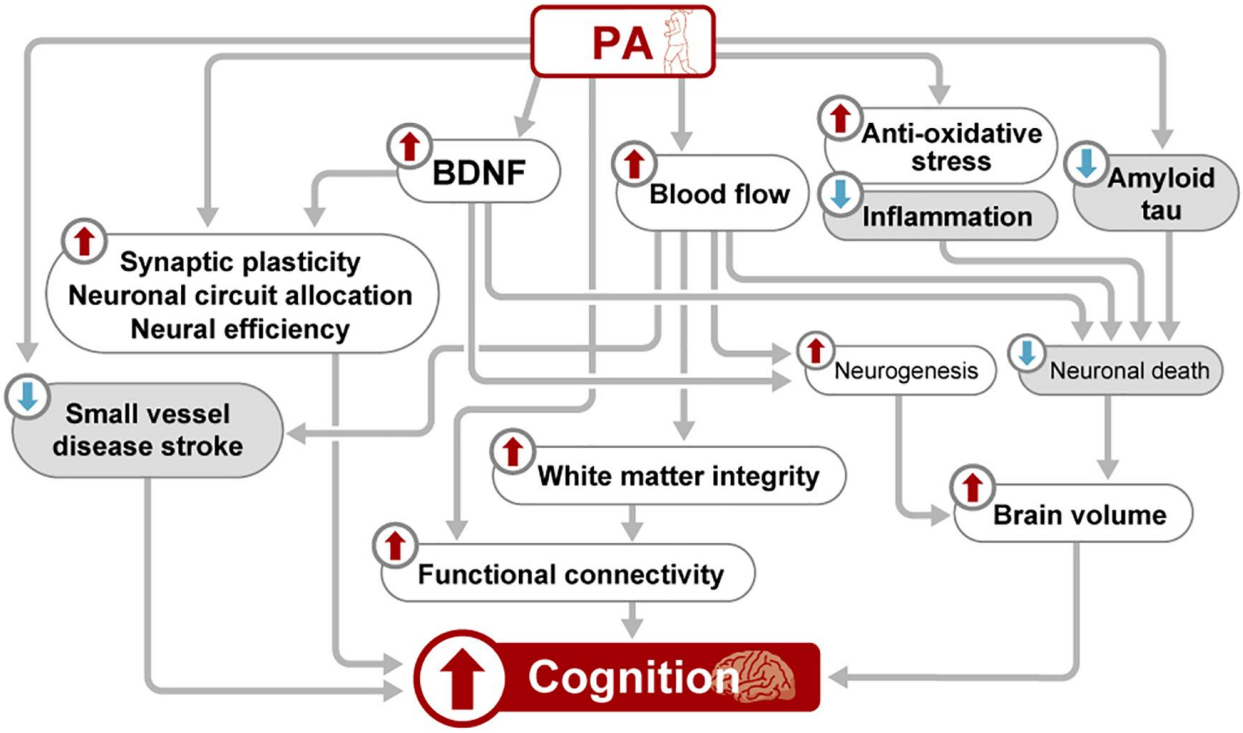

Figure 1—7: A schematic demonstrating the effects that PA has on cerebral health and how it is hypothesized to cause a cascade of positive consequences associated with eventual enhanced cognitive function. Taken from Umegaki et al., 2021

1.5.1.2 White Matter Volume and Physical Activity in Aging

A growing interest inv the relationship of WMV and PA in aging, which has generally shown beneficial effects or null relationships (Anatürk, Suri, Smith, Ebmeier, & Sexton, 2021). For example, work by Gu and colleagues (2020) identified that in a large sample of older adults, over the age of 65, WMV was positively related to PA (Gu et al., 2020). More specifically, in this study those who were meeting both the moderate-vigorous PA guidelines (>150 minutes per week of moderate to vigorous PA), and those meeting the guidelines for light PA (> 250 min per week of light PA) both had higher WMV compared to those not meeting the guidelines, showing the effect of PA to be independent of intensity. Though it is worth noting, that although the light PA guidelines were associated with enhanced WMV, those who were achieving the PA guidelines with moderate to vigorous PA showed greater benefits to WMV. These results are also consistent with data from MA showing increased WM integrity within the cuneus, precuneus and sub-gyral regions as compared to inactive controls (Tseng, Uh, Rossetti, Cullum,

Diaz-Arrastia, et al., 2013). In fact, a meta-analysis demonstrated that an overall small mean effect size was present for studies investigating the effects of PA on WM volume in aging, though it's important to note that only five papers were included in this meta-analysis (Sexton et al., 2016), three of which did not report any significant relationship between PA and WMV (Burns et al., 2008; Tseng, Uh, Rossetti, Cullum, Diaz-Arrastia, et al., 2013) (See Figure 8 for plot of effect sizes). Alongside these other studies demonstrating null results, a recent study utilizing the UK Biobank also identified a lack of relationship between WMV and PA in a large sample of over 7000 participants (Anatürk et al., 2021). Though, it is worth noting that in the study by Anaturk et al., 2021, the specificity of activities, intensity, duration, and even frequency were not appropriately captured. The overall study asked if participants went to the gym or a sports club and only differentiated their sample based on whether they went weekly, or if they went less than weekly, without any information about activities performed in other contexts than a gym. Thus, it is impossible to determine a dose response relationship from this data.

Thus, taken together, the evidence for PA having positive effects on WMV in aging is not as strong as with GMV. Given that GMV declines earlier than WMV, it is possible that for some studies the lack of a relationship is due to the WM decline not being robust enough yet to observe a difference between those who are PA and those who are not. Though beyond the scope of this thesis, investigations of microstructure are likely to provide a more sensitive marker of the effect of PA on WMV given the earlier decline of microstructural markers of WM integrity.

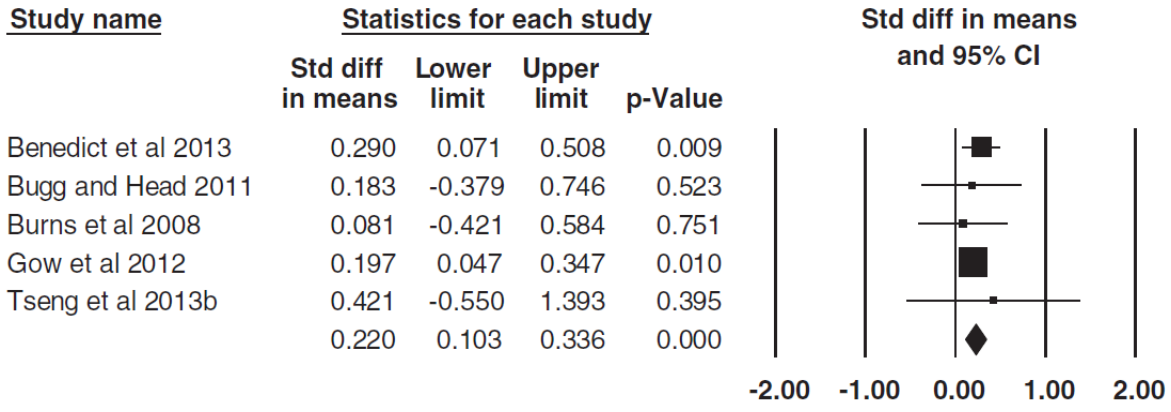

Figure 1—8: Meta-analysis by Sexton and colleagues (2016) indicating that the overall effect of PA on WMV in aging was considered to be small in the studies that met their guidelines for inclusion.

1.5.1.3 White Matter Hyperintensities and Physical Activity in Aging

It is well documented that WMH number and volume significantly increase with aging, but it has also been established, that WMH may already be present in young and middle-aged adults (see Figure 9) [(Garnier-Crussard et al., 2020)], though not to the same extent as in older adults. Thus, given that the appearance of WMH lesions tends to occur prior to global WM atrophy, it is not surprising that the relationship between WMH and PA in aging has been an area of interest for quite some time since WMH volume and number may be sensitive to the effects of PA in a crucial part of life and before widespread damage has occurred.

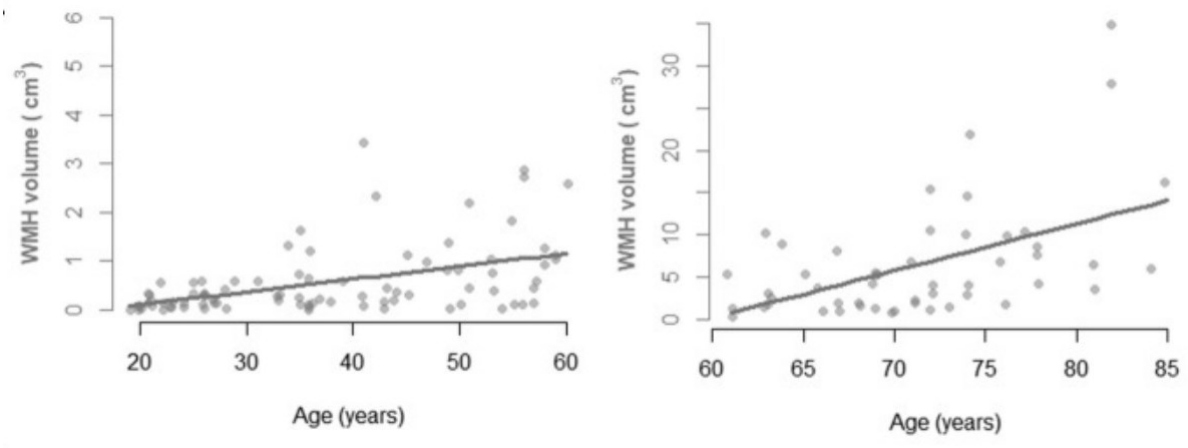

Figure 1—9: image demonstrating the presence of WMH existing in the brain of young healthy adults. Taken from Garnier-Crussard et al., 2020).

Work by Gu et al., 2020, there was an association between low PA and greater WMH volume after correcting for BMI and other comorbidities, including those that were vascular in nature, like APOE status and hypertension (Gu et al., 2020). Interestingly, old older adults (70 to 89 years of age) appear to benefit from PA compared to their inactive counterparts (Franchetti et al., 2020). More specifically, Franchetti and colleagues identified (2020) that these older adults with high PA levels had significantly lower WMH volumes than those with low PA levels, and in fact, had a volume of WMH similar to the young older adult group (50 to 69 years old)(Franchetti et al., 2020). However, there were no significant differences between the young older group with low levels of PA versus high levels of PA. These differences in WMH were found in the frontal regions, temporal lobe, and parietal lobe but not for the occipital lobe (Franchetti et al., 2020). Since the frontal lobe is particularly vulnerable to WMH during aging,

PA may be a way to reduce or attenuate development of WMH. Numerous other studies have identified the importance of higher PA levels being associated with less WMH volumes compared to those individuals who have low PA levels (Burzynska et al., 2014; Johnson, Bahrani, Powell, Jicha, & Gold, 2020; Raichlen, Klimentidis, Bharadwaj, & Alexander, 2020).

Finally, longitudinal work identified that those in their 70s who were completing more PA at baseline were less likely to experience WMH at follow-up 3 years later (Gow et al., 2012). Moreover, reduced PA was associated with increased periventricular and deep WMH in a cognitively stable group 7 years after PA was measured (Podewils et al., 2007). Others found that a 20 year follow up was not statistically significant when demographic and vascular risk factors were incorporated (Rovio et al., 2010). Finally, other studies have identified that at a six (Willey et al., 2011) and 25-year follow-up (Carmelli et al., 1999), there was no association between WMH at follow up and baseline PA. Though it is worth noting that in these studies, PA and WMH were measured at different time points, wherein PA was measured at baseline and WMH at the follow-up and it is unclear if the participants in these studies had increased, maintained, or decreased PA in the time period, though the latter is more likely as PA typically decreases across aging. This was confirmed in recent work, where Moon and colleagues identified that baseline PA and WMH were not related at baseline, but those individuals who decreased their PA during the three year follow up had a more rapid progression of WMH lesions than those who maintained their PA, and those who increased, demonstrated less progression of WMH during this three year follow up (Moon et al., 2018). Taken together, this work suggests that the complexity of the relationships between WMH and PA is dependent upon the age groups involved as well as when outcome measures were investigated.

1.5.2 Physical activity and Cerebral hemodynamics

1.5.2.1 Cerebral Blood Flow and Physical Activity in Aging

Given the positive relationship that PA and exercise has with vascular health, it is expected that these positive benefits extend to the cerebrovasculature. A number of studies have identified that with increased PA, there is also greater CBF in older adults. Some of the earliest and most convincing work comes from a study involving MA and the relationship with CBF compared to age matched inactive individuals (Thomas et al., 2013) showing that the MA had

significantly greater CBF within the posterior cingulate cortex and the precuneus. These regions are known to decline with aging and in Alzheimer's disease. Within these regions, CBF was almost 17% higher in the MA compared to their inactive counterparts, and was higher than in younger adults, though the authors do note that the overall CBF within GM was significantly reduced in MA compared to younger adults. This indicates that perhaps PA and exercise preserve CBF within these regions, offsetting the overall aging effects. Others have also found that older MA have significantly greater CBF than those who are inactive, though Tarumi and colleagues identified this to be within the occipitoparietal regions (Tarumi et al., 2015). More intriguingly is the fact that in work by Alfini and colleagues, they identified that after 10 days of cessation of exercise, MA had significantly decreased perfusion within the hippocampus, indicating what could be a robust influence of PA on CBF in an otherwise healthy aging population (Alfini et al., 2016).

Within healthy aging, and in individuals that are not considered to be MA, Tarumi and colleagues identified that in those with overall higher CVF there was a positive relationship between CVF and CBF within the occipital parietal regions. Other work revealed that within the parietal, frontal, and global regions, CBF was significantly enhanced in those with higher CVF. Notably, CBF within the hippocampus was elevated by 10 to 12% in younger and middle-aged adults 15-, 40- and 60-minutes post exercise (Steventon et al., 2020). In this work, they also looked at CVR at the same time as CBF and revealed that there were no changes in CVR after exercise. The authors hypothesized that this could indicate that exercise induced metabolic adaptive changes within the hippocampus, rather than a mechanical vascular change, as there were no changes to CVR. Interestingly, in our own work, we did not identify that CVF was significantly associated with global GM CBF in a sample of very healthy older adults (Intzandt et al., 2020). Though, it is interesting to note that work by Dougherty and colleagues revealed that CVF was related to CBF in healthy aging, but *only* in females. Thus, as in our work we did not complete a sex-disaggregated analysis, but rather investigated the relationship with sex as a covariate, it cannot be said whether our lack of relationship was driven by the males in our sample. Other work has also revealed an inverse association between CBF and CVF, particularly within the hippocampus (Olivo et al., 2021). Thus, the findings in regard to CVF and CBF are somewhat paradoxical and could reflect other physiological changes associated with greater fitness. For example, it was hypothesized by Furby and colleagues that those with greater CVF

have enhanced gas exchange at the level of the capillary bed because of greater vessel surface leading to shorter diffusion distances that have to be traveled and thus reduce the perfusion necessary as there would be more efficient nutrient exchanges occurring (Furby, Warnert, Marley, Bailey, & Wise, 2020).

1.5.2.2 Cerebrovascular Reactivity and Physical Activity in Aging

If CVR is taken to be a better measure of vascular health, then those with greater PA should have enhanced CVR as PA is known to have positive effects on vascular health. Yet, when we investigate this in older adults who are more fit, we found an inverse relationship between CVF, as measured with VO_2peak, and CVR measured during an MRI (Gauthier et al., 2013; Intzandt et al., 2020; Thomas et al., 2013). For example, Thomas and colleagues found that MA had significantly lower CVR, compared to their inactive counterparts, globally and especially within the temporal and parietal cortices (Thomas et al., 2013). Other work identified that greater CVR was associated with decreased VO_2peak within frontal regions in a group of very healthy older adults, whereas increased VO_2peak was associated with increased CVR in perivascular watershed regions (Gauthier et al., 2013). Finally, we have found that greater CVF was associated with lower CVR within parietal, temporal and frontal cortices, yet within these regions CBF was also low, indicating that these CVR findings were not due to pre dilation ((Intzandt et al., 2020) – see chapter 2 for a more in-depth description). To date, there are few studies that have investigated the effects of CVF on CVR measured with MRI, likely due to the inherent complexity and cost associated with attempting to quantify CVR in an MRI.

1.5.3 Sex Differences in the Relationships Among Cerebral Outcomes and Physical Activity

It is possible that some of these discrepancies in associations between cerebral outcomes and PA in aging are driven by sex differences, particularly as sex-specific differences have been reported to influence the effects of PA on brain health and cognition (Barha, Davis, Falck, Nagamatsu, & Liu-Ambrose, 2017). More specifically, it has been consistently identified that males and females diverge in total brain volume (Ruigrok et al., 2014), GMV (Lotze et al., 2019), WMV (Shiino et al., 2017), presence and amount of WMH lesions (Fatemi et al., 2018) as well as CBF (Aanerud, Borghammer, Rodell, Jónsdottir, & Gjedde, 2017). Differences in the

amount of PA completed by each sex (Kaplan, Newsom, McFarland, & Lu, 2001), as well as CVF (Al-Mallah et al., 2016).

1.5.3.1 Gray Matter Volume and Physical Activity: Sex Differences

There is limited research investigating the effect of sex on the relationship between PA and structural outcomes. Yet, there is work to demonstrate that in females, PA is associated with significantly greater GMV within the dorsolateral prefrontal cortex and temporal cortices, whereas the males with greater PA demonstrated more temporal lobe GMV (Castells-Sánchez et al., 2021). Barha and colleagues showed a similar association in females between PA and GMV within the dorsolateral prefrontal cortex (Barha et al., 2020). Here, it was identified that an increased amount of walking over a 10-year period was associated with this enhanced GM within the dorsolateral prefrontal cortex in females only. This positive relationship between GMV and PA in females was extended to the hippocampus (Varma, Chuang, Harris, Tan, & Carlson, 2015). Only one study to date, identified that PA was more beneficial to GMV in males within the parahippocampus (Casaletto et al., 2020), which appeared to be driven, in part, by inflammatory markers associated with exercise. Finally, a recent study revealed that there were no sex-related differences between GMV and PA (Gonneaud et al., 2022). Taken together, it appears that perhaps females, generally, might experience more beneficial effects of PA on GMV than males, though more in depth work is necessary to include other lifestyle factors, as well as immune outcomes.

1.5.3.2 White Matter Volume and Physical Activity: Sex Differences

To date, only one study has been conducted investigating differences between males and females PA levels on WMV. The FINGER study, a large randomized controlled trial to investigate the effects of multidomain interventions including diet and PA on brain health, identified that neither males nor females demonstrated a significant relationship between CVF and WMV (Pentikäinen et al., 2017).

1.5.3.3 White Matter Hyperintensities and Lesions and Physical Activity: Sex Differences

Few studies have been completed in regard to sex differences and relationships between PA and WMH lesions. However, in a 6 month long aerobic exercise RCT, it was found that

males had significantly less WMH burden after the intervention than females, even though baseline WMH burden was similar, potentially indicating that an exercise intervention was more effective at reducing the progression of WMH in males (Dao et al., 2019). Conversely, work by Vesperman and colleagues revealed that CVF was more beneficial to females in attenuating age-related WMH lesions (Vesperman et al., 2018). Finally, one group identified that in fact neither males nor females experienced beneficial effects on WMH lesions due to CVF levels (N. F. Johnson et al., 2020).

It is important to note that for all macrostructural studies to date, much of the heterogeneity and discrepancies in results between males and females reported could be driven by an assortment of factors, but most notably due to the physical construct utilized, i.e., PA versus CVF versus exercise interventions. Unfortunately, due to the lack of research in this area it was not possible to provide a holistic overview of each construct of physical health in relation to exercise, thus much work is needed in this area to parse the unique contributions PA, CVF and exercise interventions have on cerebral structure in males versus females.

1.5.3.4 Cerebral Blood Flow and Physical Activity: Sex Differences

To date, only one study has investigated the interactive effects of sex on CBF and PA in older adults. More specifically, they found that there were perfusion differences in the precuneus and posterior cingulate cortex, whereby an increase in PA in females was associated with greater perfusion in these regions, compared to males who demonstrated no association [(Gonneaud et al., 2022)] (See figure 10). It is important to note that in this work there were no sex-specific differences in the levels of PA reported.

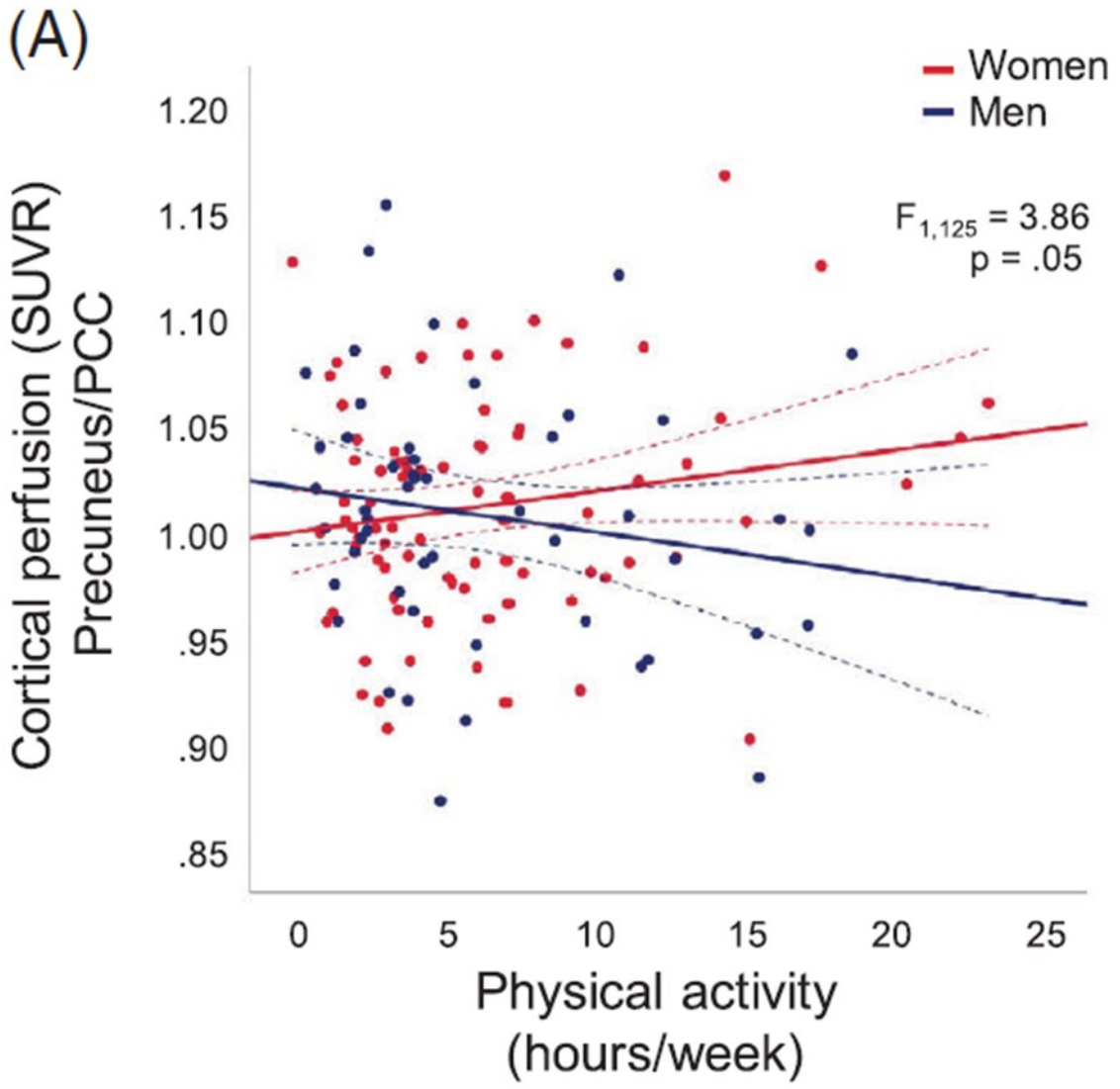

Figure 1—10 Gonneaud and colleagues demonstrating females experiencing greater perfusion than males with increasing PA, in the precuneus and posterior cingulate gyrus.

1.6 Obesity and Brain health in aging

Obesity is associated with a cascade of negative consequences, including to cerebral outcomes especially when combined with increased vascular risk and in aging. For example, a large meta-analysis that incorporated over 1.3 million participants demonstrated that greater body mass index (BMI), an indirect marker of obesity, was associated with a greater risk of dementia 20 years later (Kivimäki et al., 2018). Furthermore, some data indicates that midlife obesity may be more detrimental to brain health as compared to obesity in older age (Fitzpatrick

et al., 2009; Ronan et al., 2016), although this finding has been inconsistent (see (Pedditizi, Peters, & Beckett, 2016) for an in depth review).

There is not one underlying mechanism of action for the negative consequences of obesity in general on brain health. Yet leptin has become a particular focus of the relationship between obesity and the brain. Briefly, in normal concentrations, leptin has beneficial effects in the body, acting as a satiety hormone, promotor of fat oxidation, and is capable of freely crossing the blood brain barrier (Forny-Germano, De Felice, & Vieira, 2019). Once in the brain, the effects of leptin include neurogenesis, neuroprotection and is associated with enhanced memory (Arnoldussen, Kiliaan, & Gustafson, 2014). However, in individuals with obesity, leptin resistance has been identified within the brain (Eikelis, Wiesner, Lambert, & Esler, 2007; Izquierdo, Crujeiras, Casanueva, & Carreira, 2019), and the blood brain barrier becomes less permeable to leptin (Mantzoros, 1999). Thus, the protective effects that were observed when leptin was present in normal concentration are diminished. This is just one proposed mechanism for the relationship between obesity and diminished brain health, for more in-depth discussions see (Arnoldussen et al., 2014; García-García, Michaud, Jurado, Dagher, & Morys, 2022; Stillman, Weinstein, Marsland, Gianaros, & Erickson, 2017).

1.6.1 Structural outcomes and Obesity in Aging

1.6.1.1 Gray matter Volume and Obesity in Aging

Early work by Pannacciculi and colleagues (2006) identified that obese individuals had significantly decreased GMV within post central gyrus, frontal regions and putamen compared to their normal weight counterparts (Pannacciulli, Le, Chen, Reiman, & Krakoff, 2007). Follow up work revealed that these inverse relationship between BMI and GMV are present in frontal (Dake et al., 2021; Raji et al., 2009; Walther, Birdsill, Glisky, & Ryan, 2010), occipital (Dake et al., 2021), and subcortical regions (Dake et al., 2021; Raji et al., 2009; Walther et al., 2010) . A recent meta-analysis confirmed these results revealing that increased BMI was associated with significantly decreased GMV, putatively driven predominantly by the obese group rather than the overweight group (Han et al., 2021). Other work has also shown that increased BMI is associated with decreased GMV in the hippocampi (Raji et al., 2009; Walther et al., 2010), which is of particular importance as hippocampal GMV has a well-defined relationship with

episodic and relational memory outcomes and has been implicated in the risk of developing cognitive decline in healthy older adults (Gorbach et al., 2017). Importantly, cognition has been found to be influenced by the relationship between GMV and obesity. For example, it was revealed that those with higher BMI had lower GMV within the orbitofrontal region, and that this regional GMV was associated with better executive functioning, memory in the cerebellar regions, while visuomotor speed was associated with fusiform gyrus GMV (Walther et al., 2010). Thus, there is now convincing evidence of the negative consequences of obesity on GMV, and that these effects on GMV have a downstream impact on cognition.

However, it is important to note that in the work by Pannacciculi it was not only observed that there is an inverse relationship among GMV and BMI, but they also found that there were significant positive (Huang et al., 2019) association between GMV and increasing BMI within numerous frontal, cerebellar and subcortical regions (Pannacciulli et al., 2007). These same observations of greater GMV with higher BMI have also been revealed in other work, where Taki and colleagues identified while increased BMI was associated with GM atrophy in some regions, yet other regions revealed positive associations with GMV and BMI (Taki et al., 2008). Interestingly, these results were only observed in their male participants, whereas there appeared to be no relationship between GMV and BMI within the females. These sex-specific relationships among GMV and BMI were confirmed in other recent work, where only males experienced a significant decline to GM with increasing BMI (Huang et al., 2019; Arnoldussen et al., 2019), but no relationship in females. Here, they also identified that there was a BMI x sex interaction, where males had significantly *increased* GMV in the anterior cingulate cortex. To date, it is unclear the underlying mechanism for the apparent sex differences in the relationship between GMV and obesity, although work by Horstmann et al., revealed that, in females only, leptin influenced the relationship between GMV and obesity (Horstmann et al., 2011). Given that females produce more leptin based on their fat distribution, it is possible that females are more leptin-responsive within the brain (Lovejoy, Sainsbury, & Group, 2009). More specifically, as they possess greater leptin due to increased body fat, it could be seemingly protective for females, knowing the role that leptin has on brain health (Forny-Germano et al., 2019).

1.6.1.2 White matter volume and Obesity in Aging

Those with greater BMI have been found to have significantly increased WMV throughout the brain, compared to those with lower BMI. More specifically, Haltia et al, 2007 investigated the relationship between obese and normal weight individuals and they identified that those with obesity has significantly increased WMV within the temporal lobe, cerebellum, and brainstem (Haltia et al., 2007) . Others also found this relationship but in females only, where Increased BMI was associated with greater WMV globally (Driscoll et al., 2016), but also in frontal (Driscoll et al., 2016; Walther et al., 2010), temporal (Driscoll et al., 2016; Walther et al., 2010), parietal (Walther et al., 2010) and occipital regions (Walther et al., 2010). Notably however, a few studies also revealed no relationship between BMI and WMV (Debette & Markus, 2010; Gunstad et al., 2008; Soreca et al., 2009). These lack of associations with obesity and WMV, were also extended to cognitive functions, where executive function and memory did not relate to WMV in those with obesity (Walther et al., 2010). Taken together, it appears there is a paucity of work investigating WMV and obesity outcomes, though in females at least, obesity may have positive effects on WMV. More in depth and large-scale studies are required to make any definitive conclusions.

1.6.1.3 White matter hyperintensities and Obesity in Aging

Studies probing the associations between WMH, and BMI have revealed inconsistent results, and the results found are likely influenced by sex-related analyses. For example, work by Windham and colleagues (2017), without investigating sex-specific relationships, revealed that increased BMI was associated with decreased presence of WMH lesions (2017), and increasing BMI across the approximate five year follow up period did not relate to a greater number of lesions present (Windham et al., 2016). Five studies in females have revealed three contradictory findings. In one study, those females with increased BMI at the age of 70 had significantly greater WMH burden at age 85 than those with lower BMI (Gustafson, Steen, & Skoog, 2004). Two other studies revealed no associations in females between BMI and WMH (Alqarni et al., 2021; Arnoldussen, Gustafson, Leijsen, de Leeuw, & Kiliaan, 2019; Lampe et al., 2019), and the women's health initiative study revealed an inverse association between BMI and WMH (Driscoll et al., 2016). These varying results could be related to differences in sample sizes, age ranges included, and prevalence of cardiovascular risk factors. Finally, one study to date has

explicitly investigated these relationships in males, where Alqarni et al., identified that only males had a positive relationship with BMI and WMH (Alqarni et al., 2021).

Taken together, the relationships that exist between obesity and structural outcomes have high heterogeneity which seem to be heavily influenced by sex, however more work employing sex-specific analyses are necessary to parse apart these relationships

1.6.2 Cerebral Hemodynamics and Obesity

1.6.2.1 Cerebral Blood Flow and Obesity In Aging

A handful of studies to date have begun to investigate the effects of obesity on cerebral hemodynamics with fairly consistent results being reported. More specifically, Képes et al, found in a sample of middle-aged individuals (mean age 53.5) that those with increasing BMI had decreased perfusion within the brainstem (Képes et al., 2021) . These results were confirmed in other areas by other groups including global GM (Knight et al., 2021), parahippocampal and temporal regions (Amen, Wu, George, & Newberg, 2020; Dake et al., 2021; MacIntosh et al., 2020), frontal lobes (Dake et al., 2021; MacIntosh et al., 2020), parietal lobes (Amen et al., 2020; MacIntosh et al., 2020) as well as the posterior cingulate cortex and the precuneus (Amen et al., 2020). Interestingly, one group quantified this relationship and found that for every 1 kg/m^2 increase in BMI there was a 1.45 ml/100g of GM/ min reduction to perfusion. Interestingly, when Dake et al., 2021 extracted CBF from their ROIs in the frontal and occipital areas that demonstrated these inverse relationships between BMI and perfusion, and identified that those with lower CBF, had decreased performance on cognitive tasks involving memory and reasoning (Dake et al., 2021). However, work by Clark and colleagues revealed that after correcting for the false discovery rate, the model relating BMI and perfusion was no longer significant in their middle aged and older adult sample (Clark et al., 2019). Of all of these previously mentioned studies investigating relationships between BMI and perfusion, only Knight and colleagues completed a sex-disaggregated analyses and found that sex did not influence the relationship between obesity and perfusion (Knight et al., 2021). Though it is unclear if sex-disaggregated analyses were employed, or if sex was added as a potential outcome a statistical model.

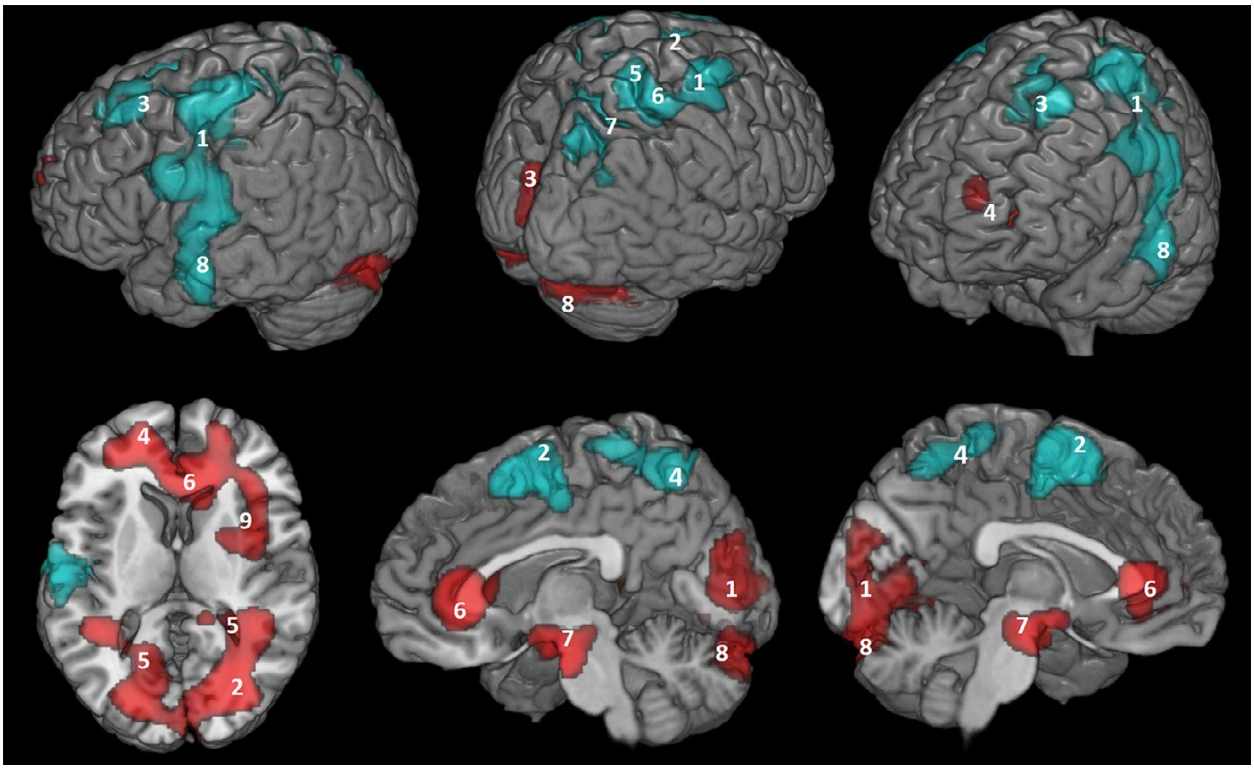

Figure 1—11: Brain regions demonstrating increased CBF in females with obesity (in red) and those regions that demonstrated a significant decline of perfusion in those with obesity in a female only sample. Taken from Silvah et al., 2020. Red areas are those with increased CBF in the females with obesity and blue are regions that were associated with decreased CBF in females.

In work that investigated the relationship between obesity and perfusion in females only, Silvah and colleagues confirmed that there are some regions with a lower CBF with increased BMI, particularly within the frontal regions, temporal regions such as the superior and medial gyri and much of the parietal lobes (Silvah et al., 2020). However, they also demonstrated significantly greater CBF within the dorsolateral prefrontal cortex, throughout the frontal lobe, amygdala, hippocampi, superior temporal gyri, occipital lobe, and limbic lobes (see Figure 11). Thus, it is possible that if previous work had investigated sex-specific relationships between these outcomes, regions demonstrating positive relationships would have been identified. Future work is necessary to further investigate this possibility.

Overall, the studies investigating the relationships between obesity and structural outcomes provide a mixed picture, with some positive and some negative regional relationships, which may be greatly affected by sex. Conversely the literature in perfusion seemingly indicates that those with obesity have significantly declined perfusion throughout the brain, though it is

possible that females demonstrate hyperperfusion patterns with increasing BMI in certain regions of the brain. Further studies are needed to confirm these findings.

Importantly, obesity is not simply defined just by excess fat, but the type and location of adipose tissue also impact its deleterious effects. Briefly, it is known that adipose tissue that is stored in the femoral regions tends to be comprised of subcutaneous adipose tissue, which is not as harmful to the overall vascular system as fat that is stored more in the abdominal regions, which also tends to be comprised of more visceral adipose tissue. Visceral adipose tissue is consistently documented to have more inflammatory and toxic consequences for the body (Chait & den Hartigh, 2020), as well as the brain (Debette et al., 2010). Given that males tend to possess a greater amount of visceral fat than females (Grauer, Moss, Cann, & Goldberg, 1984), whereas females tend to have more subcutaneous fat storage, it is important that future work investigate sex-specific relationships of obesity on brain health. It is likely that fat type, through its influence on inflammation, rather than the overall fat, is an important contributor to these brain-obesity relationships.

1.7 Interaction of Obesity and Physical activity

For decades, PA has known to protect against the negative consequences of obesity on overall health, including reducing the risk of mortality, where those individuals with obesity who have higher PA, have significantly reduced risk of death compared to their inactive obese counterparts (Tarp et al., 2021). PA has also been found to be a mediator of the relationship between cognition and obesity, whereby those with obesity had poorer cognitive outcomes, but this relationship was attenuated by greater PA (Dore, Elias, Robbins, Budge, & Elias, 2008). Participants reporting a higher level of PA but who were overweight had a significantly lower risk of cognition declining over a three-year time span, based on the results of the Mini-Mental State Exam, which is a test of global cognitive functioning, where lower scores indicate worse cognition. These findings were in comparison to older adults who were normal or underweight at baseline (Pitrou, Vasiliadis, & Hudon, 2022) (see Figure 12). Conversely, in those reporting low PA, there was no association with BMI three years later and cognitive decline, except in those underweight at baseline.

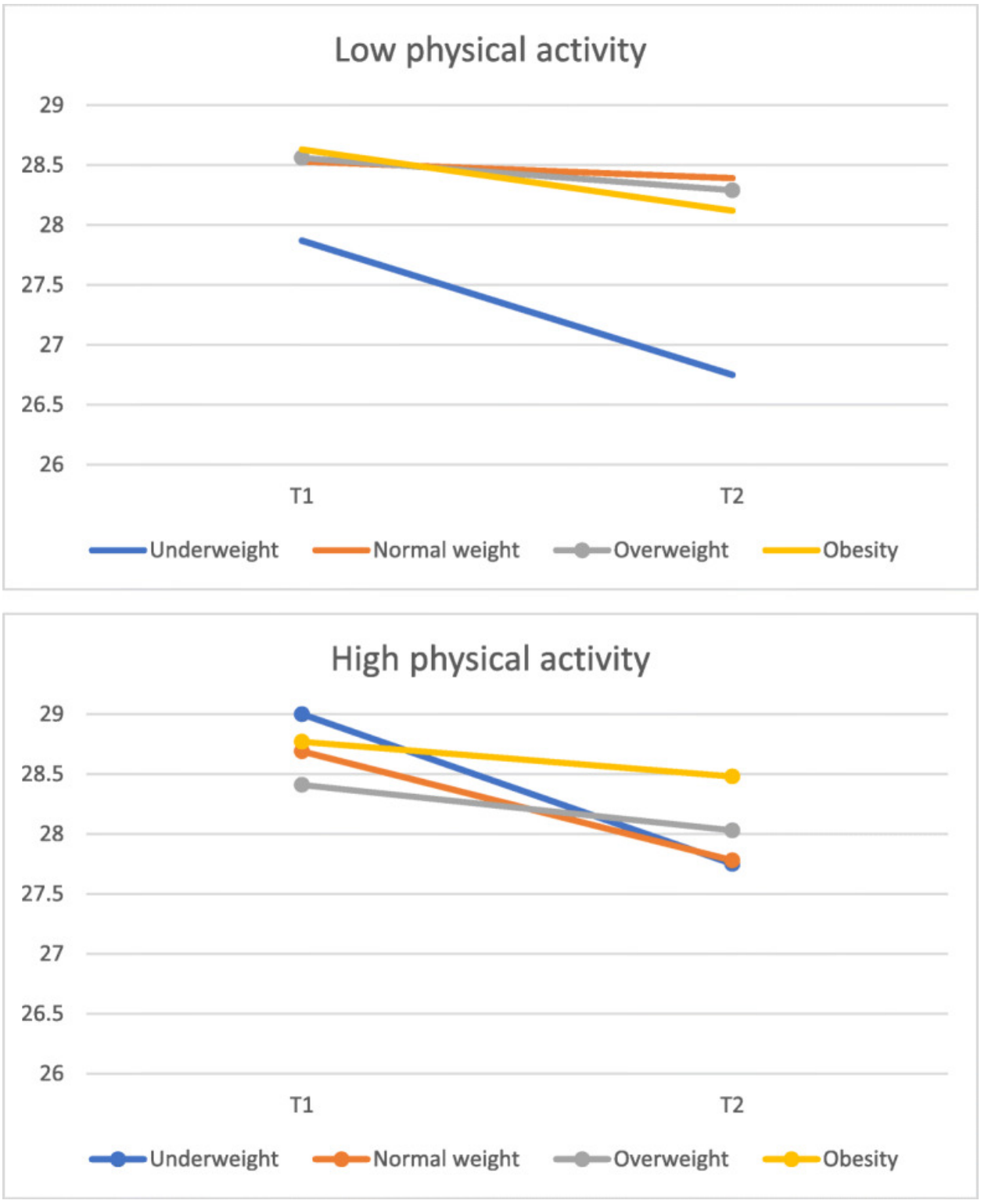

Figure 1—12: Graphical depiction of the association between those with low PA (upper graph) and those with high PA (lower graph), from baseline (T1) to a three year follow up (T2). Results indicated that individuals with high PA at baseline and who were overweight or obese had less decline to global cognition at follow up than their underweight or normal weight counterparts. In those with low levels of PA, there were no

differences between normal weight, overweight or obese individuals, however those who were underweight experienced a significant decline to global cognition at the three year follow up. Figure adapted from Pitrou et al., 2022.

To date, only one study has explicitly investigated the mediating role that PA might have on the relationship between obesity and cerebral health in aging. More specifically, recent work by Knight and colleagues revealed that those older adults that were considered to be overweight and obese, but had higher levels of PA, compared to their inactive counterparts, had significantly higher CBF. Given that obesity and exercise share some mechanistic effects on inflammation for example but have different effects on vascular health and endocrine components, this lack of work on the interaction between obesity and exercise represents a missed opportunity for the field on brain physiology and studies of aging. Future studies are urgently needed to systematically investigate the effects of obesity and exercise, and how they interact to affect brain health in aging. And crucially, these studies should investigate these effects in sex-disaggregated data to understand how male and female physiology may be differently impacted across the lifespan.

1.8 Gaps in the Literature and the Framework for this Thesis

Overall, there has been an abundance of work highlighting the importance of physical activity and exercise for brain health in aging. Yet, there are still many unanswered questions related to their physiological effects on the brain, how these effects may differ in males and females, and how these effects combine and interact with obesity. This thesis addresses these important gaps in the literature.

1.8.1 Chapter 1 Rationale

It is becoming well established that exercise training in older adults has positive effects on brain health and cognition (Colcombe et al., 2006; Herold, Törpel, Schega, & Müller, 2019; Intzandt et al., 2021). But the effects of exercise training on cerebral outcomes that can be measured non-invasively using MRI in aging have not been systematically compared to another commonly utilized non-pharmacological intervention, cognitive training,. To address this gap in knowledge, manuscript one of this thesis is a systematic review that investigates, details, and compares all studies to date that included an exercise and/or cognitive training intervention in cognitively healthy older adults and employed MRI outcomes prior to and after the intervention

measure changes due to the intervention. This provided the theoretical framework for subsequent chapters in the thesis to further comprehend how exercise and physical activity influence brain health in different samples of cognitively healthy older adults. Of note, this review highlighted an important heterogeneity in the results of studies seeking to quantify the effects of exercise. However, as several crucial factors were typically not taken into account, such as sex and obesity. Therefore, this study lay the groundwork for the original scientific work of this thesis seeking to identify the specific relationships between cerebral outcomes and influential factors like sex or obesity and how PA can influence these interactions. The aim of this work is to broaden the extant research to aid in the design of the efficacious forms of exercise interventions depending upon important parameters like sex or obesity to maintain or enhance cerebral health into aging

1.8.2 Chapter 2 Rationale

It was noted that based on the systematic review, that much work had been completed in individuals who were highly fit and had been for the entirety of their adult lives, known as Master Athletes, or in those who had numerous comorbidities. It was of interest to investigate a sample of very healthy older adults with no pre-existing conditions, unmedicated, and active but not at the Master Athlete level, to further understand the role that cardiovascular fitness has on cerebral health in the absence of other factors or conditions that could also have an influential role on brain health. To address these questions, Chapter two compares cerebral health outcomes in healthy older and younger adults.

1.8.3 Chapter 3 Rationale

Another gap that was identified in the literature was the potential for sex-specific differences in the relationship between cerebral health and PA. In addition to these direct effects of sex, the added influence of other outcomes known to have detrimental consequences for brain health and known to show sex-specific differences, in particular obesity, was not systematically addressed in the literature. Obesity was of importance as the incidence of obesity continues to rise in Canada, where 63.1% of the population over the age of 18 is considered to be overweight or obese, a number which rose by almost 2% in a three-year time period (Government of Canada, 2019). With a global pandemic occurring since the last statistics Canada census it is likely that given reduced access and ability to participate in PA (Dai et al., 2021; Knell, Robertson, Dooley,

Burford, & Mendez, 2020), a reduction in the number of daily activities (Knell et al., 2020), greater amounts and poorer food intake (Bennett, Young, Butler, & Coe, 2021), overweight and obesity levels have continued to rise significantly since. This highlights the importance of understanding if there are sex-specific differences due to varying BMI on brain health in older adults, and whether PA can mitigate these relationships in both males and females. This question is the underlying rationale of Chapter three of this thesis.

1.8.4 Chapter 4 Rationale

There is an increasing recognition that midlife is a crucial time, rather than just older age, for factors like obesity and PA to impact cerebral health. However, no study to date has comprehensively investigated the sex-specific relationships between PA and cerebral blood across the middle and older lifespan. Therefore, we sought to address these limitations in Chapter four by investigating the effects of PA on brain health over a larger age range encompassing both midlife and older age. This will contribute to our understanding of whether there are stronger relationships between PA and cerebral health at certain age ranges, and if these differ for males versus females.

2 Manuscript 1: Comparing the effect of Cognitive vs Exercise Training on Brain MRI outcomes in healthy older adults: a Systematic Review

This manuscript was published in Neuroscience and Biobehavioral Reviews (DOI:10.1016/j.neubiorev.2021.07.003 (Intzandt et al., 2021)). Brittany Intzandt, Tudor Vrinceanu, Julia Huck, Thomas Vincent, Manuel Montero-Odasso, Claudine J Gauthier and Louis Bherer.

2.1 Preface

It has been established that part of age-related cerebral declines can be reduced with non-pharmacological lifestyle strategies. A primary lifestyle intervention for the enhancement of cerebral health in aging is exercise training, as exercise has positive effects on brain health and cognition in older adults (Colcombe et al., 2006; Intzandt et al., 2021). Another common strategy to enhance cerebral functioning in aging with demonstrated positive results is cognitive training (Belleville & Bherer, 2012a; Butler et al., 2018). To date, the majority of cognitive training studies have yielded positive results, mostly involving cerebral structural enhancements, in particular volumetrics and microstructural changes (Belleville & Bherer, 2012a; Ten Brinke, Davis, Barha, & Liu-Ambrose, 2017). Exercise training has also been associated with significant improvements in volumetrics, and functional changes (Colcombe et al., 2004; Halloway, Wilbur, Schoeny, & Arfanakis, 2017; Sexton et al., 2016). It is clear that both cognitive and exercise training in isolation are capable of improving cerebral structure and function in healthy older adults. However, it is not well studied, or understood if one modality is superior to the other for enhancing overall cerebral health, or specific health markers like volumetrics or CBF. Studies directly comparing these non-pharmacological interventions would create a more in-depth knowledge base of the relative impact of each training modality on brain health and could form the framework in the design of future training programs to maximize their cerebral benefits in aging.

Therefore, manuscript one presents a systematic review of the literature comparing the effects of exercise training and cognitive training interventions on cerebral health as measured with MRI. The overall aim was to describe, detail, and synthesize the current literature that involved cognitive training *or* exercise training that employed all forms of MRI sequences

including, but not limited to, volumetrics, microstructure, connectivity, resting state, change to the blood-oxygen level dependent signal, as well as cerebral hemodynamics.

2.2 Abstract

Aging is associated with cognitive decline. Importantly cognition and cerebral health is enhanced with interventions like cognitive (CT) and exercise training (ET). However, effects of CT and ET interventions on brain magnetic resonance imaging outcomes have never been compared systematically. Here, the primary objective was to critically and systematically compare CT to ET in healthy older adults on brain MRI outcomes. A total of 38 studies were included in the final review. Although results were mixed, patterns were identified: CT showed improvements in white matter microstructure, while ET demonstrated macrostructural enhancements, and both demonstrated changes to task-based BOLD signal changes. Importantly, beneficial effects for cognitive and cerebral outcomes were observed by almost all, regardless of intervention type. Overall, it is suggested that future work include more than one MRI outcome and report *all* results including null. To better understand the MRI changes associated with CT or ET, more studies explicitly comparing interventions within the same domain (i.e., resistance vs. aerobic) and between domains (i.e. CT vs. ET) are needed.

2.3 Introduction

The population of older adults is increasing worldwide (Bohnert et al., 2015). According to the United Nations, it is projected that nearly 30% of developed countries' populations will be comprised of older adults by 2030 (United Nations, 2020). This presents health care systems and societies with important challenges due to declines in health that occur during the aging process. For example, the aging vascular system undergoes a cascade of changes that negatively affects the cerebrovascular system, leading to decreases in cerebral perfusion (Asllani et al., 2009; Chen et al., 2011; Parkes et al., 2004; Zhang et al., 2017). Given that continuous blood flow is necessary to maintain structural integrity and neuronal activity (Erecińska & Silver, 1989b), decreased perfusion has been related to declines in cognition (De Vis et al., 2018; Staffaroni et al., 2019; Xekardaki et al., 2015). Moreover, aging not only impacts cerebral perfusion, but also causes structural (Aljondi et al., 2019; Lockhart & DeCarli, 2014) and functional changes (Sugiura, 2016), which are also related to cognitive decline (Aljondi et al., 2019; Lockhart & DeCarli, 2014). These declines in cognitive functioning tend to be observed most prominently within executive functions, likely due to the fact that the frontal regions of the brain are very susceptible to low cerebral perfusion and are affected early in the course of aging (Cardenas et al., 2011; Moscovitch & Winocur, 1992a; West, 1996). Declines in executive functioning can impact working memory, divided attention, episodic memory and processing speed (Cabeza et al., 2016). The declines in executive functions have also been shown to predict memory decline (Carlson et al., 2009), further global cognitive decline (Clark et al., 2012), future functional decline (Johnson et al., 2007), and even increased mortality (Gross et al., 2016).

It is now established that part of age-related cognitive decline and dementia can be reduced, or delayed, through non-pharmacological lifestyle interventions, such as cognitive stimulation, physical exercise, social networking, and control of vascular risk factors, to name a few (Livingston et al., 2020b; Montero-Odasso, Ismail, & Livingston, 2020). However, there is still a relative lack of knowledge on *how* lifestyle factors protect against cognitive decline and impact the underlying cerebral structure and function. Among all lifestyle activities known to protect again cognitive decline, the strong evidence is in favor of physical exercise, and cognitive stimulation (Daffner, 2010). Those two types of interventions tend to be easier to isolate and study in a randomized controlled trial format. Moreover, the primary mechanism of action for these two types of lifestyle interventions have been suggested to be through the enhancement of

neuroplasticity. Neuroplasticity refers to the process by which the brain adapts to the impact of age or aging-related chronic diseases such as dementia, through changes in structure, physiology, connectivity and function (Zilles, 1992). Therefore, comparing side by side their impact on MRI outcomes reflecting neuroplasticity would help clarify if, and potentially what, common mechanisms are at work.

CT has been utilized for the enhancement of cognitive functioning, with a large extant literature investigating this subject in older adults alone. CT involves guided practice and feedback that is cognitively challenging, including increasing the difficulty as the program progresses, for an individual on standardized tasks that involve specific cognitive domains such as executive functions, attention, language or memory (Valenzuela & Sachdev, 2009). While there are currently no standardized principles which guide a CT program, there are numerous aspects that are possible to be manipulated to enhance the learning experience of the participants (Schubert et al., 2014). First, the type of parameters that can be modified in a CT program depend on the cognitive function trained. For example, a specific training program aimed at improving working memory, like the n-back, (i.e., single domain) has fewer parameters that can be altered to personalize the training program rather than a general cognitive training program (i.e., multi domain) which targets multiple cognitive functions in the same program (e.g., memory, processing speed, etc.). Despite this, the difficulty of CT can be increased by augmenting the cognitive load or shortening the practice reaction time window. The trained modality can be manipulated or combined. For example, certain CT programs like dual tasking, are combining multiple modalities (i.e., auditory, visual, motor) as part of the training program. Indeed, the dosage and duration of the CT can also play a role with very short programs not being as efficient and potentially very long ones reaching a plateau. Finally, the efficiency of a CT program can be assessed by observing an improved performance in the trained task, a task that is slightly different (near-transfer) or significantly different (far-transfer) than the trained task (Noack et al., 2014; Schubert et al., 2014).

To date, inconsistencies in brain outcomes measured using magnetic resonance imaging (MRI) have been reported for structural and functional changes after CT in healthy older adults. Thus far, it seems that there are more changes documented within structural as compared to functional outcomes. However, it is generally assumed that CT is capable of improving both

structural and functional outcomes in aging (ten Brinke et al., 2017). Furthermore, positive macrostructural changes reported in the literature following CT involve grey matter volume, cortical thickness, and enhanced white matter integrity (Belleville & Bherer, 2012). CT-related functional changes include a decrease in activation in certain areas, posited to indicate a change in neural efficiency (Belleville & Bherer, 2012). However, these findings are not always reproduced, likely due to the heterogeneous nature of the interventions, (i.e., length of intervention; interventional sessions per week; MRI sequences used), making the interpretation of these findings difficult.

ET has also become widely investigated, with several meta-analyses published in the past few years (Falck et al., 2019; Sansano-Nadal et al., 2019; Sherrington et al., 2019). ET refers to utilizing a group of muscles maintained for a period of time with the intent of improving cardiovascular fitness and/or muscular strength, endurance or power in a planned or structured program (Caspersen et al., 1985). It should be noted that ET programs tend to be guided by the FITT principles (Garber et al., 2011), characterized by their frequency (number of weekly sessions); intensity (i.e., % of maximum heart rate or % of heart rate reserve); time (minutes or hours per session per week) and type of training (i.e., aerobic; resistance or flexibility)**.** Seminal work by Colcombe and colleagues (2004) revealed that ET was capable of enhancing functional brain outcomes (Colcombe et al., 2004). More specifically, participants in the ET group showed a significantly increased BOLD signal during a Flanker task in attentional areas of the brain and decreased activation in the anterior cingulate cortex compared to those in a control group. Importantly, ET has been shown to have beneficial effects on structure as well, where it has been illustrated to prevent decline of, and in some cases increase white matter volume (Best, Chiu, Hsu, Nagamatsu, & Liu-Ambrose, 2015; Bolandzadeh et al., 2015; Colcombe et al., 2006). Notably, at a time of forced confinement, like during the COVID-19 pandemic, several papers have identified the importance of physical exercise for psychological, cognitive and physical health has resurfaced as paramount from a preventive health perspective (Ammar et al., 2020; Besnier et al., 2020; Letieri & Furtado, 2020). It is important to note however, that much like CT, regardless of MRI outcome, the results of ET studies have shown limited reproducibility, again likely explained by the high heterogeneity of the training protocols and type of outcome used to assess changes.

Magnetic resonance imaging (MRI) is now wildly employed to assess age-related cerebral changes in structure and function. MRI is a versatile imaging technique that is able to measure numerous outcomes that are affected by aging, such as grey and white matter volume, connectivity between structures, indicators of myelin integrity, and cerebral blood flow. As individuals age, overall global cerebral volume is reduced, with the most pronounced reductions taking place in the frontal and temporal lobes (DeCarli et al., 2005). In addition to volume, aging has also been associated with a reduced integrity of the white matter tracts, often observed in frontal areas (Park & Reuter-Lorenz, 2009; Salat, 2011). These tract alterations are caused by microstructural white matter changes, in particular decreases to fractional anisotropy, and increases to mean diffusivity, as well as declines to other measures of diffusivity, also often observed in frontal regions (Abe et al., 2002; Hsu et al., 2010; Ota et al., 2006; Salat et al., 2005). These frontal regions also demonstrate the fastest reductions in cerebral blood flow (Pantano et al., 1984; Zhang et al., 2018), but declines in perfusion have also been consistently identified in the temporal and parietal lobes as well (Chen et al., 2011; Gauthier et al., 2013; Parkes et al., 2004).

Several studies have completed systematic reviews investigating the effects of ET on brain structure and functions in healthy older adults (Halloway et al., 2017; Sexton et al., 2016) and one has been published for CT in healthy older adults (ten Brinke et al., 2017). It is evident that CT and ET are capable of enhancing brain structure and function in healthy older adults, yet it is currently not well studied if either modality of lifestyle intervention is superior to the other for improving these outcomes, as only one study to date has compared the effects of ET to a CT intervention with MRI as the primary outcome (Chapman, Aslan, Spence, Keebler, et al., 2016). More specifically, they found a significant increase in CBF after the CT intervention, whereas the ET group did not demonstrate a statistically significant change. Therefore, more studies directly comparing these lifestyle interventions would allow for further understanding of the relative impact of each training modality on brain health and provide more information about what future training programs should focus on to maximize their cerebral benefits in aging. By further studying CT and ET interventions in isolation, with the use of advanced MRI techniques (Tardif et al., 2016), we can gain a better understanding of their underlying mechanisms of action in isolation. Moreover, although the investigation of other lifestyle interventions that are relevant to cognitive health in aging are warranted, CT and ET have been the most extensively studied in

the aging literature, providing a more robust body of literature. Other preventive lifestyle factors known to have a protective effect for cerebral health, such as diet or social networking, tend to often be conducted alongside CT or ET, and are less often isolated and studied in relation to MRI outcomes. Thus, the present review also focused on ET and CT because they can be similar in terms of theoretical framework and experimental approach, meaning that they can be administered in the form of a training program. Moreover, the present review hopes to identify specific training components that might be more successful at predicting MRI enhancements. Thus, allowing us to detect specific training components that might be more effective at improving cognition and perhaps reducing the risk of developing age-related cognitive decline.

Therefore, the purpose of this systematic review is to compare the effects reported in intervention studies involving CT or ET on brain health measured with MRI. Here, we aim to describe the literature encompassing CT *or* ET studies from different aspects of MRI including macrostructural, such as volumetric outcomes of grey and white matter, as well as microstructural, such as diffusion weighted imaging, and functional outcomes, as in task-related BOLD changes, resting state functional connectivity or perfusion differences. That being said, although interventions including a combination of both CT *and* ET do have their merit, it is important to first understand how each intervention, in isolation, is potentially improving cerebrovascular health and cognition in older adults.

2.4 Methods

2.4.1 Search Strategies

A systematic computer-based search of PubMed-Medline, PsycINFO and EMBASE databases was conducted from June 7th, 2017, until June 12th, 2020. The search included articles that were written in English and included either a CT intervention or ET intervention. CT interventions were included if they involved any of the following (including a combination thereof): executive function, attention, working memory or set shifting. The ET intervention could be any type of intervention that included any form of physical activity such as aerobic, resistance training, dance, yoga and could also be a combination of these types of physical activity.

Search terms included “older adults”, “elderly”, “aging”, “exercise”, “aerobic training”, “resistance training”, “strength training”, “executive function training”. The full search strategy,

including MESH terms, used can be found in supplementary material Figure 1. Unique search terms were used for each database with the consultation of an academic librarian. We also supplemented database searches with reference lists found in other reviews and of those papers that were included in the review. Dates of inclusion of papers were limited to those published on or before June 12th, 2020. Data was then extracted into covidence.org, a systematic review software for screening, as well as to complete the Cochrane bias component.

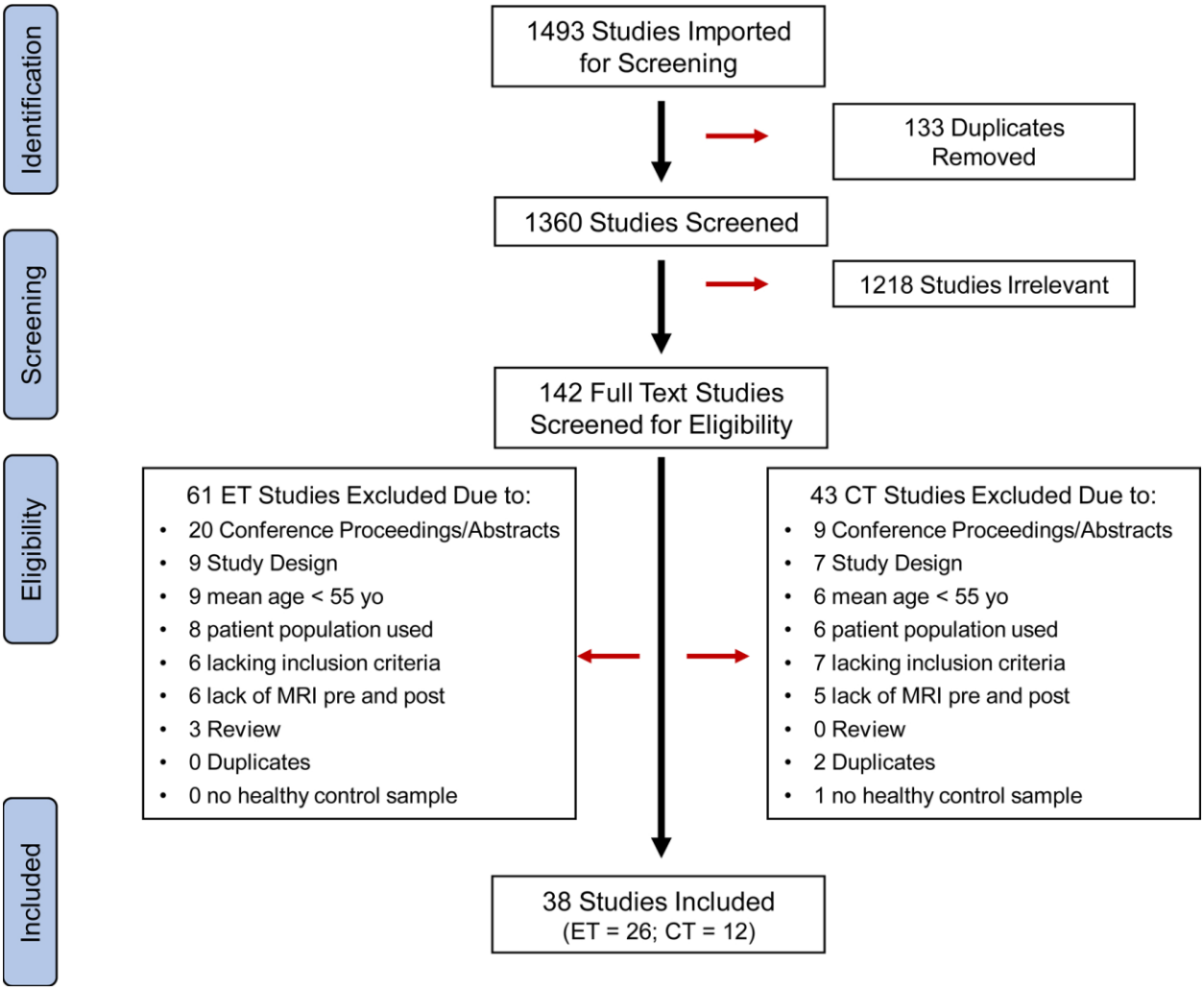

Figure 2—1 PRISMA Chart demonstrating the literature search and inclusion/exclusion for the systematic review (Shamseer et al., 2015)

2.4.2 Inclusion and exclusion criteria

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed (Shamseer et al., 2015). Articles were included if they investigated the effects of cognitive training, aerobic training, resistance training, or other exercise interventions

on the cognitive function of healthy older adults (≥ 55 years of age) with no known cognitive impairment. As many studies included participants 55 years old and over, we set this age criteria to be more inclusive. All studies were also required to include MRI acquisitions before and after the intervention. Study designs included were randomized controlled trials (RCT's) and quasi-experimental studies.

We excluded studies with participants who had known neurological or motor disorders, such as Alzheimer's disease, Mild Cognitive Impairment, Parkinson's disease, dementia, and multiple sclerosis. Those with cardiovascular risk factors were included (e.g., diabetes, hypertension), but studies with patients suffering from coronary artery disease and heart failure were excluded (excluded studies are listed in figure 1). Other studies excluded were if: the mean age of participants was below 55; it was another review; meta-analyses; abstract for conferences (i.e., conference proceeding); dissertations; or there was no healthy control group that participated in some form of non-intervention, whether that be a passive or active control group.

Finally, it was determined that an intervention could not include a combination of exercise and cognitive interventions in one intervention group. The rationale for this was that the investigation of ET interventions and CT interventions in isolation of each other would provide a more accurate inference for understanding the underlying mechanisms leading to brain enhancements in each intervention. For example, in situations where the ET intervention stated explicitly that they manipulated a cognitive load associated with the ET (e.g., dance movement interventions) then they were excluded as this training would be considered a combination of ET and CT. However, if a study compared the two interventions to each other, without combining them, then they were included. This had an exception in terms of ET, where those studies that included a combination of ET (e.g., aerobic plus resistance training, or resistance training plus balance and flexibility) were still included.

2.4.3 Selection Criteria

Two authors (BI and TV) independently screened articles initially by title and abstract for articles that did not meet the inclusion criteria. The full texts of the remaining studies were then also screened for eligibility. Disagreements were resolved through discussion, and if necessary, included one of our expert authors (see Figure 1). Risk of bias in individual studies was also

assessed independently by the two reviewers using the guidelines outlined in the Cochrane Handbook (Higgins & Green, 2008) which is reported in Table 1.

The two authors independently extracted the following information from all included full text journal articles; participant demographics (sample size; mean age, % female, type of population, education, MoCA, MMSE), intervention (length, type, frequency, duration, intensity, adherence rate, dropouts), control (type, adherence rate), physical function outcome measure (reported change), cognitive function measures (reported change), structural outcomes (sequence used, echo time [TE], repetition time [TR], slice thickness, resolution if available otherwise field of view [FOV] and matrix to calculate resolution, volume of slices, flip angle, software use to preprocess and processing of data), structural changes (if present, location, type of change), functional outcomes (sequence used, TE, TR, Slice thickness, resolution or FOV and matrix, volume of slices, flip angle, software to preprocess and processing of data), functional changes (if present, location and type of change), physical function outcome related to imaging measure, and cognitive function outcome related to imaging measure. Any discrepancies in the data extraction (e.g., number of participants for a particular study or type of MRI scanner) were discussed and solved amongst the authors. The primary outcome of interest were the results from MRI, including structural and functional changes. Secondary outcomes included behavioural results of cognitive outcomes within the domains of executive function and attention. Other secondary outcomes included results of exercise training improvement (i.e., VO_2peak, muscle strength, etc.).

2.4.4 Visualizing of Results

MRI regions of interest that were reported to be investigated by each study were individually recorded. The multi-level bootstrap analysis of stable clusters (BASC) atlas (Bellec et al., 2010) was chosen as the standardized brain image to graph results on. Macrostructural and functional data were plotted on different images, as were all the regions for ET and CT studies. Regions for each study were then coded as 1 for increases displayed in red; 2 for decreases which are in blue; and 3 for no change to regions, as shown in yellow. For regions that had disagreements among studies, for example one study observed an increase in hippocampal volume, but another demonstrated no change, these were then coded as a combination of the colors for increase and no change, with the appropriate weighting (i.e., if 2 found increases and 1

no change, it would be weighted heavier towards the increase [red] color hue). Only those regions that were reported to have one of the three conditions (e.g., increase, decrease, no change) were parcellated and color-coded systematically for both types of interventions in macrostructural and functional outcomes. The reported changes, or lack thereof, were recorded as the within group change from baseline to follow up in the intervention groups. This was completed because only a minority of studies statistically compared the intervention-related MRI change relative to the control group. In-house scripts were created to plot on a standardized brain using Nilearn in Python 3 (Pedregosa et al., 2011).

2.5 Results

A total of 1493 studies were imported for screening, with 133 being duplicates. Thus, 1360 studies were screened, with 142 of these considered for full-text screening. The final number of papers included in this review is 38 studies. Figure 1 shows a flowchart of the studies excluded and rationale for exclusion, as well as those included. Table 2 includes the basic characteristics of all studies (Supplementary Table 1 presents basic characteristics of MRI [i.e., TR, TE, etc.]), and a simplified version of all results is presented in Table 3. A Cochrane Risk Assessment was completed for all studies included (See Table 1), however due to lack of information for many components of this, we were unable to assess whether studies had high or low risk of specific biases. Figure 2 and 3 show macrostructural (a) and functional (b) changes in the intervention groups, respectively for CT (figure 2) and ET (figure 3), on a standardized brain using the BASC atlas (Bellec et al., 2010)**.**

2.5.1 Cognitive Training

Of the 38 studies included in this paper, a total of 12 were CT interventions. Table 2 shows the details of the interventions. The results are categorized into the following sections: 1) structural outcomes; 2) functional outcomes; 3) correlation between imaging and secondary outcomes. These studies ranged in length of intervention from 2 to 24 weeks, with a range of frequencies (1 to 5 times per week) and time per session (45 to 120 minutes) in those that reported these values (8 studies). Figure 2 provides visualization of the changes reported in the intervention group**,** where studies reported increases, decreases or no change after each

intervention in the specific regions of interest, particularly within frontal, parietal and hippocampal regions.

2.5.1.1 Structural outcomes

A total of eight of the twelve cognitive training studies included structural outcomes, where five reported significant changes and two did not report correlational analyses between the cognitive outcomes and imaging (Hampstead et al., 2012; Lövdén et al., 2010). Overall, the majority of the CT studies found that their control, (i.e., *non*-intervention groups) demonstrated a change, in particular, an increase in mean diffusivity (MD) over time, within the frontal-occipital fasciculus, inferior and superior longitudinal fasciculus and uncinate fasciculus (de Lange et al., 2017, 2018), as well as the genu of the corpus collosum (Lövdén et al., 2010). Furthermore, these studies demonstrated a relative decrease to MD which was related to the CT interventions (de Lange et al., 2017, 2018; Lövdén et al., 2010), although these changes were reported in different areas of the brain for each study, suggesting widespread decreases to MD. Others saw decreases of fractional anisotropy (FA) (Chapman et al., 2015; de Lange et al., 2017, 2018; Lövdén et al., 2010) which was explained as an age-related decline in white matter microstructure. Three of the studies demonstrated an increase in FA due to the intervention (Chapman et al., 2015; de Lange et al., 2018; Lövdén et al., 2010), specifically in the white matter tracts adjacent to the default mode and central executive network (Chapman et al., 2015) and in the areas where a change in MD was identified in the control group (de Lange et al., 2017, 2018; Lövdén et al., 2010). It should be noted, that de Lange and colleagues (2017) found that only the controls (compared to the memory training group), had significant decreases in FA, and increases in MD, and radial diffusivity (RD) throughout the brain including the corticospinal tract, corpus callosum, superior longitudinal fasciculus and the anterior thalamic radiation, following a 10-week intervention (de Lange et al., 2017) .

2.5.1.2 Functional outcomes

Eight of the studies measured functional MRI outcomes before and after the interventions. Specifically, five studies investigated task-related BOLD changes, one study investigated cerebral blood flow (CBF) (Chapman et al., 2017) and another functional connectivity (Chapman et al., 2015). The in-scanner tasks that were completed included a 3-back task (Heinzel et al., 2014, 2017), a visuospatial working memory task that had two load

conditions (Brehmer et al., 2011), and an object location association memory test (Hampstead et al., 2020). Of those investigating task-related BOLD changes (Table 3; Figure 2b), four demonstrated *decreased* BOLD signal after the interventional period, ranging from two (Hampstead et al., 2020) to four weeks (Heinzel et al., 2014, 2017) and up to five weeks (Brehmer et al., 2011), within the frontal and parietal regions (Brehmer et al., 2011; Heinzel et al., 2014, 2017), as well as decreases within hippocampal regions (Brehmer et al., 2011) and the occipital lobe (Hampstead et al., 2020). In contrast, the other two studies and that by Hampstead et al. (2020) demonstrated increased BOLD signal during a face/scene delayed matching task (Adnan et al., 2017) a multi-source interference task (with two conditions (Kim, Chey, & Lee, 2017), and the object location association memory task (Hampstead et al., 2020) in some of the same areas (frontal, parietal and hippocampal) as well as temporal (Hampstead et al., 2020 only) after their two (Hampstead et al., 2020), five (Adnan et al., 2017) and eight-week (Kim et al., 2017) interventions. Chapman and colleagues also found after a 12-week intervention, that there was overall improved connectivity within the default mode network and the central executive network (Chapman et al., 2015). Moreover, Chapman and colleagues found that the CBF in their cognitive group increased 7.9% from pre-testing to the halfway point (6-weeks) and remained at this level until post-testing. They also completed a voxel-wise analysis and found that there was a significant increase in the cognitive group compared to the control group in the left middle temporal, superior medial and inferior frontal gyrus.

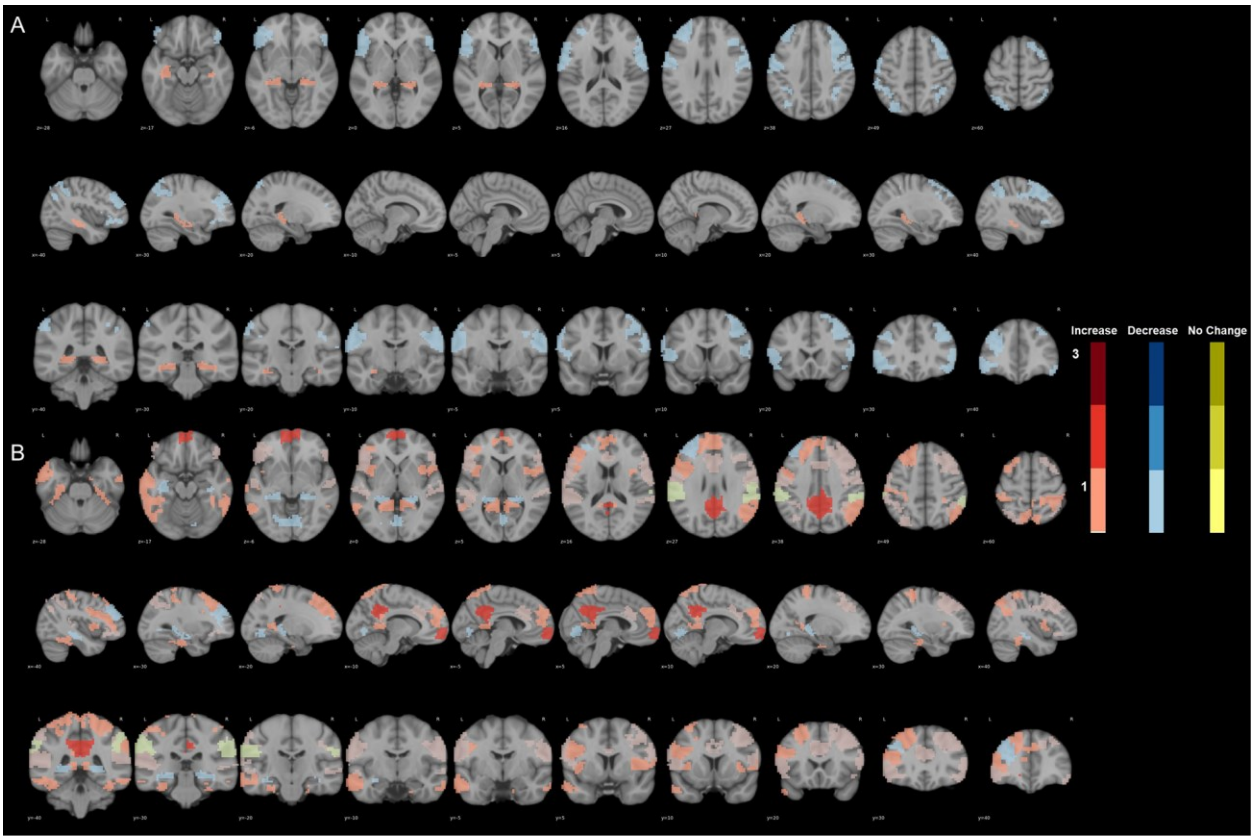

Figure 2—2: Standardized brain demonstrating regions where CT studies reported macrostructural and functional changes within the CT groups after the intervention. Increases in regions within the intervention group are identified in red, where the lightest color represents that one study investigated this region out of all 12 CT studies and found a significant increase. The color's increasing intensity represents a greater number of the 12 studies observing an increase in this region, up to 3 studies which is the most intense, or darkest of all the colors. This same pattern occurred for studies demonstrating decreases, as represented in blue and studies observing no changes as indicated in yellow. For studies that demonstrated differential findings, for example 1 study found an increase and another 1 decrease, the colors for these two intensities were overlaid to provide a combination of those colors. The maximum number of studies reporting the same direction of changes per region was 3, thus, this was set as our threshold. a) Macrostructural regions. b) Functional regions.

2.5.1.3 Relationship between imaging and cognitive performances

Nine of the twelve studies included statistical analyses to investigate the potential relationship between imaging outcomes and cognitive measures. Microstructural improvements were related to the cognitive outcomes for de Lange and colleagues in multiple articles, (de Lange et al., 2016, 2018, 2017) where negative relationships existed between MD and memory improvements (de Lange et al., 2016, 2017) within the corpus callosum, inferior fronto-occipital fasciculus and anterior thalamic radiation (de Lange et al., 2017). Conversely, those older adults with a frontal FA above the mean FA for young adults were found to have the largest increase in memory performance compared to those older adults with FA below this level (de Lange et al.,

2016). In their 2018 paper they found MD at pre-test had a positive relationship with memory, whereas at every time point onwards, they shared an inverse relationship, indicating a change in microstructure or behavior (de Lange et al., 2018). Yet, others who attempted to relate their cerebral and cognitive outcomes did not find any relationships. For example, Lövdén and colleagues found no correlations between changes in FA or MD with changes in working memory, episodic memory or perceptual speed (Lövdén et al., 2010). This lack of relationship between microstructural and cognitive outcomes was also reported by another group**,** where after a 2-week training intervention, healthy older adults demonstrated no relationship between MRI outcome and cognitive outcomes (Hampstead et al., 2012).

The few groups who reported functional changes with cognitive improvements did have positive findings. In particular, Chapman and colleagues demonstrated that the mean changes in their test of strategic learning and similarities outcomes were correlated with mean changes between groups for CBF in the temporal lobe, anterior and posterior cingulate as well as the superior medial frontal gyrus (Chapman et al., 2015). Finally, performance was related to widespread activity decreases throughout the frontal, parietal, temporal, subcortical and occipital lobes during the working memory condition, where those who had the largest BOLD signal decreases in memory and attention related areas, tended to be those who gained the most from training.

2.5.2 Exercise Training

Of the 38 studies included in this review, 26 employed a form of exercise training. In general, these studies varied in length (from six to 135 weeks), range of frequencies (1 time per week to daily) and length per session (10 to 90 minutes) in those that reported these values. See Figure 3 for a visualization of the imaging results in the interventional groups of increases (red), decreases (blue), no change (green) or a combination of such, after ET in macrostructural and functional outcomes, which appeared to be spread quite globally throughout the brain.

2.5.2.1 Structural Outcomes

Seminal work by Colcombe and colleagues (2006) reported increased grey matter volume in some frontal and temporal regions as well as the anterior cingulate cortex following an aerobic intervention as can be visualized in Figure 3a (Colcombe et al., 2006). Two other studies observed significant increases to grey matter volume within some of these same regions,

particularly the frontal (Ji et al., 2017; Müller et al., 2017), parietal and cerebellar regions (L. Ji et al., 2017) as well as parahippocampal regions (Müller et al., 2017). As seen in Figure 3a, the increased hippocampal volume was confirmed by numerous studies (Kleemeyer et al., 2016; Müller et al., 2017; Niemann, Godde, & Voelcker-Rehage, 2014; Rehfeld et al., 2017; Rosano et al., 2010), yet others observed no change to the hippocampus (Maass, Düzel, Goerke, Becke, Sobieray, et al., 2015; Sexton et al., 2020). Moreover, when comparing their resistance training group to control group, Müller's study found no difference (in contrast to their aerobic group) (Müller et al., 2017).

Several groups also investigated changes in white matter volume, lesion load and microstructure. White matter lesion volume was significantly less compared to a control group after a 12 month intervention, but only in those who trained two times per week, not the group who trained once weekly (Bolandzadeh et al., 2015). This same study found that the twice-weekly resistance training group showed a significant decrease in white matter cortical atrophy (the white matter immediately below the cortical grey matter area) at the 2-year follow-up compared to those in the control group, with no differences again between the once weekly and control (Best et al., 2015). Colcombe and colleagues also found a significant increase in overall white matter volume in their exercise group compared to controls (Colcombe et al., 2006). A recent study, found that their aerobic group did not have worsening white matter hyperintensity grade after the intervention, but that their health education group had an 18.8% worsening of white matter hyperintensities grades (Shaaban et al., 2019). In terms of changes in microstructure, one group found that when there was a significant increase in fitness after the intervention, MD within the hippocampus was decreased (Kleemeyer et al., 2017). Moreover, two groups found no change after their ET intervention for any of the diffusion outcomes (Sexton et al., 2020; Voss et al., 2013).

Finally, one group used more complex MRI outcomes to investigate changes after their 24-month intervention (Shaaban et al., 2019), in particular the identification of cerebral blood vessel tortuosity, length of venules and microbleeds identified by susceptibility-weighted images. They observed that those in the aerobic intervention had a significant increase in the percentage of straight venous length from baseline to 24 months, and the tortuosity ratio declined from baseline to follow-up by 33.2% compared to the control group. However, this was not statistically different. It was also found that both the aerobic group and the control group over the

two-year intervention had a significant increase in microbleed count, but it was not statistically different between the two groups.

2.5.2.2 Functional outcomes

Five groups investigated functional connectivity, four of which found increased connectivity within the default mode and central executive networks (Chao et al., 2020; McGregor et al., 2018; Voss, 2010; Voss et al., 2013). In another study by Voss and colleagues, they did not find a significant change within the default mode network, or any of the other three networks investigated (Voss, Sutterer, et al., 2019). The four studies that investigated task-related BOLD signal changes all used varying in-scanner tasks: a number Stroop hybrid task (Wu et al., 2018), a Flanker task (Voelcker-Rehage, Godde, & Staudinger, 2011), Digit-Symbol Verification task (Motes et al., 2018) and a semantic verbal fluency task (Nocera, Crosson, Mammino, & McGregor, 2017). Of these four, two found increased BOLD signal activation within frontal (Voelcker-Rehage et al., 2011; M.-T. Wu et al., 2018), and one in parietal and thalamic areas after coordination training (Voelcker-Rehage et al., 2011). On the other hand, Voelcker-Rehage and colleagues found that their aerobic training group demonstrated decreased BOLD signal change within frontal and temporal regions, a finding that was also observed by Nocera et al. (2017) using a different task (semantic verbal fluency)(Nocera et al., 2017). These discrepancies, as well as lack of BOLD-task related change (Motes et al., 2018) can be visualized in Figure 3b.

Some studies investigated changes in more fundamental physiological and signal properties. A 6-week daily Wii exercise program demonstrated a decrease in amplitude low frequency fluctuations (ALFF) and regional homogeneity within the precuneus cortex, whereas increases were found in subcortical structures(Ji et al., 2017). Finally, after a 12-week aerobic intervention Maass and colleagues found that there was a significant increase in cerebral blood flow and volume within the hippocampus compared to the control group (Maass, Düzel, Goerke, Becke, Sobieray, et al., 2015; Maass et al., 2016). Of the four studies that investigated perfusion changes (Chapman et al., 2015; Flodin, Jonasson, Riklund, Nyberg, & Boraxbekk, 2017; Maass, Düzel, Goerke, Becke, Sobieray, et al., 2015; Motes et al., 2018), only one group reported changes to perfusion, specifically a within group analysis found increases in resting cerebral

blood flow and cerebral blood volume within the hippocampus after ET as indicated in red in Figure 3b (Maass, Düzel, Goerke, Becke, Sobieray, et al., 2015; Maass et al., 2016).

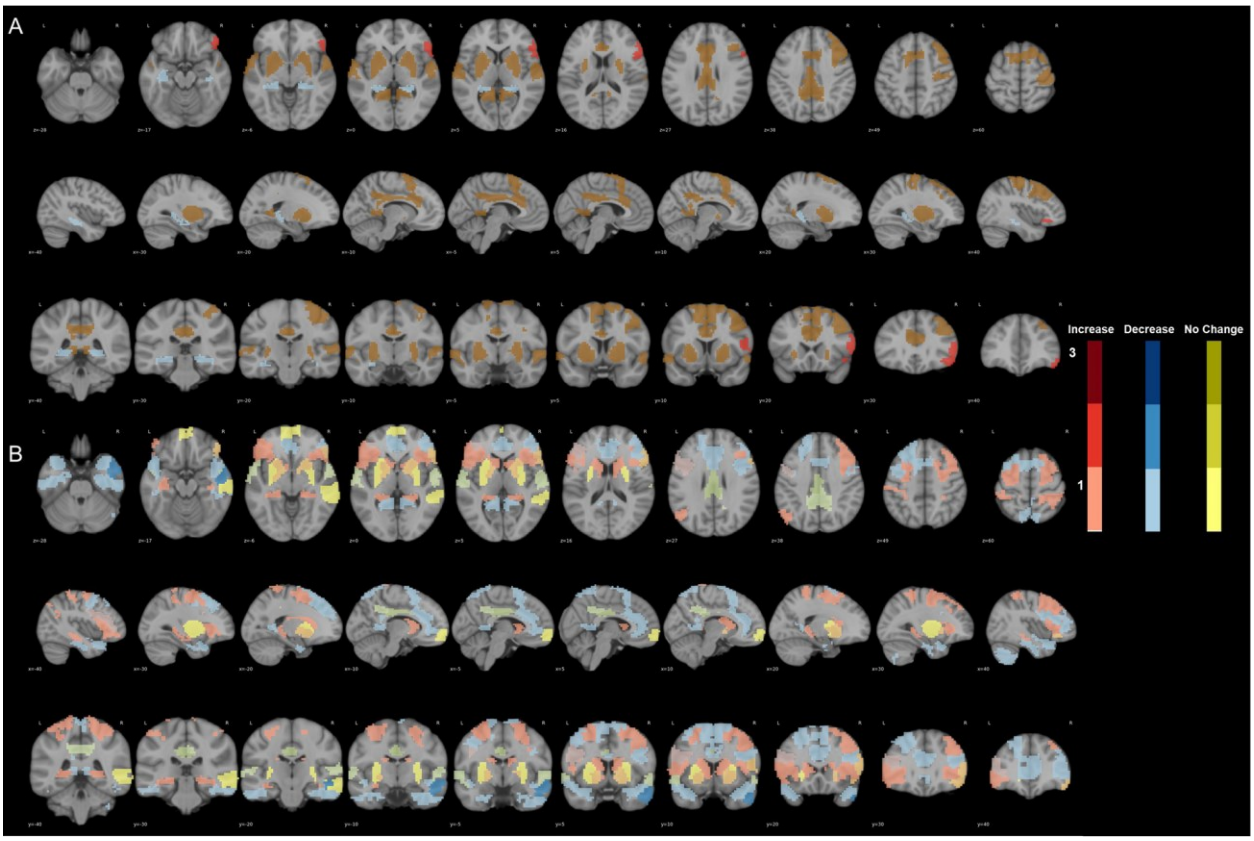

Figure 2—3: Standardized brain demonstrating regions where ET studies reported macrostructural and functional changes after the ET group intervention. Increases within regions within the intervention group are identified in red, where the lightest color represents that one study investigated this region out of all 26 ET studies and found a significant increase. The color's increasing intensity represents a greater number of the 26 studies observing an increase in this region, up to 3 studies which is the most intense, or darkest of all the colors. This same pattern occurred for studies demonstrating decreases, as represented in blue and studies observing no changes as indicated in yellow. If studies that demonstrated differential findings, for example 1 study found an increase and another 1 decrease, the colors for these two intensities were overlaid to provide a combination of those colors. The maximum number of studies reporting the same direction of changes per region was 3, thus, this was set as our threshold. a) Macrostructural regions. b) Functional regions.

2.5.2.3 Relationship between imaging and secondary outcomes

Out of the 26 studies on ET, 13 reported the relationship between the imaging outcome and changes to fitness or a physical activity improvement. Specifically, groups found that greater fitness after the intervention was associated with increased prefrontal and temporal FA (Voss et al., 2013), lower MD (Kleemeyer et al., 2017), and increased connectivity between the default mode network and the frontal pole (Flodin et al., 2017). Yet, another group found that the changes in connectivity were not related to changes in fitness (i.e., VO_2max) but were associated

with percentage of time spent in higher heart rate zones. Rosano and colleagues found that those who attended a greater number of sessions over two years had a significantly increased hippocampal volume (Rosano et al., 2017). Whereas, another study discovered that a maintenance in gait speed was associated with decreased white matter lesions (Bolandzadeh et al., 2015). In terms of functional outcomes and fitness, higher VO_2max was found to be related to decreased BOLD activation throughout frontal and temporal lobes, during a Flanker task, in the aerobic group, whereas in the control group there was increased activation related to decreased VO_2max (Niemann et al., 2014). Conversely, others found that increased VO_2max was related to greater BOLD activity during a semantic verbal memory task, within frontal regions (Nocera et al., 2017). Flodin and colleagues (2017) found that BOLD signal variability was negatively correlated with VO_2max, as was the ALFF (Flodin et al., 2017). Finally, another group, reporting in two articles, found no significant relationships between hippocampal subfields and balance (Müller et al., 2017; Rehfeld et al., 2017), whereas Sexton and colleagues found that the change in fitness was not associated with hippocampal volumes, global FA, AD or RD (Sexton et al., 2020).

2.5.3 Comparison of Cognitive and Exercise Interventions

One study, reported in two articles (Chapman, Aslan, Spence, Keebler, F, et al., 2016; Motes et al., 2018) compared a cognitive to an aerobic intervention and a wait-listed group (Motes et al., 2018). Specifically, in their 2016 article, Chapman and colleagues reported that the cognitive training group increased global cerebral blood flow by 7.9% at the halfway mark of the intervention (6-weeks) and maintained this CBF increase at the end of the intervention within frontal areas, whereas those in the aerobic group did not significantly increase their CBF, although the percent change was not reported (Chapman, Aslan, Spence, Keebler, F, et al., 2016). Neither group demonstrated significant changes to cerebrovascular reactivity after the interventions. In their follow-up study, they found no significant task-related BOLD signal change after either intervention, however when investigating the reaction-time related coefficients during the task, they found those in the cognitive training had faster reaction times that were associated with less BOLD signal change, whereas the aerobic and waiting-list group demonstrated a decrease in the association between the reaction time and BOLD signal change.

2.6 Discussion

2.6.1 Summary

We aimed to investigate the effect that two different lifestyle interventions, CT and ET, have on the cerebral structure and function of healthy older adults. In general, the literature thus far can be viewed with cautious optimism. The results of this review demonstrate a mixed picture of *how* and, in some cases, *if* some forms of lifestyle interventions influence brain structure and function, as can be seen in Figures 2 and 3. It's important to note however that there was significant heterogeneity in the findings among studies, which could partially reflect the variability in outcomes utilized (e.g., resting state fMRI versus perfusion versus voxel-based morphometry), with little overlap between studies for imaging technique employed, especially for CT versus ET. Nevertheless, it was possible to identify some patterns across studies, such as improvements to white matter microstructure after CT interventions, macrostructural enhancements post ET studies and both forms of interventions associated with changes in the BOLD signal. Generally, although the studies reported in this review differed greatly on several parameters, CT studies tended to be shorter in length than ET, ranging from 2 to 24 weeks with 5 to 36 sessions which were 25 to 60 minutes in length each session. Conversely, ET studies were conducted over a 6 to 72-week intervention period, ranging from once a week to weekly sessions that were from 10 minutes to 90 minutes in length per session.

2.6.1.1 Effects of CT on Structural outcomes

Notably, only two CT studies investigated the effects on structural outcomes where neither found a significant change to grey matter volume, or white matter volume (Hampstead et al., 2012; Heinzel et al., 2014). Interestingly, of the twelve CT studies included in this review, the majority reported that T1 sequences were acquired for registration purposes only (Adnan et al., 2017; Brehmer et al., 2011; Chapman et al., 2015; Chapman, Aslan, Spence, Keebler, F, et al., 2016; Hampstead et al., 2020; Heinzel et al., 2017; Kim et al., 2017; Lövdén et al., 2010). Therefore, the images necessary to investigate volumetric outcomes are being collected but volumetric results are not being reported. This could potentially be due to null findings, or to the data not being analyzed. More studies reporting volumetric findings, null or otherwise, are needed to conclude whether CT has the potential to change tissue macrostructure.

Four diffusion-weighted imaging (DWI) studies reported positive outcomes in the interventional groups compared to individuals in control groups. More specifically, increased fractional anisotropy (FA) for the interventional group was reported (Chapman et al., 2015; Lövdén et al., 2010), with decreased FA in the control group (de Lange et al., 2016, 2018, 2017). These studies demonstrate the normal trends of aging over interventional periods within the controls and that during this time, CT interventions likely maintain or improve DWI outcomes. In other words, the CT intervention is seemingly able to ward off age-related brain decline in white matter tracts or at least maintain their integrity, which was perhaps most eloquently revealed by de Lange and colleagues (de Lange et al., 2018). In this study, periods of rest were interspersed in between interventional periods, where FA and MD were observed to be improved in the intervention group as compared to the control group (which showed a time-dependent decrease in FA and increase in MD) during the interventional periods and the opposite during rest periods**.** Thus, exhibiting the potential specificity of CT on white matter microstructural integrity.

2.6.1.2 Effects of CT on Functional Outcomes

The functional outcomes for CT are seemingly more promising in terms of beneficial changes. These enhancements were seen as changes in the BOLD signal, although the directionality of change was inconsistent across studies. For example, Hampstead et al., 2020 demonstrated an *increase* to BOLD signal activation during an episodic memory task within the prefrontal areas. Whereas, during working memory tasks BOLD signal activation was reported to *decrease* in the dorsolateral prefrontal cortex, (Brehmer et al., 2011; Heinzel et al., 2014, 2017). Some groups observed *increased* BOLD signal during attentional tasks, within frontal and parietal areas (Adnan et al., 2017; Kim et al., 2017). The differences in directionality of the signal changes could be due to the type of cognitive task (i.e., working memory versus episodic memory versus attentional) or the varying number of intervention sessions completed for each study; leading to the debate of increased resources (potentially associated with increased BOLD signal) or increased efficiency (potentially associated with decreased BOLD signal). Conversely, the answer could lie within the nature of the BOLD signal, which is known to be physiologically ambiguous, and represents a change from an unknown baseline (Gauthier & Fan, 2018). Thus, it is not possible to interpret these changes in terms of underlying neural resources directly. For this

to be a possibility, studies need to include other vascular or metabolic outcomes that are known to determine subcomponents of the BOLD signal, such as CBF or the cerebral metabolic rate of oxygen consumption (Gauthier & Fan, 2018; Tardif et al., 2016).

Importantly, one group (disseminated in two studies) investigated resting CBF and found that perfusion was increased after CT within the frontal lobe and cingulate cortex (Chapman et al., 2015,2016). They also demonstrated increased functional connectivity within the default mode and central executive network (Chapman et al., 2015). An extension of this study (Motes et al., 2018), reported BOLD signal increases after a digit span verification test in the CT group within the prefrontal cortex, a region demonstrating increased resting CBF in their earlier study (Chapman, Aslan, Spence, Keebler, F, et al., 2016). Therefore, one could postulate that increases in resting CBF and BOLD signal in the same region indicates that these changes could be due to a combination of vascular or metabolic properties (potentially including, but not limited to neuronal resources). Interestingly, resting CBF was increased but not CVR, consistent with the recruitment of more resources (i.e., BOLD signal is increased, but not vasodilatory potential per se). Thus, it is possible to conclude in this case, that there are likely more resources (versus increased efficiency) recruited after this form of CT, indicating the utility of groups using *multiple* functional sequences in one study (i.e., BOLD, CBF and CVR).

Although half of the CT studies did find functional changes, five did not report changes However, the studies not reporting changes tended to have a shorter length of intervention and the number of total sessions, with the exception of Lövdén and colleagues, yet it is not clear how many weeks the 101 sessions were completed in (Lövdén et al., 2010). A potential explanation for lack of functional BOLD signal changes is that there were no transfer effects following CT, only improvements on the trained task, indicating a learning effect only.

2.6.1.3 Effects of ET on Structural outcomes

Notably, ET studies reported a greater number of changes to structural outcomes than CT. All the studies that reported structural improvements were at least 16 weeks in length, except for Ji et al., 2017 whose intervention length was only 6 weeks, but was *daily*, potentially demonstrating that for structural changes to occur, a specific volume of ET is required (Chao et al., 2020; Ji et al., 2017; Kleemeyer et al., 2017; Müller et al., 2017; Niemann et al., 2014; Rehfeld et al., 2017, 2017; ten Brinke et al., 2015). This is further confirmed by studies

observing no changes to hippocampal volume (Maass, Düzel, Goerke, Becke, Sobieray, et al., 2015; Sexton et al., 2020), grey or white matter volume as well as DWI outcomes (Sexton et al., 2020) after 12-week, three times weekly, interventions. This could be extended to the lack of volumetric changes reported in CT studies, as CT interventions tended to be shorter in length and overall volume of intervention. (volume = length of intervention [total number of weeks] x frequency of sessions [times / week] x length of each session [minutes / session]). This remains to be demonstrated conclusively however since not all studies reported the necessary outcomes for dosage to be calculated and accounted for**.** It is also possible that studies that did not report changes (including CT) are, in part, due to the standard MRI techniques employed with 3T MRI, which may not have been sensitive enough to detect small changes (microlevel) that are occurring during shorter time periods. Thus, it is possible that larger changes to structure need to occur before it can be detected using MRI volumetry at the voxel size typically used. Finally, changes to grey matter volume, or lack thereof, should be interpreted with caution as it is not physiologically specific and can represent an array of changes at this level (i.e., angiogenesis, gliogenesis, neurogenesis)(Tardif et al., 2016; Tardif et al., 2017).

Importantly, a decreased presence of white matter lesions and atrophy, compared to a control group over a two-year time period was also observed (Bolandzadeh et al., 2015). Others employing ET for two years found that the aerobic group maintained their white matter hyperintensity gradings, but those in the control group demonstrated a 20% grading deterioration (Shaaban et al., 2019). Those investigating changes to DWI outcomes after a 26 week ET intervention, found MD was significantly decreased in the hippocampus (grey matter structure) after the intervention (Kleemeyer et al., 2016), which might be driven by different physiological processes than the decreases to MD found in white matter after CT. Yet others, found no changes to DWI outcomes after their 12-week intervention, again possibly indicating that there is a minimal volume of ET necessary to induce changes (Sexton et al., 2020). Taken together, results from the above studies demonstrate that ET is capable of maintaining cerebral white matter structure, potentially through the prevention of age-related vascular decline in the white matter.

Surprisingly, the majority of ET studies did not report measuring white matter microstructural outcomes. It is well documented that cerebral white matter is vulnerable to vascular changes, such as changing cerebral blood flow (Bahrani et al., 2017; Giezendanner et al., 2016; Pantoni Leonardo, Garcia Julio H., & Gutierrez Jorge A., 1996). Furthermore, a recent

review (Badji et al., 2019), identified that white matter changes were consistently associated with arterial stiffness. Thus, presenting a unique opportunity to those investigating ET to target plasticity within white matter microstructure in response to the vascular changes (i.e., decreased arterial stiffness) that tend to occur after exercise (Seals, Nagy, & Moreau, 2019). It is likely that if studies investigated white matter, improvements after ET would be found alongside CBF increases. This is further highlighted by novel work demonstrating ET promoted cerebral small vein integrity (Shaaban et al., 2019), which, the authors speculate may suggest that ET promote endothelial functioning and an increase of nitric oxide through the maintenance of shear stress and CBF, thereby contributing to maintain the health of vessels. Thus, it would be valuable for future studies to assess white matter outcomes, including DWI, to clarify if ET can enhance white matter micro and macrostructure given that ET interventions seem to enhance vasculature at the micro and macro levels.

2.6.1.4 Effects of ET on Functional Outcomes

Four of the exercise studies investigated task-related BOLD signal changes. Much like the task-related BOLD changes after CT training, the results were heterogeneous, likely due to the differing in-scanner task (i.e., response inhibition; processing speed; verbal ability and/or executive control). However, one group found intriguing results demonstrating that the change to the BOLD signal and the corresponding brain location could be dependent on the mode of ET (i.e., aerobic versus coordinative training) (Voelcker-Rehage et al., 2011). Specifically, the aerobic group showed *decreased* BOLD activation compared to the controls, within frontal (superior and middle) and temporal regions, whereas those in coordination training demonstrated *increased* activation within frontal (inferior) and parietal regions. These directions of BOLD signal findings in specific regions was replicated by later work, that found decreased BOLD signal in the temporal regions after aerobic training, and increased BOLD signal in the frontal (inferior) regions after coordinative exercising (Nocera et al., 2017). Though not compared in the same study, the middle frontal gyrus demonstrated these same trends, with decreased BOLD signal activity after aerobic training in one group, (Voelcker-Rehage et al., 2011) but increased BOLD signal activity following a Tai Chi intervention, which is a form of coordinative exercise (Wu et al., 2018). Therefore, it would be useful for future work to not only compare to a control

group, but among exercise training modalities to identify how each type of exercise can influence the brain and if this is region-specific.

Of the four studies that included perfusion, only one found significant changes after the intervention (Maass, Düzel, Goerke, Becke, Sobieray, et al., 2015; Maass et al., 2016). Aerobic ET (the intervention used in all four of these studies), is employed to, primarily, improve the cardiovascular system and is thought to have generally beneficial vascular effects. Given this known enhancement to the peripheral vasculature, it has been hypothesized that these benefits should also extend to the cerebral vasculature (Barnes & Corkery, 2018). Thus, the lack of results in changes to perfusion is quite surprising yet, can be explained by a few rationales. Firstly, perfusion changes could be taking place earlier on in the course of the interventions. However, Chapman and colleagues (2016) acquired an MRI halfway through their intervention and did not find a statistically different change in perfusion for the ET compared to the CT, although if there was any change *within* the ET group, this was not indicated (Chapman, Aslan, Spence, Keebler, F, et al., 2016). These results reveal that ET might not induce enhancements to perfusion but could still be associated with a maintenance effect, preventing decline to CBF. However, no study to date has measured perfusion changes after ET that has been longer than 12 weeks, making it difficult to conclude if only maintenance occurs, or if changes to the cerebrovascular system require more time to transpire. Conversely, previous work has indicated that macrostructural changes can occur without alterations to functional outcomes (Chen et al., 2011), introducing the possibility that ET is perhaps capable of causing structural changes more so than perfusion changes. Finally, it could be that given the low SNR of ASL and its' generally low spatial resolution, it is not able to appropriately capture subtle changes that occur within 12 weeks of an ET intervention.

This low SNR of ASL can be overcome with the use of contrast agents such as gadolinium. Maass and colleagues used this approach to investigate cerebral blood flow and cerebral blood volume in the hippocampi (Maass, Düzel, Goerke, Becke, Sobieray, et al., 2015). They sub-divided their sample into old and younger older adults and found that those who were considered younger had increased hippocampal perfusion after the intervention, whereas those who were older had a decrease in perfusion compared to baseline. Thus, this final study might indicate that the effect of ET on the vasculature may be dependent on age. It is possible that from

a biological standpoint, older adults have decreased ability to initiate the plasticity response, such as angiogenesis for example, initiated by exercise.

2.6.2 The relationship between behavioural and MRI outcomes

Roughly half of the CT studies demonstrated associations between cognitive improvement and changes to imaging outcomes. This suggests that the changes between the two are not linearly linked due to one outcome potentially having a plateau at some point, and the other outcome continuing to change. On the other hand, it is possible that perhaps training protocols need to be longer in order to detect a direct association between the two. It could also be the case, as it was with ET for structural enhancements, that the relationship between cognitive and MRI outcomes is modality dependent. Importantly Chapman et al. (2016) found that increased CBF was related to increased cognition after their CT intervention, thus providing a window into an underlying physiological mechanism of *how* CT improves cognition in healthy aging. Moreover, one group found that individuals with higher FA prior to the CT intervention were those who had greater improvements in memory at the end of the intervention, indicating that more resources to begin with might allow for greater improvements to cognition (de Lange et al., 2016). Contrary to this, 10 of the 12 ET studies that reported relationships between the fitness outcome and MRI, indicated a change in fitness was related to a change in an imaging outcome. Suggesting that if an intervention has a sufficient dose to change fitness, it could be that the dose of the intervention is then also enough to cause these cerebral enhancements.

2.6.3 Comparison of CT and ET Studies

Given the heterogeneity of the length and design of the CT and ET studies, as well as the varying MRI outcomes that were measured before and after the interventions, it is difficult to make any solid conclusions when comparing the two. In particular, there were few overlapping MRI outcomes reported for the two forms of interventions. Yet, of those that were, it seems that both CT and ET interventions are capable of influencing the BOLD signal during a task-related outcome, specifically within the frontal, parietal and temporal lobes, with both demonstrating increases and decreases to the signal, respectively. Perfusion changes and enhancements to the white matter microstructure were observed predominantly in CT interventions, with only one study reporting these types of outcomes for the ET interventions. Conversely, ET studies tended to report more enhancements to connectivity and macrostructural outcomes (e.g., grey and white

matter integrity), although it is unclear if this is due to lack of investigation from the CT studies or reporting bias. Future studies should aim to explicitly compare ET to CT in the same study with MRI at pre and post intervention to identify if there are potential synergistic effects on cerebral health in older adults.

2.7 Limitations

The studies included in this systematic review were highly heterogenous, in many aspects previously discussed but also in the moderators that were included as covariates. A limitation to this review is that moderators could not be formally evaluated. It should be noted that in many instances, moderators such as sex, age, and cognitive status, were included as covariates in statistical models. In order to further disentangle these relationships between lifestyle interventions and brain outcomes, it is imperative that future work attempt to disaggregate this data a priori (i.e., males versus females; younger versus old older adults) to identify what other factors could be influencing the effects that ET or CT has on cerebral health.

Furthermore, while we included studies that had a control group present, whether they were active or passive, the nature of the control group could influence results. The use of active only control groups is superior to passive only, as it allows to control for all interventional confounding factors (e.g., social interaction, time exposure, etc.) and better isolates the effect of the intervention itself. Seven of the CT studies had active controls (with three of them being from the same study), whereas all but three of the ET studies *had* an active control, making it unclear for the CT studies if the improvements were due to the intervention itself, or due to social interaction. However, some of the CT studies in this review were better able to capture the natural decline associated with aging through the use of passive control groups. In turn, this allowed for a more nuanced examination of maintenance versus increased resources due to the intervention. Studies including only an active control group were maybe less able to capture this difference. Thus, ET studies should also include a passive group, or even within the active groups, to plot what the actual decline is when they are not in a true intervention. This is particularly relevant for variables such as CBF which is known to decline by 0.35% per year over the lifespan, whereas GMV declines approximately 0.85% annually (Chen et al., 2011).

Of note, only one study (Chapman., 2016; Motes et al., 2018), directly compared a CT intervention to an ET intervention, both of the same length, time per session, and number of

sessions. Future work should aim to replicate this form of study design to attempt to disentangle specifically the underlying mechanisms for improving cerebral health of each type of intervention.

2.8 Conclusion: Future Directions and Recommendations

In conclusion, our systematic review provides evidence to support that participation in CT or ET intervention provides benefits to cerebral health in aging, which tend to extend to behavioural cognitive outcomes. These observations suggest that CT and ET interventions are promising means to enhance and maintain cognition, and to prevent cognitive decline associated with aging. Yet, there are potential approaches that would advance this area of study much more effectively by probing the mechanisms behind the improvement of cerebral health after either a CT or ET intervention.

From a structural standpoint this review shows that: i) CT interventions either do not see changes to structure unless they are at least 10 weeks in length; ii) they are not reporting volumetric changes as they are either not being measured or not being reported due to null results. If the latter is the case, it is suggested that these results are reported despite being null, to enable a better understanding of the impact of CT on brain health. For example, if it is true that CT does not find volumetric changes but does find changes to FA and MD, based on their mechanisms of change, it would be indicative that either neuronal process remodeling or myelination were occurring, rather than neurogenesis for example. Furthermore, it is suggested that studies begin to use measures that are more sensitive to microstructural changes, such as myelination. Thus, sequences such as quantitative T1 outcomes, fractional anisotropy and magnetization transfer should be employed to further investigate the microstructure of white matter, where more subtle changes might be occurring over shorter periods of time. On the other hand, volumetric changes occurred in many of the ET studies. The underlying mechanisms of plasticity that are associated with volumetric changes (Tardif et al., 2016) such as angiogenesis, synaptogenesis, and neurogenesis, have all unsurprisingly been associated with ET interventions in animals**.** Although insufficient evidence exists at this point, this review would suggest, that based on the studies presented here in older adults, aerobic training might be more capable of enhancing grey matter volume, whereas resistance training seems to have a greater effect on white matter volume. Others have also suggested that there are modality unique alterations to

cerebral outcomes (Montero-Odasso et al., 2018; Stillman, Esteban-Cornejo, Brown, Bender, & Erickson, 2020) due to the potentially different underlying physiological mechanisms induced by each ET type (see Herold et al., 2019; Voss et al., 2011 for in-depth reviews). However, there is currently insufficient evidence to assess these effects. Future work should compare unique ET modalities with multi-modal imaging across the lifespan to investigate if this is the case.

In terms of functional changes, it seems as though BOLD changes can occur within as little as four weeks, though the underlying meaning of these changes are ambiguous unless studies measure other vascular outcomes as well, such as CBF (Gauthier & Fan, 2018). In fact, it is suggested that calibrated fMRI be employed, as it presents a unique opportunity to disentangle if changes that are occurring are more metabolic or vascular in nature. Calibrated fMRI is a technique able to separate the BOLD signal into its vascular and metabolic sub-components, allowing a better appreciation of whether the changes observed after an intervention are more linked to changes in the vasculature, or neuronal resources and metabolic efficiency.

Moreover, as many of the changes observed following ET seem to be localized in the hippocampi, future studies should pay particular attention to the structure of the hippocampus, as well as its vascular measures to identify which component is changing (i.e. is it more cerebral blood volume, or cerebral blood flow, etc.) (Erickson et al., 2009; Maass, Düzel, Goerke, Becke, Sobieray, et al., 2015; Voss, Soto, et al., 2019). By furthering this understanding, we will be able to uncover the underlying mechanism and better understand *why* the hippocampus and memory improve after ET interventions. Furthermore, this could extend to the Alzheimer Disease and Dementia literature to give us an indication as to why ET seems to be able to slow the disease-related cognitive decline once it is already present (Bherer, Erickson, & Liu-Ambrose, 2013). In the same token, it is also suggested that future work attempt not only region of interest analyses (as is the case with the hippocampus) but should also employ voxel-wise/whole brain approaches, to investigate the effects of ET on the whole brain.

Furthermore, work by Chen et al. (2011) indicates the importance of studies collecting and *reporting* on more than one form of MRI outcome, including non-significant outcomes. This would provide the literature with a more robust body of data (i.e., GMV, connectivity, and perfusion). Moreover, in order to better assess reliability of findings, future studies should aim at better reporting design, outcomes, interventions, and statistical analyses, according to the Cochrane Collaboration's tool for assessing risk of biases.

Overall, the heterogeneity in the implementation of the interventions and outcome measures renders interpretation of the results somewhat tentative. However, given the positive outcomes that generally were identified by each form of intervention, a combination of both CT and ET would likely be ideal to target specific pathways that are impacted in aging, but also to enhance global brain health. It is imperative to first better understand how CT and ET, in isolation, are potentially improving cerebrovascular health and cognition in older adults to be able to efficiently couple the magnitude of their enhancements.

Table 2-1 Cochrane Risk of Bias Assessment

Study	Random Sequence Generation	Allocation Concealment	Blinding Participant	Blinding trainers	Blinding assessors	Incomplete Outcome data	Selective Reporting
Best et al., 2015	?	?	?	?	?	-	-
Bolandzadeh et al., 2015	-	-	?	?	-	+	-
Brehmer et al., 2011	-	-	?	?	?	?	-
Chao et al., 2020	+	+	+	?	?	?	-
Chapman et al., 2016	-	?	-	-	?	-	-
Chapman et al., 2015	?	?	?	?	?	-	-
Colcombe et al., 2006	-	+	?	?	?	?	-
de Lange et al., 2016	+	?	?	?	?	+	+
Hampstead et al., 2012	-	-	-	-	-	-	-
Hampstead et al., 2020	-	-	-	-	-	+	+
Heinzel et al., 2017	+	+	+	+	+	?	-
Heinzel et al., 2014	+	+	?	?	?	+	-
Ji et al., 2017	+	?	?	?	?	-	-
Kleemeyer et al., 2016	?	?	?	?	?	-	-
Lövdén et al., 2010	+	+	?	?	?	-	-
Maass et al., 2016	-	-	?	?	?	-	+
Maass et al., 2015	-	-	?	?	?	-	+
Muller et al., 2017	-	?	?	?	?	+	+
Niemann et al., 2014	+	?	?	?	?	+	-
Flodin et al., 2017	?	?	?	?	?	-	-
Norcera et al., 2017	?	?	?	?	?	-	-
Motes et al., 2018	?	?	?	?	?	-	-

de Lange et al., 2017	+	?	?	?	?	+	+
Adnan et al., 2017	?	?	-	-	-	-	-
Kim et al., 2017	?	?	?	?	?	-	-
de Lange et al., 2018	+	?	?	?	?	+	-
McGregor et al., 2018	?	?	?	?	?	-	-
Rosano et al., 2017	?	?	+	+	-	+	+
Sexton et al., 2020	-	-	-	-	-	-	-
Shaaban et al., 2019	-	-	-	-	-	+	+
ten Brinke et al., 2015	-	-	+	?	-	-	-
Voelcker Rehage et al., 2011	+	?	?	?	?	+	+
Voss et al., 2013	?	?	?	?	?	?	-
Voss et al., 2010	?	?	?	?	?	?	-
Voss et al., 2019	?	?	?	?	-	+	-
Rehfeld et al., 2017	+	?	?	?	?	?	-
Wu et al., 2018	?	?	?	?	-	-	-

+ = high risk of bias was present; - = low risk of bias; ? = risk of bias could not be assessed due to lack of information

Table 2-2a Basic Study Characteristics of Cognitive Training Studies

Study	Participants	Intervention	Control	Physical Function Outcome	Cognitive Function Outcome
Chapman et al., 2015	Sample Size : 18 Mean age: 61.8 (3.3) % Female: 55 Education: minimum high school MoCA: 27.9 (1.4) MMSE: NR	Intervention Length: 12 wks Type: Strategy-Based Training --> *Verbal and written* Frequency: 3x/wk Duration: 60 min Intensity: apply strategies as well at home Dropouts: 0 Adherence Rate: NR	Type: Wait Listed Control Sample Size: 19 Mean age: 64.0 (3.6) % Female: 74 Education: 3.5 (1.2) MoCA: 28.2 (1.4) MMSE: NR Dropouts: NR Adherence Rate: NR	Outcome: NA Change: NA	*Strategic Reasoning* -Test of strategic learning *Executive Function*: -Daneman and Carpenter -TMTB-A -Similarities *Immediate memory* -California Verbal Learning Test *Attention* -Delis Kaplan Executive function -Color Word Interference -Backward Digit Span Change: ↑ Strategic Reasoning and Similarities
de Lange et al., 2018	Sample Size: 57 Mean age: 72.8 (2.6) % Female: 49 Education: 15.4 (3.6) MoCA: NR MMSE: 28.6 (1.3)	Intervention Length: 10 wks active; 10 weeks rest; repeat Type: Memory Training □ *Computerized Training* Frequency: 1x/wk, 8 home assignments, at least 4 must be done Duration: NR Intensity: Increase difficulty Dropout: NR Adherence Rate: 69-74%	Type: Active Control Sample Size: 18 Mean age: 73.5 (2.9) % Female: 61 Education: 16.2 (2.7) MoCA: 28.2 (1.5) MMSE: NR Dropouts: NR Adherence Rate: NR		Outcome: - verbal recollection - Wechsler digit span - Rey-O complex figure test - paired-words test -CVLT learning and recall trials Change: ↑ after active intervention and further during second active phase
	Sample Size: 50 Mean age: 73.5 (3.2) % Female: 68	Intervention Length: 10 wks rest; 10 weeks active - repeat Type: Memory Training		Outcome: NA Change: NR	

	Education: 14.2 (2.6) MoCA: NR MMSE: 28.8 (1.1)	□ *Computerized Training* Frequency: 1x/wk, 8 home assignments, at least 4 must be done Duration: NR Intensity: Increase difficulty Dropout: NR Adherence Rate: 69-74%			
de Lange et al., 2016	Sample Size: 76 Mean age: 73.6 (3.0) % Female: 76 Education: 15 (2.7) MoCA: NR MMSE: 28.8 (1.2)	Intervention Length: 10 wks active; 10 weeks rest; repeat Type: Memory training□ *Computerized Training* Frequency: 1x/wk and eight weekly home assignments (at least four completed) Duration: NR Intensity: word list increased by 5 words each week Dropouts: 9 Adherence Rate: 74%			
	Sample Size: 18 Mean Age: 73.5 (2.9) % Female: 61.1 Education: 16.2 (2.7) MoCA: NR MMSE: 28.2 (1.5)	Intervention Length: 10 wks rest; 10 weeks active - repeat Type: Memory Training □ *Computerized Training* Frequency: 1x/wk and eight weekly home assignments (at least four completed) Duration: NR Intensity: word list increased by 5 words each week Dropouts: 0 Adherence Rate: 70%	Type: Passive Sample Size: 49 Mean Age: 73.4 (3.2) % Female: 67.3 Education: 14.2 (2.6) MoCA: NR MMSE: 28.8 (1.1) Dropouts: 1 Adherence: NR	Outcome: NA Change: NR	Outcome: -verbal recollection Change: ↑ after memory training

de Lange et al., 2017	Sample Size: 44 Mean age: 73.3 (2.7) % Female: 53 Education: 15.7 (3.1) MoCA: NR MMSE: 28.8 (1.3)	Intervention Length: 10 wks active; 10 weeks rest; repeat Type: Memory Training □ *Computerized Training* Frequency: 1x/wk Duration: NR Intensity: word list increased by 5 words each week Dropouts: 13 Adherence Rate: 74%	Type: Passive Sample Size: 49 Mean Age: 73.4 (3.2) % Female: 67.3 Education: 14.2 (2.6) MoCA: NR MMSE: 28.8 (1.1) Dropouts: 1 Adherence: NR	Outcome: NA Change: NR	Outcome: -verbal recollection Change: ↑ after memory training
	Sample Size: 18 Mean Age: 73.5 (2.9) % Female: 61.1 Education: 16.2 (2.7) MoCA: NR MMSE: 28.2 (1.5)	Intervention Length: 10 wks rest; 10 weeks active; repeat Type: Memory Training □ *Computerized Training* Frequency: 1x/wk Duration: NR Intensity: word list increased by 5 words each week Dropouts: 0 Adherence Rate: 70%			
Lövdén et al., 2010	Sample Size: 12 Mean age: 68.9 (2.7) % Female: 58.3 Education: NR MoCA: NR MMSE: NR	Intervention Length: 24 weeks Type: Working memory □ *Computerized training* Frequency: 101 sessions over 180 days Duration: 60 min Intensity: not adjusted Dropouts: NR Adherence Rate: NR	Type: Passive Control Sample Size: 13 Mean age: 69.7 (3.5) % Female: 30.8 Education: NR MoCA: NR MMSE: NR Dropouts: NR Adherence Rate: NA	Outcome: NA Change: NR	Outcome: *Working Memory* *Episodic Memory* *Perceptual Speed* Change: all ↑ after training
Heinzel et al.,	Sample Size: 19	Intervention Length: 4 weeks	Type: Younger Control	Outcome: NA	Outcome

2014	Mean age: 66.0 (3.7) % Female: 68 Education: 15.6 (3.3) MoCA: NR MMSE: NR	Type: Working memory □ *Computerized training* Frequency: 3x/wk Duration: 45 min Intensity: increased according to performance Dropouts: NR Adherence Rate: NR	Sample Size: 18 Mean age: 24.1 (2.4) % Female: 55.6 Education: 16.4 (1.9) MoCA: NR MMSE: NR Dropouts: NR Adherence Rate: NA	Change: NR	*Short term memory* -digit span forwards and backwards *Processing Speed* -digit symbol substitution *Executive function* -Verbal fluency -Stroop task *Abstract Reasoning* -Raven's Standard Progressive Matrices -Figural Relations of German intelligence Change: ↑ digit span forward; digit symbol; figural relations
Heinzel et al., 2017	Sample Size: 18 Mean age: 65.8 (3.0) % Female: 61 Education: 15.4 (2.8) MoCA: NR MMSE: 29.2 (1.2)	Intervention Length: 4 weeks Type: Working memory □ *Computerized training* Frequency: 3x/wk Duration: 45 min Intensity: increased according to performance Dropouts: NR Adherence Rate: NR	Type: No contact control Sample Size: 16 Mean Age: 65.0 (3.7) % Females: 68.8 Education: 16.3 (3.6) MoCA: MMSE: 29.1 (0.99) Dropouts: NR Adherence Rate: NR	Outcome: NA Change: NR	Outcome: -N-back task -Transfer-task Change: - ↑ performance for 1 through 3-back - ↑ dual task performance - ↓ dual-task cost
Adnan et al. 2017	Sample Size: 11 Mean age: 65.9 (5.2) % Female: 73 Education: 17.3 (1.8) MoCA: NR MMSE: NR	Intervention Length: 5 weeks Type: goal-directed attention behavior □ *verbal and written* Frequency: 13 sessions and 20 hr at home Duration: 43 hours Intensity: progressively challenging situations	Type: Educational control Sample size: 13 Mean Age: 69.4 (5.2) % Female: 53.8 Education : 17.1 (2.3) MoCA: NR MMSE: NR Dropouts: 4 across both groups	Outcome: NA Change: NR	Outcome: - face/scene delayed matching task in scanner - selective attention Change: ↔

		Dropouts: 4 across both groups Adherence Rate: NR	Adherence Rate: NR		
Brehmer et al., 2011	Sample Size: 12 Mean age: 63.6 % Female: NR Education: NR MoCA: NR MMSE: NR	Intervention Length: 5 weeks Type: working memory, *computerized training* Frequency: once daily (5x/wk) Duration: 25 min Intensity: individually adjusted – increased or decreased based on performance Dropouts: 1 Adherence Rate: 100%	Type: Control (low level practice); same as intervention did not increase difficulty Sample Size: 11 Mean age: NR % Female: NR Type of Pop: NR Education: NR MoCA: NR MMSE: NR Dropouts: 0 Adherence Rate: 100%	Outcome: NA Change: NR	Outcome -Digit span - PASAT - Stroop - RAVEN *In scanner* -spatial delayed task Change: ↑ digit span backwards; PASAT - In Scanner: ↔
Hampstead et al., 2012	Sample Size: 11 Mean age: 73.2 (7.7) % Female: NR Education: 16.1 (3.4) MoCA: NR MMSE: 28.2 (1.5)	Intervention Length: 2 weeks Type: Mnemonic strategy *Computerized Training* Frequency: 5 sessions over 2 weeks Duration: 60 to 90 min Intensity: new sets introduced Dropouts: 1 Adherence Rate: NR	Type: Active control Sample Size: 10 Mean age: 72.5 (6.8) % Female: NR Education: 16.4 (2.0) MoCA: NR MMSE: 27.2 (2.2) Dropouts: 0 Adherence Rate: NR	Outcome: NA Change: NR	Outcome: - *encoding* - *retrieval* Change: ↔
Kim et al., 2017	Sample Size: 14 Mean age: 71.6 (3.9) % Female: 93 Education: 6.3 (4.0) MoCA: NR MMSE: NR	Intervention Length: 8 wks Type: Multi-Domain Training Frequency: 3x/wk Duration: 60 min Intensity: adjusted difficulty Dropouts: NR Adherence Rate: NR	Type: No contact control Sample Size: 13 Mean age: 71.3 (3.2) % Female: 100 Education: 7.3 (3.9) MoCA: NR MMSE NR Adherence Rate: NR	Outcome: NA Change: NR	Outcome: *Processing speed* -Stroop word-reading and color naming *Cognitive Control* -CTT-2 -Stroop color-word interference *Memory* -immediate and delayed recall

	Dropouts: NR	-recognition on verbal paired association for Korean Wechsler Memory Scale *Attention* -Digit span forward and backward - Digit symbol substitution Dementia Rating Scale-2 *In Scanner* -multi source interference task Change: - ↑ cognitive control; processing speed; and Dementia rating scale
Hampstead et al., 2020		

Note: NR = Not Reported; NA = Not Applicable; VO_2 = maximal/peak oxygen uptake; 3x/wk = 3 training sessions per week; min = minutes; MoCA = Montreal Cognitive Assessment; MMSE = Mini-mental Status Exam; ↑ = increase for that outcome; ↓ = decrease for that outcome; ↔ = no change for that outcome

Table 2-2b Basic Study Characteristics for Exercise Training Studies

Study	Participant	Intervention	Control	Physical Function Outcome	Cognitive Function Outcome
Motes et al., 2018	Sample Size: 19 Mean age: 62.9 (3.3) % Female: 71.4 Education: minimum high school MoCA: 27.8 (1.4) MMSE: NR	Intervention Length: 12 weeks Type: aerobic (cycle ergometer) Frequency: 3x/week Duration: 60 min Intensity: 50-75% max heart rate Dropouts: 5 Adherence: >90%	Type: Wait-listed control Sample Size: 15 Mean Age: 63.8 (3.4) % Female: 73.3 Type of Pop: Healthy Education: minimum high school MoCA: 28.4 (1.2) MMSE: NR Dropouts: NR Adherence: NA	Primary Outcome: VO_{2peak} Change: NR	Primary Outcome: Digit Symbol Verification Task (while in scanner) Change: NR
Chapman et al., 2016	Sample Size: 18 Mean age: 64.0 (4.3) % Female: 72 Education: minimum high school MoCA: 27.8 (1.5) MMSE: NR	Intervention Length: 12 weeks Type: aerobic (cycle ergometer) Frequency: 3x/week Duration: 60 min Intensity: 50-75% of VO_2max Dropouts: 0 Adherence: >90%	Type: Wait-listed control Sample Size: 20 Mean Age: 64.0 (3.6) % Female: 75 Education: minimum high school MoCA: 28.4 (1.4) MMSE: NR Dropouts: NR Adherence: NA	Primary Outcome: VO_{2peak} Change: NR	Outcome *Executive Function* - WAIS-III Similarities - Daneman Carpenter -Delis-Kaplan Executive Function System Sorting Test *Semantic verbal fluency* *Phonemic verbal fluency* *Working Memory* - California verbal learning test - Wechsler Memory Scale Logical memory subtest - Trails B Change: Unclear

Voss et al., 2013	Sample Size: 35 Mean age: 65.17 (4.4) % Female: 68.6 Education: 16.1 (3.0) MoCA: NR MMSE: 55.1 (1.8) [*modified mini]*	Intervention Length: 52 weeks Type: aerobic Frequency: 3x/wk Duration: 10 min and increased to 40 min in increments of 5 min Intensity: 50-60% max HRR up to week 7 then 60-75% after Dropouts: NR Adherence: 79%	Type: Flexibility training Adherence Rate: 80.9% Sample Size: 35 Mean Age: 64.6 (4.5) % Female: 60 Education: 16.2 (3.1) MoCA: NR MMSE: 55.2 (1.8) [*modified mini]* Dropouts: NR Adherence: 81%	Primary Outcome: Composite score of VO_2peak and the Rockport 1-mile test Change: ↑ for aerobic	Outcome: *Short term memory* -forward digit span -backward digit span *Executive control* -spatial working memory task - Wisconsin card sorting task Change: ↔
Voss et al., 2010	Sample Size: 30 Mean age: 65.4 (5.2) % Female: 73 Education: 15.9 (2.8) MoCA: NR MMSE: 55.2 (1.4)	Intervention Length: 52 weeks Type: aerobic Frequency: 3x/wk Duration: 50 min Intensity: 50-75% max HR Dropouts: 0 Adherence Rate: 76 %	Type: Flexibility and Balance Sample Size: 35 Mean Age: 65.8 (5.2) % Female: 71% Education: 15.9 (2.7) MoCA: NR MMSE: 54.8 (1.9) Dropouts: NR Adherence Rate: 80%	Primary Outcome: VO_{2peak} Change: ↑ for aerobic	Outcome *Short term memory* -forward digit span -backward digit span *Executive control* -spatial working memory task Wisconsin card sorting task Change: ↔
Rehfeld et al., 2017	**Dance:** Sample Size: 20 Mean age: 68.1 (4.3) % Female: 60 Education: 15.3 (2.3) MoCA: NR MMSE: 28.3 (0.95)	Intervention Length: 24 weeks Type: Dance Frequency: 2x/wk Duration: 90 min Intensity: more demanding and complex moves and beats per min Dropouts: 6	Type: See below Adherence Rate	Primary Outcome: Postural control (sensory organization test) Change: ↑ somatosensory; visual and vestibular	Outcome: NR Change: NA

		Adherence Rate: >70%			
	Multimodal Sample Size: 18 Mean age: 68.7 (2.7) % Female: 44 Education: 16.3 (1.4) MoCA: NR MMSE: 28.8 (0.79)	Intervention Length: 24 weeks Type: Multimodal exercise Frequency: 2x/wk Duration: 90 min Intensity: Not clear Dropouts: 8 Adherence Rate: >70%	Type: See above Adherence Rate	Primary Outcome: Postural control (sensory organization test) Change: ↑ somatosensory and vestibular	Outcome: NR Change: N/A
McGregor et al., 2018	Sample Size: 18 Mean age: NR % Female: 66 Education: NR MoCA: 26.8 (1.6) MMSE: NR	Intervention Length: 12 weeks Type: Aerobic Frequency: 3x/wk Duration: 20 min and worked to 45 min Intensity: 50-75% of Karvonen method Dropouts: 6 Adherence Rate: NR	Type: Balance Training Sample Size: 28 Mean age: NR % Females: 63.2 Education: NR MoCA: 26.8 (1.6) MMSE: NR Dropouts: 9 Adherence Rate: NR	Primary Outcome: estimated VO_2max (YMCA submaximal) Change: significant ↑	Outcome: NR Change: N/A
Wu et al., 2018	Sample Size: 16 Mean age: 64.9 (2.8) % Female: 81 Education: 13.8 (2.4) MoCA: 28.3 (1.5) MMSE: NR	Intervention Length: 12 wks Type: Tai-Chi Chaun Frequency: 3x/wk Duration: 60 min Intensity: 65.4% max HR Dropouts: 0 Adherence Rate: NR	Type: Passive control Dropouts: 4 Sample Size: 15 Mean Age: 64.9 (3.2) % Female: 100 Education: 13.4 (2.6) MoCA: 28.4 (1.5)	Primary Outcome: Muscle strength; 6 MWT Change: ↑ muscle strength; 6MWT	Outcome: Intra/Extra-Dimensional Set Shift Change: ↓ IED errors

			MMSE: NR Dropouts: NR Adherence Rate: NR		
Kleemeyer et al., 2016	Sample Size: 25 Mean age: 66.1 (4.2) % Female: 60% Education: 11.0 (1.6) MoCA: NR MMSE: 29.2 (1.3)	Intervention Length: 26 weeks Type: aerobic Frequency: 2 to 3 x/wk Duration: 25 – 50 min Intensity: 80-110% of ventilatory threshold Dropouts: not clear Adherence Rate: 94.2%	Type: low intensity Sample Size: 27 Mean Age: 65.9 (4.6) % Female: 63 Education: 11.1 (1.7) MoCA: NR MMSE: 28.9 (1.4) Dropouts: NR Adherence Rate: 92%	Primary Outcome: -VO_2max Change: ↔	Outcome: *Perceptual Speed* *Executive Control* *Episodic Memory* *Reasoning* *Vocabulary* Change: NR
Voelcker-Rehage et al., 2011	**Aerobic Training** Sample Size: 33 Mean age: 68.5 (3.1) % Female: 70.1 Education: 13 (3.0) MoCA: NR MMSE: NR	Intervention Length: 52 weeks Type: aerobic Frequency: 3x/wk Duration: 60 min Intensity: HR above aerobic threshold Dropouts: 16 Adherence Rate: NR	Type: Relaxation and Stretching Sample Size: 27 Mean Age: 69.3 (3.3) % Female: 54.5 Education: 12.1 (2.3) Dropouts: 16 Adherence Rate: NR	Primary Outcome: -submaximal VO_2max Change: ↑ VO_2 for aerobic	Outcome: *Executive control* *Perceptual speed* Change: both exercise ↑ performance
	Coordination Training Sample Size: 31 Mean Age: 71.1 (4.6) % Female: 63 Education: 12.1 (3.6)	Intervention Length: 52 weeks Type: Coordinative Frequency: 3x/wk Duration: 60 min Intensity: NA Dropouts: 15			

	MoCA: NR MMSE: NR	Adherence Rate: NR			
Rosano et al., 2017	Sample Size: 10 Mean age: 74.9 (4.4) % Female: 70% Education: 12 had high school or less MoCA: NR MMSE: NR	Intervention Length: 24 months Type: multi-modal exercise Frequency: 187 sessions Duration: 10 - 30 min Intensity: aerobic: RPE 12-14; strength: 15 to 16 Dropouts: NR Adherence Rate: 67%	Type: Health education Sample Size: 16 Mean Age: 76.8 (6.1) % Female: 87.5 Education: 5 had high school or less MoCA: NR MMSE: NR Dropouts: NR Adherence Rate: 91%	Primary Outcome: gait speed and body mass index Change: NR	Outcome: NR Change: NA
Nocera et al., 2017	Sample Size: 16 Mean age: 69.7 % Female: 63 Education: 16.1 (2.8) MoCA: 28.2 (1.2) MMSE: NR	Intervention Length: 12 weeks Type: aerobic Frequency: 3x/wk Duration: 20-45 min Intensity: 50-75% of max HRR Dropouts: 1 Adherence Rate: NR	Type: Balance Training Sample Size: 14 Mean Age: 72.1 (6.4) % Female: 42.9 Education: 15.5 (3.2) MoCA: 27.6 (1.1) MMSE: NR Dropouts: 1 Adherence Rate: NR	Primary Outcome: estimated VO_2max (YMCA submaximal) Change: ↑ VO_2max	Outcome: *Executive Function/Memory* - Letter & semantic fluency -Hopkins verbal learning -forward & reverse digit span Change: trend for increase; in-scanner verbal fluency ↑
Muller et al. 2017	**Dance Group** Sample Size: 12 Mean age: 68.3 (3.9) % Female: 50 Education: 15.5 (2.1)	Intervention Length: 72 weeks Type: Aerobic Frequency: 1- 2x/wk Duration: 90 min Intensity: increasing	**Sports Group**	Outcome: Physical working capacity 130 test Change: ↔	Outcome: *Verbal short- and long-term memory attention battery test* Change: both groups ↑

	MoCA: 28.3 (1.1) MMSE: NR	coordination and time pressure increase Dropouts: total study 8 Adherence Rate: 70%			
	Sports Group Sample size: 10 Mean age: 68.6 (2.8) % Female: 40 MoCA: 29.1 (0.6) MMSE: NR	Intervention Length: 72 weeks Type: Multimodal Frequency:1 to 2x/wk Duration: 90 min Intensity: Adapted based on HR Dropouts: total study 8 Adherence Rate: 70%			
ten Brinke et al., 2015	**Resistance** Sample Size: 12 Mean age: 73.8 (3.7) % Female: 100 Education: NR MoCA: 21.4 (3.6) MMSE: 26.7 (2.6)	Intervention Length: 26 wks Type: Resistance Frequency: 2x/wk Duration: 60 min Intensity: increased when 2 sets of 6-8 reps were completed with proper form and without discomfort Dropouts: 2 Adherence Rate: 54%	Type: Balance and Tone Training Sample Size: 13 Mean Age: 75.5 (3.9) % Female: 100 Education: 12.1 (2.3)	Outcome: NA Change: NA	Outcome: -Rey auditory verbal learning test Change: Report in relation to MRI
	Aerobic Sample Size: 14 Mean age: 76.1 (3.4)	Intervention Length: 26 wks Type: Aerobic			

	% Female: 100 Education: NR MoCA: 21.9 (3.1) MMSE: 27.5 (1.5)	Frequency: 2x/wk Duration: 60 min Intensity: 40-80% HRR Dropouts: 4 Adherence Rate: 60%	MoCA: 23.0 (2.7) MMSE: 27.2 (1.9) Dropouts: NR Adherence Rate 59%		
Bolandzadeh et al., 2015	**1x-wk** Sample Size: 22 Mean age: 69.6 (2.6) % Female: 100 Education: NR MoCA: 25.8 (2.9) MMSE: 28.9 (1.0)	Intervention Length: 52 wks Type: Resistance training Frequency: 1x/wk Duration:60 minutes Intensity: increased using the seven-repetition maximum method Dropouts: 4 Adherence Rate: 71%	Type: Balance training Sample Size: 15 Mean Age: 69.3 (2.8) % Female: 100 Education: NR MoCA: 24.4 (3.5) MMSE: 28.7 (1.3) Dropouts: 3 Adherence Rate: 62%	Outcome: - quadriceps strength Change: ↑ power 2x compared to control	Outcome: *Executive function* -Stroop task Change: Report in relation to MRI
	2x-wk Sample Size: 17 Mean Age: 69.2 (3.1) % Female: 100 Education: NR MoCA: 25.6 (2.9) MMSE: 28.8 (1.1)	Intervention Length: 52 wks Type: Resistance training Frequency: 2x/wk Duration: 60 minutes Intensity: increased using the seven-repetition maximum method Dropouts: 4 Adherence Rate: 70%			
Best et al., 2015	**1x/wk RT** Sample Size: 29; 10 at 2 year Mean age: 69.5 (2.7) % Female: 100 Education: NR	Intervention Length: 52 wks Type: Resistance training Frequency: 1x/wk Duration:60 minutes Intensity: increased using the			

	MoCA: NR MMSE: 28.5 (1.3)	seven-repetition maximum method Dropouts: 3 Adherence Rate: 70%	Type: Balance training Sample Size: 15 Mean Age: 70.0 (3.3) % Female: 100 Education: NR MoCA: NR MMSE: 28.8 (1.2) Dropouts: 3 Adherence Rate: 62%	Outcome: - quadriceps strength Change: ↑ power 2x compared to control	Outcome: *Executive function* -Stroop task -TMT A and B -backward digit span -digit symbol substitution test Change: ↑ executive function (1x and 2x/wk) and memory (2x/wk)
	2x/wk RT Sample Size: 21; 9 at 2 year Mean age: 69.4 (3.0) % Female: 100 Education: NR MoCA: NR MMSE: 28.6 (1.5)	Intervention Length: 52 wks Type: Resistance training Frequency: 2x/wk Duration: 60 minutes Intensity: increased using the seven-repetition maximum method Dropouts: 5 Adherence Rate: 71%			
Colcombe et al., 2006	Sample Size: 59 (total; half in intervention) Mean age: 65.5 % Female: 53 Education: 13.5 MoCA: NR MMSE: 29 (1.2)	Intervention Length: 24 wks Type: aerobic Frequency: 3x/wk Duration: 60 min Intensity: 40-70% HRR Dropouts: NR Adherence Rate: >85%	Type: Stretching and toning Sample Size: Mean Age: 66.9 % Female: 57 Education: 14 MoCA: NR MMSE: 29.4 (1.4) Dropouts: NR Adherence Rate: >85%	Primary Outcome: -VO_2peak Change: ↑ for aerobic	Outcome: NA Change: NA
Flodin et al., 2017	Sample Size: 22 Mean age: 68.4 (2.6) % Female: 59 Education: 13.8 (3.7) MoCA: NR	Intervention Length: 24 weeks Type: aerobic Frequency: 3x/wk Duration: 30 to 60 min Intensity: 40-80% max HR Dropouts: NR	Type: Stretching and Toning Sample Size: 25 Mean Age: 69.2 (3.0) % Females: 56 Education: 13.8 (5.0)	Primary Outcome: -VO_2peak Change: ↑ for aerobic	Outcome: *Verbal episodic memory* *Executive Function* *Working Memory* *Processing Speed* Change: NR

	MMSE: NR	Adherence Rate: NR	MoCA: NR MMSE: NR Dropouts: NR Adherence Rate: NR		
Ji et al., 2017	Sample Size: 12 Mean age: 67 (6.4) % Female: 42 Education: 17.2 (2.1) MoCA: NR MMSE: NR	Intervention Length: 6 weeks Type: exercise with Wii Frequency: daily Duration: 30 min Intensity: NR Dropouts: NR Adherence Rate: NR	Type: Wait-list control Sample Size: 12 Mean Age: 73.0 (8.0) % Females: 58.3 Education: 16.3 (2.6) MoCA: NR MMSE: NR Dropouts: NR Adherence Rate: NR	Outcome: NA Change: NR	Outcome: *Memory* -Hopkins Verbal Learning test-revised -Immediate and delayed story recall *Processing Speed* WAIS-III Digit symbol substitution Trails A *Working Memory* Digit Span *Executive Function* Trails B Stroop Colour and word test Change: ↑ Digit symbol
Maass et al., 2015	Sample Size: 21 Mean age: 68.8 (4.5) % Female: 52 Education: NR MoCA: NR MMSE: 28.95 (0.92)	Intervention Length: 12 wks Type: aerobic Frequency: 3x/wk Duration: 40 min Intensity: 65-85 % of Karvonen heart rate Dropouts: NR Adherence Rate: NR	Type: progressive muscle relaxation Sample Size: 19 Mean Age: 67.9 (4.1) % Female: 58 Education: MoCA: NR MMSE: 29.0 (0.9) Dropouts: NR Adherence Rate: NR	Outcome: aerobic threshold VO_2 Change: ↑ in VO_2	Outcome: *Verbal learning memory* - REY-O complex Change: only report in relation to MRI
Maass et al.,	Sample Size: 21	Intervention Length: 12 wks	Type: progressive muscle	Outcome:	Outcome:

2016	Mean age: 68.8 (4.5) % Female: 52 Education: NR MoCA: NR MMSE: 28.95 (0.92)	Type: aerobic Frequency: 3x/wk Duration: 40 min Intensity: 65-85 % of Karvonen heart rate Dropouts: NR Adherence Rate: NR	relaxation Sample Size: 19 Mean Age: 67.9 (4.1) % Female: 58 Education: NR MoCA: NR MMSE: 29.0 (0.9) Dropouts: NR Adherence Rate: NR	aerobic threshold VO_2 Change: ↑ in VO_2	*Verbal Learning Memory* -REY-O complex Change: only report in relation to MRI
Niemann et al., 2014	**Coordination Training** Sample Size: 19 Mean age: 69.6 (5.1) % Female: 68 Education: 11.9 (3.4) MoCA: NR MMSE: NR	Intervention Length: 52 weeks Type: Coordination training Frequency: 3x/wk Duration: 45-60 min Intensity: different exercise equipment; Dropouts: 16 excluded across 3 groups due to missing more than 33% of training Adherence Rate: NR	Type: Stretching and relaxation Sample Size: 49 Mean age: 68.8 (2.6) % Female: 54 Education: 12.2 (2.1) Dropouts: 16 excluded across 3 groups due to missing more than 33% of training Adherence Rate: NR	Primary Outcome: -VO_2peak Change: ↑ in VO_2	Outcome: NA Change: NA
	Aerobic Training Sample Size: 17 Mean age: 68.8 (2.6) % Female: 71 Education: 11.2 (2.1) MoCA: NR MMSE: NR	Intervention Length: 52 weeks Type: aerobic training Frequency: 3x/wk Duration:45-60 min Intensity: 60% of VO_2max Dropouts: 16 excluded across 3 groups due to missing more than 33% of training Adherence Rate: NR			

Chao et al., 2020	**Treadmill** Sample Size: 9 Mean age: 71.2 (1.4) % Female: 56 Education: 13.8 (0.7) MoCA: NR MMSE: NR	Intervention Length: 16 weeks Type: Treadmill training Frequency; 3x /wk Duration: 50 min Intensity: 55-69% of age predicted MHR Dropouts: NR Adherence Rate: 84%	Type: NR Sample Size: 9 Mean age: 67.7 (1.1) % Female: 55.6 Education: 6.4 (1.1) Dropouts: NR Adherence Rate: NR	Outcome: NR Change: NR	Outcome: Cognitive Abilities Screening Instrument Change: ↑ for dance compared to control
	Dance Sample Size: 10 Mean age: 68.3 (1.3) % Female: 60 Education: 11 (1.1) MoCA: NR MMSE:NR	Intervention Length: 16 weeks Type: Dance training Frequency: 3x /wk Duration: 50 min Intensity: 55-69% of age predicted MHR Dropouts: NR Adherence Rate: 90%			
Sexton et al., 2020	Sample Size: 23 Mean age: 65.5 (4.0) % Female: 65 Education: 3.0 (1.1) MoCA: NR MMSE: NR	Intervention Length: 12 weeks Type: aerobic Frequency: 3x/wk Duration: 30 min Intensity: 55-85% max HR Dropouts: 2 Adherence Rate: 89.2%	Type: No contact Sample Size: 23 Mean age: 67.7 (6.0) % Female: 61 Education: 3.5 (1.2) MoCA: NR MMSE: NR Dropouts: 2 Adherence Rate: NR	Outcome: VO_2 max Change: ↑ in VO_2 for aerobic	Outcome: *Executive Function* -Digit Span -letter and category fluency -TMT B -one and two back *Memory* - Hopkins Verbal Learning -Rey O Figure *Processing Speed* -TMT A -digit coding -CANTAB Change: ↔

Note: NR = Not Reported; NA = Not Applicable; VO_2 = maximal/peak oxygen uptake; 3x/wk = 3 training sessions per week; min = minutes; MoCA = Montreal Cognitive Assessment; MMSE = Mini-mental Status Exam; ↑ = increase for that outcome; ↓ = decrease for that outcome; ↔ = no change for that outcome

Table 2-3 Simple MRI Results

Study	GMV	WM	DWI	BOLD	CBF	Connectivity
			COGNITIVE TRAINING			
Chapman et al., 2015			↑		↑	↑
de Lange et al., 2017			↔			
de Lange et al., 2018			↓ MD, RD, AD ↑ FA			
Lövdén et al., 2010			↓MD ↑FA			
Heinzel et al., 2014	↔			↓		↔
Heinzel et al., 2017				↓		
de Lange et al., 2016						
Adnan et al., 2017				↑		
Brehmer et al., 2011				↓		
Hampstead et al., 2012	↔	↔				
Chapman et al., 2016					↑	
Kim et al., 2017				↑		
Hampstead et al., 2020				↑ and ↓		
			EXERCISE TRAINING			
Motes et al., 2018				↑	↔	
Chapman et al., 2016					↔	
Voss et al., 2013						↑
Voss et al., 2010						↑
Rehfeld et al., 2017	↑	↑				
McGregor et al., 2018						↑
Wu et al., 2018				↑		
Kleemeyer et al., 2016	↑		↑ MD			
Voelcker-Rehage et al., 2011				↓aerobic ↑coordination		
Rosano et al., 2017	↑					
Norcera et al., 2017				↓		
Muller et al., 2017	↑					
ten Brinke et al., 2015	↑aerobic ↔ resistance					
Bolandzadeh et al., 2015		↓WML				
Best et al., 2015		↓WM atrophy				

Colcombe et al., 2006	↑							
Flodin et al., 2017						↔	↔	
Ji et al., 2017	↑							
Maass et al., 2015	↔						↑	
Maass et al., 2016								
Niemann et al., 2014	↑							
Chao et al., 2020								↑
Sexton et al., 2020	↔	↔	↔					
Shaaban et al., 2019		↓ WMH grade						
Voss et al., 2019			↔					

Simple table demonstrating if studies (separated into CT and ET) observed changes to magnetic resonance imaging outcomes after each intervention. A blank cell represents that this outcome was not measured in this study; "↑" demonstrated an increase to said outcome; "↓" decrease to that outcome after the intervention; "↔" dictates no change observed after the intervention. GMV= grey matter volume; WM= white matter: DWI= diffusion-weighted imaging; BOLD = blood oxygenated level dependent signal; CBF=cerebral blood flow; MD= mean diffusivity; RD = radial diffusivity; AD: axial diffusivity; FA = fractional anisotropy; WML= white matter lesions

3 Manuscript 2: Higher cardiovascular fitness level is associated with lower cerebrovascular reactivity and perfusion in healthy older adults

This manuscript was published in Journal of Cerebral Blood Flow and Metabolism (DOI: 10.1177/0271678X19862873 (Intzandt et al., 2020)). Brittany Intzandt, Dalia Sabra, Catherine Foster, Laurence Desjardins-Crépeau, Richard D Hoge, Christopher J Steele, Louis Bherer, and Claudine J Gauthier.

3.1 Preface

During aging, there are significant changes in the vascular system that can negatively affect the cerebrovascular system. Importantly, given the positive effect that cardiovascular fitness has been found to have on the peripheral vascular system, it was hypothesized that these results would extend to the cerebrovascular system. Indeed, those individuals with higher cardiovascular fitness have been found to have enhanced GMV as well as CBF. However, recent work has suggested that perhaps CBF is not a sensitive enough marker of cerebrovascular health in isolation and that more dynamic components of cerebral hemodynamics in aging, like CVR, could be valuable. CVR, as a marker of vascular reserve rather than function, is known to decline earlier than CBF in aging and disease, and thus could be an effective biomarker of cerebrovascular health. Therefore, it would be hypothesized that increased cardiovascular fitness would be associated with greater CVR, as it is assumed to represent the health of the cerebral vasculature, yet this is not always reported. For example, some have reported the inverse association in Master Athlete's, with higher fitness relating to lower CVR, and other have found no difference. The current study presented in Chapter 3, aimed to address in a sample of non-Master Athletes, but healthy older adults, if in fact cerebral hemodynamics, in particular CVR, were positively related to cardiovascular fitness. To investigate this, we included a sample of younger adults, as well as healthy older adults to identify age-related differences in cerebrovascular health, and to identify if they were influenced by cardiovascular fitness. All participants underwent a peak oxygen uptake test on a cycle ergometer to assess VO_2peak as well as an MRI where T1-weighted scans to quantify GMV, and dual-echo pCASL scans were acquired at rest and during exposure to a carbon dioxide breathing manipulation, to quantify CBF and CVR respectively.

3.2 Abstract

Aging is accompanied by vascular and structural changes in the brain, which include decreased grey matter volume (GMV), cerebral blood flow (CBF), and cerebrovascular reactivity (CVR). Enhanced fitness in aging has been related to preservation of GMV and CBF, and in some cases CVR, although there are contradictory relationships reported between CVR and fitness. To gain a better understanding of the complex interplay between fitness and GMV, CBF and CVR, the present study assessed these factors concurrently. Data from fifty participants, aged 55 to 72, was used to derive GMV, CBF, CVR and VO_2peak. Results revealed that lower CVR was associated with higher VO_2peak throughout large areas of the cerebral cortex. Within these regions lower fitness was associated with higher CBF and a faster hemodynamic response to hypercapnia. Overall, our results indicate that the relationships between age, fitness, cerebral health and cerebral hemodynamics are complex, likely involving changes in chemosensitivity and autoregulation in addition to changes in arterial stiffness. Future studies should collect other physiological outcomes in parallel with quantitative imaging, such as measures of chemosensitivity and autoregulation, to further understand the intricate effects of fitness on the aging brain, and how this may bias quantitative measures of cerebral health.

3.3 Introduction

Continuous and optimal blood flow is thought to be necessary for structural integrity and normal neuronal activity in the brain (Erecińska & Silver, 1989). During aging, the vascular system undergoes a cascade of events that negatively affect the integrity of the cerebrovascular system, leading to decreased perfusion. However, it may be possible to reduce these deficits, and in some instances, reverse them as a result of plasticity. Plasticity refers to the capacity of the brain to change its function, hemodynamics and microstructure in response to cognitive or physiological challenges (Knaepen, Goekint, Heyman, & Meeusen, 2010; Kraft, 2012). In aging, there is some indication that physical activity may be capable of inducing beneficial plastic changes (Erickson & Kramer, 2009; C. Sexton et al., 2016). Notably, aerobic exercise has become a subject of particular interest for maintaining and even enhancing cognition and brain integrity (Erickson, Leckie, & Weinstein, 2014a;Erickson & Kramer, 2009; Gomes-Osman et al., 2018). It is likely that these effects are mediated by changes in cerebrovascular health given the well-established positive influence of exercise on the cardiovascular system in aging (Heckman & McKelvie, 2008; Seals, Walker, Pierce, & Lesniewski, 2009). It has been demonstrated that more highly fit individuals have enhanced endothelial function (Ashor et al., 2015) and reduced arterial stiffness (Monahan, Tanaka, Dinenno, & Seals, 2001; Seals et al., 2009), both of which are impaired in aging (Meyer et al., 2015; Pugh & Wei, 2001; Zieman, Melenovsky, & Kass, 2005). Of note, individuals who are more "highly fit" have higher cardiovascular fitness (VO_2peak), which can be quantified in multiple ways. Specifically, VO_2max is considered the gold standard measure (Saltin & Strange, 1992). However, reaching a true VO_2max is difficult to attain for many older adults, thus utilizing VO_2peak is a more feasible option (Hollenberg, Ngo, Turner, & Tager, 1998; Huggett et al., 2005). These measurements will therefore be referred to as VO_2peak for the remainder.

Given the positive relationship between the vascular system and exercise, there is an increasing body of work investigating the relationship amongst aging, VO_2peak, cerebral structural integrity and hemodynamics. Magnetic Resonance Imaging (MRI) is the method of choice to study these relationships as it is a versatile technique which can be used to measure several of these parameters, including grey matter volume (GMV), cerebral blood flow (CBF) and cerebrovascular reactivity (CVR). In general, GMV and CBF are positively associated with VO_2peak in cross-sectional (Thomas, Dennis, Bandettini, & Heidi, 2012; Tseng, Uh, Rossetti,

Cullum, et al., 2013; Zimmerman et al., 2014) and longitudinal studies (Chapman et al., 2013; Colcombe et al., 2003, 2006; Erickson et al., 2010; Maass, Düzel, Goerke, Becke, Lovden, et al., 2015). However, many of the existing studies showing this beneficial effect have used GMV as a marker of "structural integrity". This is problematic because GMV has been shown to be mainly qualitative and physiologically non-specific (Tardif et al., 2016; Tardif et al., 2017), making a mechanistic interpretation of these effects difficult.

More physiologically specific approaches have involved looking at the relationship between CBF and VO_2peak. In cross-sectional studies, it has been demonstrated that there is a positive relationship between VO_2peak and CBF (Tarumi et al., 2013; Thomas et al., 2013; Zimmerman et al., 2014). This also seems partly supported by intervention studies. For instance, Chapman et al., 2013 (Chapman et al., 2013) found that individuals who completed a 12-week aerobic training program demonstrated significant increases in CBF compared to the passive control group. Yet, in a later study Chapman et al. (2016)(Chapman, Aslan, Spence, Keebler, et al., 2016) found CBF to be unchanged after the same aerobic training program. While this could be due to an insufficient exercise dose, it is possible that CBF is not a sensitive enough marker of cerebrovascular health in isolation. This could be both due to its relatively limited signal-to-noise ratio (Petcharunpaisan, Ramalho, & Castillo, 2010) and the fact that homeostasis seeks to maintain CBF to ensure adequate perfusion to maintain oxygen and glucose delivery (Willie, Tzeng, Fisher, & Ainslie, 2014). There are indications that while CBF does steadily decrease across the lifespan (Chen & Pike, 2010), more dynamic aspects of hemodynamics, such as cerebrovascular reactivity (CVR) may change earlier than CBF in the course of aging (de Vis et al., 2015; Gauthier et al., 2013; Jefferson et al., 2018).

CVR is measured as the hemodynamic response (in terms of CBF or blood-oxygen-level dependent (BOLD) change for example) to a vasodilatory challenge, such as hypercapnia (Liu, De Vis, & Lu, 2018), breath-holds (Bright & Murphy, 2013) or acetazolamide (Inoue, Tanaka, Hata, & Hara, 2014b). CVR is hypothesized to represent the health of the cerebral vasculature (Mandell et al., 2008). If it is assumed that CO_2-related local chemosensitivity is consistent across age and disease groups, it could be treated as a vascular vasodilatory capacity biomarker. Furthermore, if CVR is taken to be a marker of vascular health, it can be posited that those with higher VO_2peak levels would have greater CVR, as their vascular system would be more

compliant and therefore have an increased ability to respond to a vasodilatory stimulus. Consistent with this hypothesis, it has been demonstrated that CVR is decreased in aging (Gauthier et al., 2013; Lu et al., 2011), stroke (Krainik, Hund-Georgiadis, Zysset, & von Cramon, 2005) and carotid artery stenosis (Hartkamp, Hendrikse, van der Worp, de Borst, & Bokkers, 2012). Yet, the literature has found conflicting results *within* healthy populations, where some have observed elevated CVR in relation to higher VO_2peak levels (Bailey et al., 2013; Barnes, Taylor, Kluck, Johnson, & Joyner, 2013; Braz, Flück, Lip, Lundby, & Fisher, 2017; Tarumi et al., 2015), while others have found that lower CVR is related to increased VO_2peak (Thomas et al., 2013), and others have found no difference (Krainik et al., 2005; Lu et al., 2011; Mandell et al., 2008) in aging. It is unclear, however, if this is due to differences in measurement method, spatial localization of the measurement or an interesting physiological interplay between multiple hemodynamic aspects of brain health.

In summary, there is an assortment of negative consequences that can occur due to an aging vascular system that causes deterioration of brain microstructure and hemodynamics. Importantly, there is evidence that exercise is capable of mitigating some of these adverse age-related complications. Yet, the fitness literature suggests that the effects of exercise on brain hemodynamics may be complex, so a more comprehensive imaging approach is necessary to understand the interplay between the effects of aging and VO_2peak on cerebral hemodynamics. The present study explores the relationship between aging, VO_2peak, cerebral hemodynamics and GMV using a cross-sectional dataset employing a comprehensive imaging approach in healthy younger and older adults of varying VO_2peak.

3.4 Methods

3.4.1 Participants

A total of 28 young adults (7 females, mean age 24 ± 3 years) and 50 older adults (37 females, mean age 63 ± 5 years) participated in this study. Participants were recruited through participant databases at the Centre de recherche de l'Institut universitaire de gériatrie de Montréal and Laboratoire D'Etude de la Santé cognitive des Ainés.

Inclusion criteria were comprised of being between 18 to 40 years for young adults and 55 to 75 years for older adults; approval by a geriatrician to participate (older adults), non-smoker (for at least five years), no evidence of cognitive impairment as determined through cognitive tests conducted by a neuropsychologist, and ability to complete the peak oxygen uptake test (VO_2peak) and MRI. Exclusion criteria included taking prescription medication that could be vasoactive (e.g., diuretics, calcium channel blockers, statins, thyroid replacement hormones, etc.), presence of cardiac disease, hypertensives, neurological or psychiatric illnesses, diabetes, asthma, thyroid disorders, or excessive drinking (more than two drinks per day). Finally, a neuropsychologist completed the Mini Mental Status Examination, a global cognitive screening tool for dementia; participants with scores less than 26 (out of 30) were excluded (Kurlowicz & Wallace, 1999).

All procedures were approved by Comité mixte d'éthique de la recherche du Regroupement Neuroimagerie/Québec and were conducted according to the Declaration of Helsinki. All participants provided written informed consent.

3.4.2 MRI acquisition

All acquisitions were completed on a Siemens TIM Trio 3T MRI system (Siemens Medical Solutions, Erlangen, Germany). A 32-channel head coil was used for all brain acquisitions. An anatomical $1mm^3$ MPRAGE acquisition (TR/TE/flip angle = 300ms/3ms/90°, 256x240 matrix) was acquired for registration and GMV estimation. A fluid attenuation inversion recovery (FLAIR) acquisition with parameters: TR/TE/flip angle 9000 ms/107 ms/120° with echo train length of 15, an inversion time of 2500 ms, 512 x 512 matrix for an in-plane resolution of 0.43 x 0.43 mm and 25 slices of 4.8 mm was used to estimate the presence and severity of white-matter lesions in older adults. A pseudo-continuous arterial spin labeling (pCASL) acquisition (Wu, Fernández-Seara, Detre, Wehrli, & Wang, 2007), providing simultaneous BOLD contrast using dual-echo readouts (TR/TE1/TE2/flip angle = 2000ms/10ms/30ms/90°, 4x4x7mm voxels, 64x64 matrix and 11 slices, post-label delay = 900ms, tag duration = 1.5s, and a 100mm gap) was acquired during a hypercapnia challenge.

3.4.2.1 Aortic Exam

As described in (Gauthier et al., 2015), during the MRI session a thoracic aortic exam was also acquired using simultaneous brachial pressure recording (Model 53,000, Welch Allyn,

Skaneateles Falls, NY USA) using a 24-element spine matrix coil. Black blood turbo spin echo sagittal oblique images were acquired to visualize aortic arch (TR/TE/flip angle: 700ms/6.5 ms/180°, 1.4 x 1.4 mm in-plane resolution, 2 slices at 7.0 mm). A perpendicular plane to the ascending and descending aorta was defined from these images. A cine phase-contrast velocity encoded series was collected (TR/TE/flip angle: 28.6ms/1.99ms/30°, 1.5 x 1.5 mm x 5.5 mm) during 60 cardiac cycles in three segments, with velocity encoding of 180 cm/s. A series of cine FLASH images were also acquired in the same plane (TR/TE/flip angle: 59ms, 3.44ms, 15°; 1.2 x 1.2mm x 6mm) over 60 cardiac cycles in 8 segments.

3.4.2.2 Hypercapnia

The hypercapnic manipulation used here has been described previously (Gauthier et al., 2015; Gauthier et al., 2013). Briefly, it was completed with a computer-controlled gas system with a consecutive gas delivery circuit (Respiract™ GEN3, Thornhill Research Inc., Toronto Canada) (Slessarev et al., 2007). End tidal O_2 was targeted to be 100mmHg throughout the manipulation, while CO_2 had a target of 45mmHg during the hypercapnia blocks and 40 mmHg during normocapnia. More specifically, two hypercapnia blocks of two minutes each in duration, were completed after, and followed by two-minute blocks of breathing room air. Participants breathed through a soft plastic mask (Tegaderm 3M Healthcare, St. Paul MN) that was secured on their face with adhesive tape to ensure that no leaks were present. Participants completed the breathing manipulation once prior to being in the scanner (to ensure comfort and tolerance to procedure), and once during the MRI session.

3.4.3 VO_2peak

Participants completed a maximal oxygen consumption test (VO_2peak) to approximate their VO_2peak, where a greater amount of oxygen consumed indicates enhanced VO_2peak (Storer, Davis, & Caiozzo, 1990). The test was completed on a stationary cycle ergometer and was monitored throughout by an electrocardiogram under medical supervision to ensure participant safety. Initial workload was set based on the body weight of the individual (1 watt (W) / kg) and then increased incrementally by 15 W every minute until voluntary exhaustion. Oxygen uptake was determined using an automated system that averaged in 30-second

increments (Moxus, AEI Technologies, Naperville, IL). The highest oxygen uptake over a 30-second period during the test was considered as the VO_2peak (ml/kg/min).

3.4.4 Data Analysis

3.4.4.1 Grey Matter Volume

T1-weighted MPRAGE images were preprocessed using SPM's Computational Anatomy Toolbox (CAT)12 (Ashburner & Friston, 2000; Gaser & Dahnke, 2016; Penny, Friston, Ashburner, & Kiebel, 2011) to calculate voxel-based morphometry (VBM) after data were segmented into grey matter, white matter and cerebrospinal fluid (CSF). VBM calculates the difference between the volume estimated for tissue from an individual compared to the expected volume of tissue from a template. This provided a statistical map for each voxel type which are then classified into the structural category with the highest probability, allowing for analysis between participants.

The registration matrix was calculated as part of the VBM pipeline and was then applied to the GMV, CBF and CVR maps (described below) to bring them from native to MNI space. Individual BOLD-CVR, resting CBF and CBF-CVR were produced for each participant. Co-registration of these maps from native to native T1 space was performed using a non-linear rigid registration with ANTS (Avants, Epstein, Grossman, & Gee, 2008) with a b-spline interpolation. CAT12 (Ashburner & Friston, 2000; Gaser & Dahnke, 2016; Penny et al., 2011) was used to register from T1 to standard space using a uniform non-linear registration with 12 degrees of freedom and smoothing of the data employed a Gaussian filter of 8 mm. An average grey matter mask from each age group was also created to restrict voxel-wise analyses to the grey matter.

3.4.4.2 CVR Analysis

Preprocessing of the BOLD-CVR have been described previously and was performed using Neurolens2 (www.neurolens.org) (Gauthier et al., 2013). All raw images were preprocessed with motion correction[52] and spatial smoothing with a 6mm Gaussian kernel. The BOLD signal was extracted from the second echo series with a linear surround addition (Gauthier et al., 2012; Gauthier & Hoge, 2012; Liu & Wong, 2005). The BOLD fractional change during hypercapnia was obtained by fitting a general linear model to the BOLD signal and dividing the estimated effect size by the estimated constant term. Glover's parameters (1999)

(Glover, 1999) for a single-gamma hemodynamic response function were used when fitting the linear models, which also included linear, quadratic, and third order polynomials representing baseline signal and drifts. The BOLD percent change obtained was then divided by the average end-tidal CO_2 change during the hypercapnia manipulation to yield BOLD-CVR. CBF-CVR was calculated in the same way as BOLD-CVR, but the CBF signal was isolated from the first series of echoes using linear surround subtraction (Liu & Wong, 2005).

3.4.4.3 Resting CBF analysis

Resting CBF was quantified using the first echo of the whole pCASL data time series, using the first two minutes of the time series, before the beginning of the first hypercapnia block. The average of the control images was used for each participant with modeling of the T1-recovery to obtain the fully recovered magnetization (M0) using AFNI, FSL and in-house scripts. CSF masks were created for each older adult participant to use as CSF M0 in the CBF quantification. To do this, 10 voxels were chosen in the same axial slice for all older participants where the lateral ventricles were clearly located, except for four participants where a more superior, or inferior slice was required to clearly identify the ventricles from the pCASL scans. All individual masks were visually inspected to ensure the ROIs were located in the ventricles. For the younger adults, one participant was chosen at random, and the same method was used to identify 10 voxels. A single CSF mask was used for all younger participants as this mask was confirmed to be located in the ventricles in all participants upon visual inspection. However, this was not possible with the older adults due to varying anatomical structures. FSL's BASIL (Chappell, Groves, Whitcher, & Woolrich, 2009) toolkit was then utilized to quantify CBF, with the following standard parameters : labelling: cASL/pCASL; bolus duration: constant (1.5s), post label delay: 0.9 s; calibration image: average of the control images; reference tissue type: CSF; mask: CSF mask for each participant; CSF T1: 4.3s; TE: 10 ms; T2 : 750 ms; blood T2: 150 ms; arterial transit time: 1.3 s, T1: 1.3s , T1 blood: 1.65s, inversion efficiency: 0.85.

3.4.4.4 Vascular lesion quantification

The volume of white matter hyperintensities (WMH) in the brain was estimated in a semi-automatic way as described in (Gauthier et al., 2015). Briefly, a single trained rater, who was blinded to clinical information, visually identified WMH on the FLAIR images, which were

then delineated using Jim image analysis package, version 6.0 (Xinapse Systems Ltd, Northants, UK).

3.4.4.5 Pulse Wave Velocity Data

The aortic data was analyzed using the ARTFUN software (Herment et al., 2010), where pulse wave velocity (PWV) was computed between the ascending and descending aorta using the cine phase contrast images for blood velocity and the cine images for aorta delineation. PWV was calculated as described in (Gauthier et al., 2015). This data was included as a covariate, so that any relationships that might be present between VO_2peak and the hemodynamic brain outcomes were not due to differences in arterial stiffness in large arteries among the older adults but rather to brain-specific properties.

3.4.4.6 Voxel-wise analyses

Using FSL's toolbox Randomise (Winkler, Ridgway, Webster, Smith, & Nichols, 2014); permutation-based threshold-free cluster enhancement (TFCE) (Smith & Nichols, 2009), using 10,000 permutations, was employed to test for spatial relationships between VO_2peak and structural or hemodynamic outcomes. These analyses were restricted to GM using a group mask of all GM voxels present in all participants (i.e. the intersection of all participants GM segmentation mask in MNI space). A separate group GM mask was created for younger and older adults. Voxel-wise general linear models were used to identify the relationship within GM between: i) VO_2peak and GMV; ii) VO_2peak and BOLD-CVR; iii) VO_2peak and resting CBF; and iv) VO_2peak and CBF-CVR data for young and older adults. Age and sex were included for both young and older adults as covariates. For the older adults we also included sex-specific estimated absolute multivariate risk scoring with the Framingham cardiovascular risk factor, as proposed by(B et al., 2008), to estimate general cardiovascular risk and future cardiovascular risk as a confound.. Volume of WMH and PWV were also used as potential confounds in the older adults to remove the potential effects of existing WM lesions and central arterial stiffness.

3.4.4.7 Regions of Interest

Voxels that exhibited a significant relationship between BOLD-CVR and VO_2peak were extracted and binarized to be used as regions of interest (ROI) for further analysis. Specifically, this ROI was then used to further investigate if VO_2peak and GMV, resting CBF, or CBF-CVR

were related to each other in these regions, in an attempt to disentangle the physiological relationship amongst these factors in aging and VO_2peak. This ROI was then multiplied by each individual's VBM map to create individual ROI masks. The values from each participant for this individual ROI were then extracted for all maps using weighted average with FSLmeants to correct for possible GM atrophy.

Finally, a finite impulse response (FIR) analysis was completed as reported in (Gauthier et al., 2013) to estimate the temporal course of the BOLD response to hypercapnia in order to identify whether dynamic aspects of the response could be linked to VO_2peak. Briefly, the average time course for BOLD during hypercapnia was determined, where the temporal response was measured starting 15 seconds prior to and after the end of each hypercapnic block. The beginning of the upward phase of the response, as well as the plateau were identified manually and the linear fit for the values between these two points (slope of the upward response) was identified using a linear regression in the SPSS 20.0 software (IBM, Armonk, New York, USA) for each participant. The BOLD time course was averaged within the BOLD-CVR VO_2peak ROI for both young and older adults, these values were then extracted. With the exclusive intent of facilitating visualization, the older adult group was then rank ordered according to their VO_2peak. Once rank ordered, they were subdivided into five bins based on VO_2peak to further visualize the relationship between response shape and VO_2peak.

3.4.5 Statistical Analysis

Statistical analysis of the behavioural data was completed using SPSS to identify if relationships were present between VO_2peak and demographic data with correlational analyses. A partial correlation was used to identify if there were relationships between VO_2peak and values extracted from the significant CVR-BOLD VO_2peak ROI, while accounting for the covariates described above (e.g., age, sex, PWV, Framingham Risk Factors, white matter hyperintensity volume). As the white matter hyperintensity volumes were found to be non-normal, it was necessary to log transform this data to allow for parametric statistical analyses with the data. All other data were found to be normally distributed. Finally, a partial correlation analysis was also utilized to investigate potential relationships between VO_2peak and the slope of the BOLD upward response where age was included as a covariate. Statistical significance was set to $p \leq 0.05$ for all outcomes and Tukey's post-hoc analysis was used where applicable.

3.5 Results

3.5.1 Younger versus older adults

A total of 50 older adults and 26 young adults participated in this study, demographics for both are listed in Table 1.

3.5.2 VO_2peak, brain structure and hemodynamics in GM

The mean values over all GM for hemodynamic parameters in each participant versus VO_2peak for both young and older adults are shown in *Figure 1*. It was found that younger adults had a significantly higher GMV ($p = 4.43x10^{-15}$), BOLD-CVR ($p = 1.4x10^{-4}$) and resting CBF ($p = 0.015$) in whole GM than older adults. There were no differences between age groups for CBF-CVR in whole GM ($p = 0.315$) (*Table 1).*

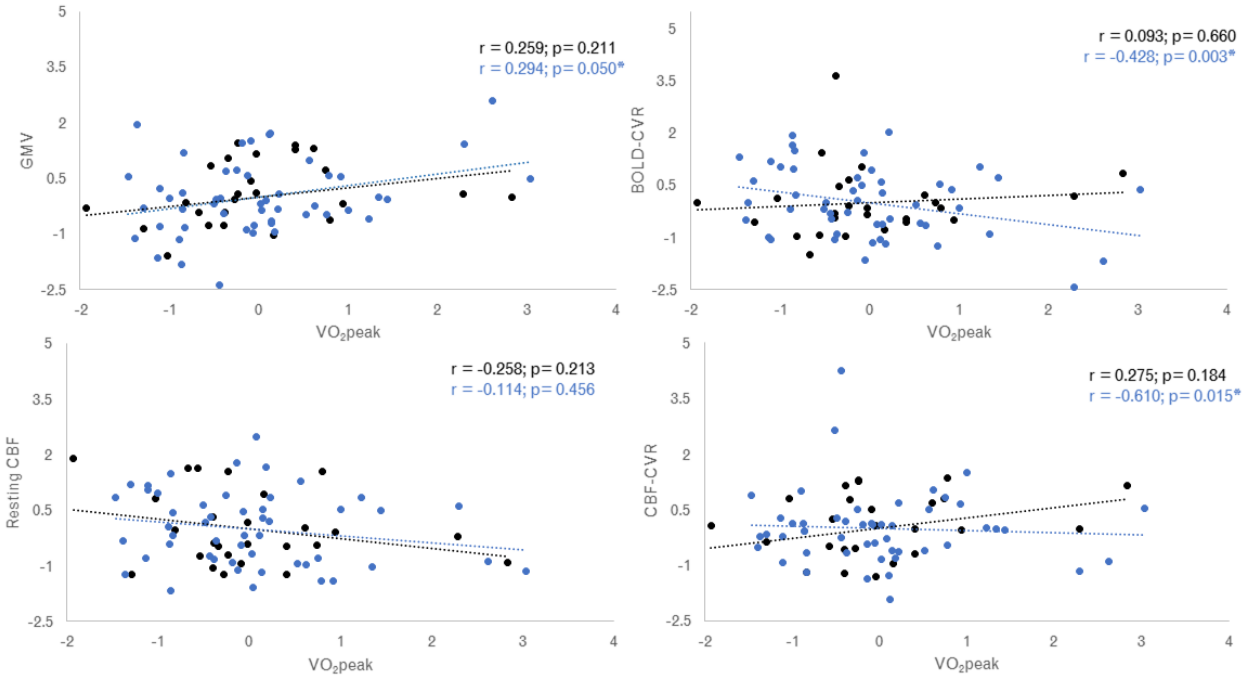

Figure 3—1: Results from voxel-wise analysis for relationships between structural and hemodynamic outcomes with VO2peak z-scores (ml/kg/min) for young adults (black dots) and older adults (blue dots). (a) grey matter volume z-score (mm3); (b) BOLD-CVR (%BOLD/mmHg CO2) z-score; (c) resting CBF (ml/100g/min) z-score and; (d): CVR CBF (ml/100g/min/mmHg CO2) z-score. The regression line for each group is plotted in their corresponding colours. *Indicates significant correlation ($p \leq 0.05$).

3.5.2.1 Young Adults

Correlations found no significant relationships between VO_2peak, and the mean extracted values for GMV, BOLD-CVR, resting CBF or CBF-CVR in GM for young adults ($p > 0.05$).

3.5.2.2 Older Adults

A partial correlation in older adults including all covariates (e.g., age, sex, Framingham Risk Factor score, WMH and PWV) revealed a significant relationship between VO_2peak and: i) all GMV ($r = 0.294$; $p = 0.05$); ii) BOLD-CVR in GM ($r = -0.428$; $p = 0.003$); and iii) CBF-CVR in GM ($r = -0.361$; $p = 0.015$). No significant correlation was found between VO_2peak and resting CBF in all GM ($p > 0.05$).

3.6 VO_2peak, structure and hemodynamics

Voxel-wise analyses within the younger adults did not reveal any significant relationships between VO_2peak and GMV or between VO_2peak and the hemodynamic outcomes ($p > 0.05$) within GM. In older adults, voxel-wise analyses within GM revealed a significant positive relationship between GMV and VO_2peak ($r = 0.320$; $p = 0.025$) and a significant negative association between BOLD-CVR and VO_2peak ($r = -0.392$; $p = 0.005$). The positive relationship between GMV and VO_2peak was present within the superior temporal gyrus (*see Figure 2a).* The negative association between BOLD-CVR and VO_2peak was found in large portions of temporal, parietal cortices, and smaller amounts of the frontal lobes (*see Figure 2b*). No relationship was found between VO_2peak and resting CBF or CBF-CVR ($p>0.05$).

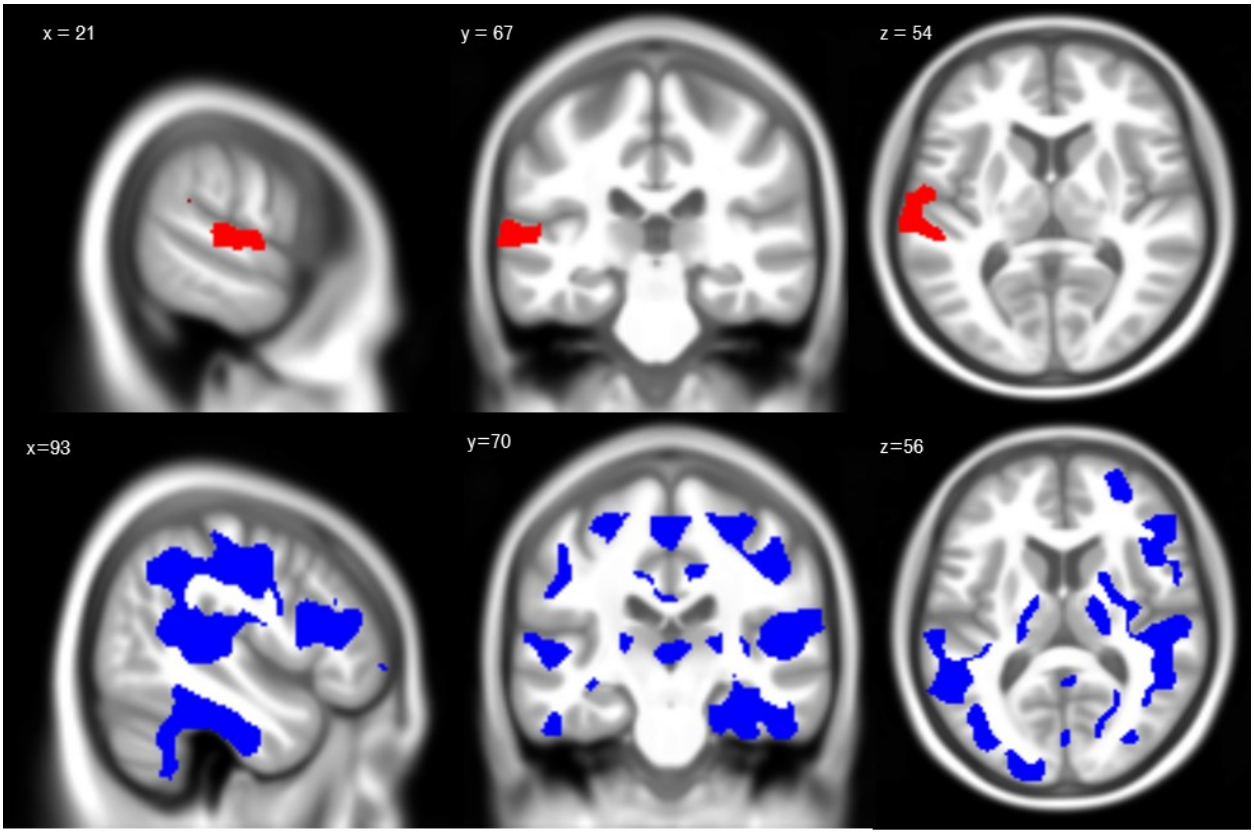

Figure 3—2 : Voxel-wise analyses results in older adults. Significant regions identified with the voxel-wise analysis between VO_2peak z-score and GMV z-score (a). This figure shows areas of the brain where there is a positive association between VO_2peak z-score and GMV z-score (red), indicating that in these areas, those with higher fitness have significantly higher GMV compared to those with lower fitness ($p<0.05$). Significant regions identified with the voxel-wise analysis between VO_2peak z-score and BOLD-CVR z-score. Areas of the brain where there is a negative association between VO_2peak and BOLD-CVR (blue), indicating that in these areas, those with higher fitness have significantly reduced BOLD-CVR compared to those with lower fitness ($p<0.05$).

3.6.1 Region of Interest Analysis

To understand whether the relationship between VO_2peak and other structural or hemodynamic parameters could help to explain the negative association between VO_2peak and BOLD-CVR, other parameters were averaged in the areas significantly negatively related between BOLD-CVR and VO_2peak. Within these ROI a significant negative relationship was identified between VO_2peak and resting CBF ($r = -0.328$, $p = 0.025$), and VO_2peak and CBF-CVR ($r = -0.322$, $p = 0.029$). The relationships between all structural or hemodynamics outcomes within these ROI with VO_2peak are shown in Figure 3.

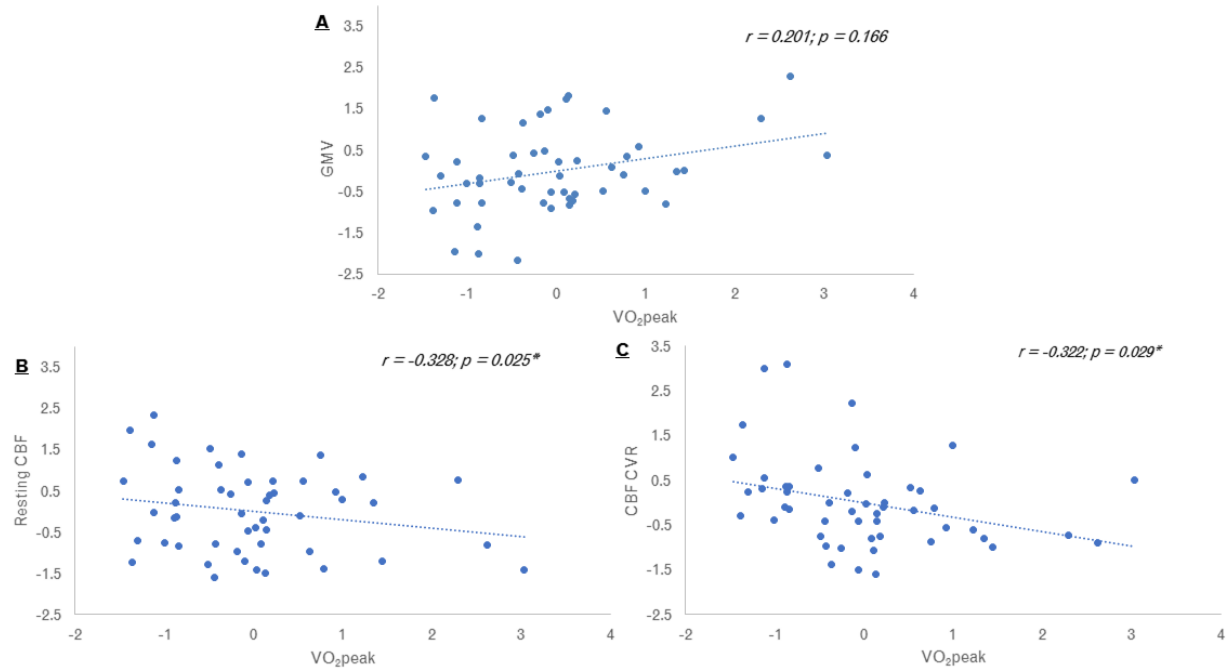

Figure 3—3: Association between fitness, structure, and hemodynamics in the BOLD-CVR vs VO2peak ROI. Relationships from the CVR VO2peak z-score ROI in; (a): GMV z-score; (b): Resting CBF z-score; and (c). CBF-CVR z-score. Graphs demonstrate the relationship between each of these parameters and fitness in older adults. *Represents significant correlation ($p < 0.05$).

3.6.2 Finite Impulse Response

Finally, to identify potential relationships between VO_2peak and BOLD response dynamics, a Finite Impulse Response (FIR) analysis was run within the ROI derived from the voxel-wise analysis of CVR and VO_2peak. For visualization purposes, the BOLD time course to hypercapnia in these areas for older adults consisted of rank ordering based on VO_2peak, then creating five different bins according to their rank order (see Figure 4a). The partial correlation analysis revealed that there was a significant negative correlation between VO_2peak and the slope of the linear regression ($r = -0.441$; $p = 0.002$). This relationship is shown in Figure 4b.

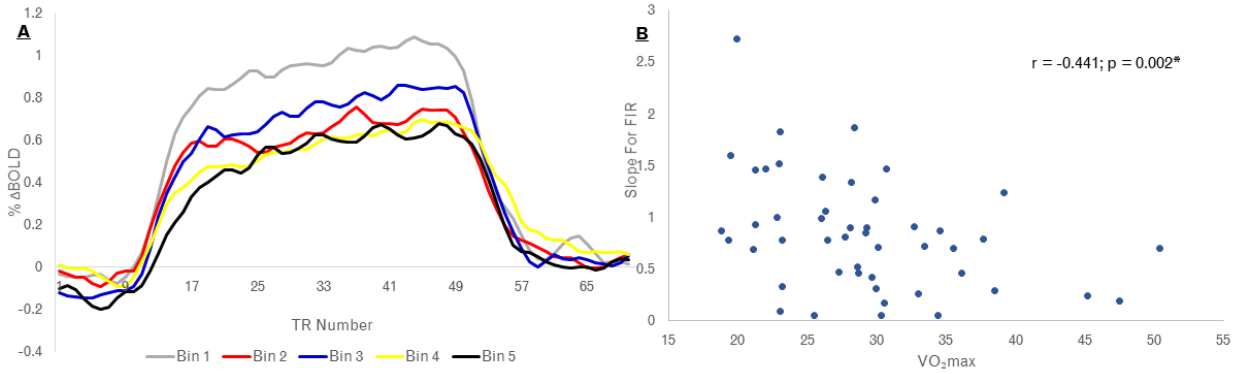

Figure 3—4: Time course of the BOLD response to hypercapnia. (a) Time course showing the percent BOLD response to hypercapnia in BOLD-CVR VO_2peak ROI. Where the fitness level for older adults was binned into five categories; Bin 1 representing the lowest VO_2peak bin, and increasing until Bin 5, which includes the data from those with the highest binned VO_2peak in this sample. (b) Linear regression of the relationship between the slope of the upward portion of the response and fitness in older adults.

3.7 Discussion

This study investigated the relationship between VO_2peak, GMV and brain hemodynamics in a population of healthy older adults. This group showed the expected pattern of reduced GMV, BOLD-CVR and resting CBF as compared to healthy younger adults. Voxel-wise analyses over all GM demonstrated a significant positive relationship between VO_2peak and GMV and a somewhat surprising significant inverse relationship between BOLD-CVR and VO_2peak in older adults in a number of GM regions throughout the cortex. A more in-depth review of hemodynamics within these regions demonstrated that the relationship between VO_2 and other hemodynamic parameters also exhibited this inverse relationship. Specifically, there was no relationship between VO_2peak and GMV, but a significant negative relationship between VO_2peak and resting CBF, and between VO_2peak and CBF-CVR. To determine whether these relationships between VO_2peak and BOLD-CVR were confined to response amplitude or if it was also present in response dynamics, we performed an analysis of the time course of the BOLD response to hypercapnia. This analysis revealed a slower ramp-up towards a plateau in those with higher VO_2peak, regardless of age as demonstrated in figure 4b. Together, these results indicate that the relationship between VO_2peak and hemodynamics in aging is more complex than previously thought and that BOLD-CVR in particular may be biased by physiological mechanisms affected by exercise.

3.7.1 Age-group comparisons

The impact of healthy aging on brain structure and hemodynamics is an active field of research and the age group comparisons performed as part of this study are consistent with these existing results. In comparison to young adults, older adults were found to have lower: GMV (Braz et al., 2017; Farokhian, Yang, Beheshti, Matsuda, & Wu, 2017; Maillet & Rajah, 2013), CVR (Catchlove, Parrish, et al., 2018; de Vis et al., 2015; Flück et al., 2014; Gauthier et al., 2013; Peng et al., 2018b), and resting CBF (de Vis et al., 2015; Gauthier et al., 2013).

3.7.2 Regional relationships between VO_2peak, structure and hemodynamics

The main result from this study is the finding that BOLD-CVR in GM is negatively correlated with VO_2peak in older adults. Voxel-wise analysis revealed large sections of GM including temporal, parietal and frontal regions were responsible for this negative relationship. Given that higher CVR is typically interpreted as being related to better cerebral health (Mandell et al., 2008), this reverse relationship was counter-intuitive. Interestingly, to date, only one other published study (in addition to our own work (Gauthier et al., 2015)) has also demonstrated a negative relationship between VO_2peak and BOLD-CVR in older adults (Gauthier et al., 2015; Thomas et al., 2013). Specifically, Thomas et al. (2013) (Thomas et al., 2013) found that Master athletes had significantly lower BOLD-CVR compared to their sedentary counterparts over most of cerebral cortex, including the parietal and temporal cortices. Notably, most studies investigating VO_2peak and hemodynamics have used transcranial Doppler (TCD) to identify a positive relationship between CVR and VO_2peak (Bailey et al., 2013; Barnes et al., 2013; Braz et al., 2017; Tarumi et al., 2015). To the best of our knowledge, MRI studies have only identified a negative relationship, perhaps reflecting the different vascular compartments and properties imaged with both techniques. TCD images flow velocity in major arteries, while the BOLD signal reflects a mixture of blood flow, blood volume and oxidative metabolism arising from the parenchyma and veins. Therefore, it is possible that changes in the venous system, such as venous collagenosis, or related to the parenchymal vasculature leads to the BOLD-CVR results measured using MRI.

The voxel-wise analysis also revealed a positive relationship between VO_2peak and GMV within the superior temporal gyrus. This is consistent with other studies pointing to a general association between VO_2peak and GMV (Erickson et al., 2014a), and specifically within the superior temporal gyrus (Zheng et al., 2018) . However, as mentioned previously, GMV

should be interpreted with caution as it is qualitative, not physiologically specific, and may be biased by differences in blood volume (Tardif et al., 2016; Tardif et al., 2017).

Notably, the lack of relationship with other hemodynamic parameters could be attributable to the fact that the present study involved a very healthy group of older adults. Exclusion criteria were numerous, including but not limited to, taking most medication regularly, suffering from chronic diseases, or cardiovascular risk factors. Moreover, the Framingham scores for this group is low, with the average (8.8) just below the score expected solely due to the average age of the group (9), indicating overall absence of cardiovascular risk factors within the group. Furthermore, participants in this study had VO_2peak values that were greater than the 50^{th} percentile for their age and sex, thus demonstrating higher than average VO_2peak levels (Kaminsky, Imboden, Arena, & Myers, 2017). Therefore, it is possible that the relationship between VO_2peak and these other hemodynamic parameters is below the detection limit in this healthy group of older adults, especially in the context of the limited SNR provided by ASL and the stringent thresholding required by the numerous multiple comparisons performed in voxel-wise analyses. Our findings suggest that CVR may be one of the first hemodynamic properties to decline in aging and indicates that it may be more sensitive to aging-related changes in the cerebral vasculature, than CBF and GMV, in line with previous published work (Gauthier et al., 2013).

3.7.3 Physiological underpinnings of BOLD-CVR and fitness association

To better understand the physiological underpinnings of this negative relationship between VO_2peak and BOLD-CVR, a more in-depth investigation of the relationship between VO_2peak and other hemodynamic parameters and GMV within these regions was performed. No relationship between GMV and VO_2peak was revealed, however resting CBF and CBF-CVR had significantly negative associations with VO_2peak, indicating that lower fit individuals had higher CBF and CBF-CVR. These findings are in opposition to those reported in the extant literature by Tarumi et al. (Tarumi et al., 2013), where endurance-trained older adults showed a higher CBF in the occipitoparietal area as compared to their sedentary counterparts. These results are difficult to compare to those of the present study. Firstly, because the coordinates for the areas used in Tarumi et al. are not available, so that any putative overlap between region and ROI used in the present study is impossible to determine. Secondly, the endurance trained group had

considerably higher VO_2peak than this cohort. Zimmerman and colleagues (Zimmerman et al., 2014) also found higher global, frontal and parietal CBF in those with greater VO_2peak levels. However, 39% of their participants were taking blood pressure medication, thus it could be that medication impacted these results given the vasoactive nature of these molecules. Future studies, with both larger VO_2peak and cardiovascular health ranges, are therefore necessary to determine whether non-linear effects in the link between CBF and VO_2peak can account for these contradictions in the literature.

While hyperperfusion is not typically associated with aging, one area of research that has identified a pattern of hyperperfusion in similar areas is the APoE ε4 literature (Scarmeas, Habeck, Stern, & Anderson, 2003; Thambisetty, Beason-Held, An, Kraut, & Resnick, 2010; Wierenga et al., 2013). Scarmeas and colleagues (2003) found that both young and older individuals with the APoE ε4 gene demonstrated hyperperfused areas of the brain compared to non-carriers (Scarmeas et al., 2003). Furthermore, a longitudinal study in older adults found that areas that were hyperperfused at baseline in carriers as compared to non-carriers, had significantly lower CBF at the 8-year follow-up (Wierenga et al., 2013). Given the similarity in the hyperperfusion pattern, it is possible that part of our results could be explained by putative over-representation of APoE ε4 carriers in the low VO_2peak participants. However, as we did not measure APoE expression in our participants, we cannot assess whether this is the case. In general however, one could speculate that these patterns of hyperperfusion in APoE ε4 carriers and in the less fit individuals included in this study could indicate that there exists a set of physiological compensatory mechanisms which initially seem like preserved hemodynamics, but that are in fact associated with poorer health or greater damage over time.

3.7.4 Chemosensitivity and autoregulation

In addition to the relationship between BOLD-CVR and VO_2peak already discussed (Figure 4A), we also identified a relationship between the slope of the upswing of the response to hypercapnia and VO_2peak. The slower BOLD response to hypercapnia in more highly fit older adults could be indicative of a local desensitization to CO_2, or to pre-dilation (Halani, Kwinta, Golestani, Khatamian, & Chen, 2015), however the latter is unlikely here as lower resting CBF was found to be linked to higher VO_2peak within these same regions. Further studies including

additional measurement of autoregulation and the respiratory response to exercise, for example, could help untangle the physiological underpinning of these response dynamics.

Overall, there are a few rationales that could explain our results of low BOLD-CVR in higher fit individuals. The first, hypothesized by Thomas and colleagues (Thomas et al., 2013), is that perhaps higher fit individuals have decreased local sensitivity to CO_2 , likely, a lifetime of increased exposure because of increased aerobic activity. This idea is consistent with studies showing that endurance training reduces the ventilatory response at a given workload, indicating a decrease in local chemosensitivity (Katayama et al., 1999; McConnell & Semple, 1996). Nitric oxide is the primary mechanism to respond to changing pH levels from CO_2 in an attempt to maintain homeostasis in the brain (Haas, Brigitte, Biessmann, & Wildemann, 2002; White, Vallance, & Markus, 2000). It is thus possible that higher fit individuals could have lower levels of nitric oxide in response to hypercapnia than lower fit individuals, which in turn would explain the reduced blood flow response to hypercapnia. Moreover, it has also been proposed that cerebral inflammation could lead to increased nitric oxide signaling (Haas et al., 2002), thus lower fit individuals could have increased nitric oxide due to the presence of inflammation. This would also be consistent with the higher resting CBF observed in lower fit individuals. The presence of inflammation is, however, unlikely to be the main explanation for our results, given the overall health of this cohort. Lastly, nitric oxide and CO_2 have an effect on cerebral autoregulation (White et al., 2000); when present, it increases the ability of the cerebral blood vessels to dilate or constrict in response to a sudden change in blood pressure, allowing for sufficient blood to flow. For example, it has been found that those with arterial hypertension, have greater central chemosensitivity than those without (Malenfant et al., 2017). Moreover, during exhaustive exercise cerebral autoregulation was decreased compared to rest (Ogoh et al., 2005), and was observed to be reduced in young master athletes compared to sedentary counterparts (Mikkel et al., 2011). It is therefore possible, given the interplay between CO_2 sensitivity (local versus central), nitric oxide presence and cerebral autoregulation, that in combination this may account for the reduced BOLD-CVR in higher fit individuals in aging.

The results of this and other studies have shown that quantitative techniques such as MRI measurements of CVR and CBF may be biased by health components not typically taken into account in MRI studies (e.g., local or central chemosensitivity and cerebral autoregulation). This

is problematic as it may lead to bias in group comparisons or longitudinal studies. Though we were not able to test these additional parameters in the present study, it highlights the need for comprehensive studies that seek to measure all the components of the complex relationship between cerebral hemodynamics and VO_2peak. These studies are necessary to make these techniques truly quantitative and reveal the physiological changes that occur in aging and disease.

3.8 Limitations

Although we found that higher VO_2peak is related to decreased BOLD-CVR in aging, it is difficult to interpret our results in comparison to other studies due to the high level of variability of BOLD-CVR in the aging literature. For example, some report 0.19% BOLD/mmHg in line with our results (Bhogal et al., 2016), yet another study has reported higher levels at 0.28% (Larissa et al., 2018) and lower levels at 0.13% (Leoni et al., 2017). This indicates that there is physiological variability within individuals and between studies, and potentially technical variability (i.e., type of scanner, delivery of CO_2, amount of CO_2 inhaled). Moreover, given that our CO_2 challenge was 5 mmHg, it could be that our data suffers from worse SNR than what would be expected with a greater amount of CO_2 delivered, such as 10 mmHg**.** Therefore, more work is necessary to further comprehend inter-individual variability, and to implement more robust study designs with a greater breadth of outcome measures and to implement progressive hypercapnia in addition to block designs.

A limitation of the use of ASL for measuring CBF is that extensive coverage of the entire brain is typically not possible without advanced parallel imaging techniques. Given that the original aim of this study at the time of data collection was more focused on executive functions and the frontal lobes it was not possible to capture structural and hemodynamics of the hippocampus. Therefore, while the hippocampus is a structure associated with VO_2peak-related changes, we are unable to test for associations between the hippocampus and VO_2peak here. Furthermore, the post-label delay chosen here is suboptimal for older adults, so that lower perfusion measured could be the result of slower transit time, rather than lower perfusion. Moreover, given that blood flow velocity is likely increased during hypercapnia, and it is known that labeling efficiency decreases as blood velocity increases (Aslan et al., 2010), there is a potential for our CBF data during hypercapnia to be underestimated as we assumed a consistent

labeling efficiency which is likely not the case. Thus, future work aiming to disentangle the relationships among aging, cognition and VO_2peak should optimize the acquisition, using a multi-band acquisition approach for example, to capture both the entire cerebral cortex and the hippocampus, and multiple post-label delays to better capture perfusion across age and VO_2peak.

Another limitation to this study is its cross-sectional design, which makes it difficult to draw clear conclusions about the relationships between VO_2peak, aging and brain health**.** While large longitudinal cohorts exist, none have so far also included measurement of CVR and VO_2peak, likely because these techniques are challenging to implement. On the other hand, ASL acquisitions are becoming more common and future studies could attempt to use cohorts of older adults for studying the relationship between physical activity, CBF and other measures of vascular health. Dedicated longitudinal studies over several years including VO_2peak, CBF and CVR would however be necessary to truly understand these relationships. Although VO_2max is considered the gold standard of cardiovascular fitness, there are some indications from the literature that a true VO_2max may not be practically attainable in older adults (Huggett et al., 2005). Thus, we used VO_2peak here. It is also noteworthy that there are inherent limitations to using either as an outcome, as they can be influenced by genetics, pulmonary function, skeletal muscle limitations, cardiac output, to name a few (see (Bassett & Howley, 2000) for in depth review), which were not measured in this study.

3.9 Conclusions

Overall, this paper identified a negative relationship between BOLD-CVR and VO_2peak in a very healthy older adult sample. Within the ROI's that demonstrated a significant relationship, other hemodynamic outcomes also showed negative relationships with VO_2peak. These negative relationships could be the result of changes in CO_2 sensitivity, or autoregulation. In addition, our findings suggest that quantitative measures of CVR and CBF could be biased by unknown physiological changes in these autoregulatory and chemosensitivity properties, and that studies using these markers in aging and disease may underestimate their effects on cerebral hemodynamics. Thus, to further understand and attempt to disentangle the modulatory effect that VO_2peak has on hemodynamics in aging, more comprehensive studies of physiological outcomes are necessary.

Table 3-1: Participant demographics separated by age group

Demographic	Young Adults (n=26)	Older Adults (n=50)
Sex (M/F)	19/7 *	17/33 *
Age (years)	23.7 (2.9) *	63.4 (4.9) *
Education (years)	16.7 (1.4)	16.4 (3.6)
VO_2peak (ml/kg/min)	42.7 (7.6) *	29.1 (7.0) *
MMSE (out of 30)	--	28.8 (0.9)
Framingham Risk Factor Score	--	8.8 (2.6)
Log WMH volume	--	0.367 (0.162)
Grey Matter Volume (mm^3)	0.551 (0.038) *	0.466 (0.034) *
BOLD-CVR (%change/mmHg CO_2)	0.261 (0.094) *	0.176 (0.041) *
Resting CBF (ml/100g/min)	48.6 (10.7) *	42.4 (9.9) *
CBF-CVR (ml/100g/min/mmHg CO_2)	5.13 (1.22)	4.63 (2.35)

Note: independent samples t-tests were used to identify differences between young and older adults. * Statistically different $p < 0.05$; all values reported are mean (±standard deviation)

4 Manuscript 3: Sex-Specific Relationships Underly the Interactions between Obesity and Physical Activity on Gray and White Matter Volume in a Sample of Cognitively Unimpaired Older adults

This manuscript is under review at GeroScience. Brittany Intzandt, Safa Sanami, Julia Huck, PREVENT-AD Research group, Sylvia Villeneuve, Louis Bherer, and Claudine Gauthier

4.1 Preface

Obesity is on the rise in aging populations and its presence has important vascular impacts, including increased risk of diabetes, cardiovascular disease, and early mortality. In the brain, obesity has been associated with a reduction to GMV and WMV in aging populations, however this has not always been a consistent finding. The relationship between obesity and volumetric outcomes could be influenced by sex-specific differences. For example Taki and colleagues revealed that only males had significantly declined GMV with obesity (Taki et al., 2008). Conversely, PA has been consistently shown to be associated with increased GMV in aging (Domingos, Pêgo, & Santos, 2021; Erickson et al., 2010; Papenberg et al., 2016), but appears to also be influenced by sex, where some report that females benefit more from PA than males (Varma et al., 2015), and others the opposite (Casaletto et al., 2020). Yet, to date, no study has investigated the interaction of obesity and PA on volumetrics in aging, since it is possible that higher PA levels in individuals with greater BMI could be driving some of the positive relationships, The effects of sex could also play an important role in these interactions given the sex-dependent effects associated with both obesity and PA.

In manuscript three, we attempted to disentangle these interactions in a sample of normal cognitively unimpaired older adults which forms the baseline data from the PREVENT-AD data set. A total of 340 participants were included in this manuscript and BMI was measured. A PA questionnaire was also collected allowing us to quantify amount of weekly METs for moderate-vigorous PA as well as total, though the latter is only included in supplementary information given its overlap with intensity-specific findings. Finally, all participants also completed an MRI session, where an assortment of sequences were collected see (Breitner, Poirier, Etienne, &

Leoutsakos, 2016; Tremblay-Mercier et al., 2021) for more information. For the purposes of this manuscript only the T1-weghted sequence was used to quantify GMV and WMV in regions that are associated with age and cognitive related decline, to understand the effects of obesity and PA on these outcomes.

4.2 Abstract

BACKGROUND: During aging, different studies have found obesity to be associated with both poorer or better brain structural integrity compared to their normal weight counterparts. Conversely, those with greater physical activity (PA) levels are consistently reported to have enhanced cerebral structural outcomes. Thus, the protective effects of PA could alleviate the negative effects of obesity and could partially explain why overweight and obese individuals sometimes are reported to have enhanced cerebral health. Sex-related differences may also contribute to some of these discrepancies, as it is known that in aging, an individual's sex influences cerebral health. Thereby, the influence of obesity and PA on structural integrity in aging should be investigated with sex-disaggregated analyses. Here, we aimed to examine potential sex differences in the relationships among PA, obesity, and cerebral structure in aging.

METHODS: The PREVENT-AD dataset was utilized here. 247 females (62.6 years old ± 4.9) and 93 males (62.8 years old ± 4.9) participated in this study. All participants underwent a 3T Magnetic resonance imaging (MRI) acquisition, including a T1-weighted scan to quantify grey matter volume (GMV) and white matter volume (WMV) All participants had their height and weight measured to calculate body mass index (BMI). A PA questionnaire was used to quantify weekly total Metabolic Equivalents. For each sex, BMI and PA outcomes were converted to z-scores. Polynomial regressions were used, controlling for age, education, Framingham Cardiovascular Risk Factor scores and presence of APOE ε4 alleles. The relationships between i) BMI and GMV Regions of Interest (ROIs) and WMV ROIs; ii) Moderate-vigorous PA and GMV and WMV ROIs; iii) the interaction of moderate PA with BMI on GMV and WMV ROIs were also explored.

RESULTS: Increased BMI was associated with higher GMV in frontal and temporal regions in female, whereas males demonstrated an inverse U shape in frontal, temporal, and parietal regions. In females an inverse U relationship was found between moderate PA and GMV in frontal and temporal regions. Males demonstrated a positive linear relationship between moderate PA in the hippocampi. Finally, females with higher PA levels demonstrated increased GMV across the BMI spectrum, whereas male with high PA and greater BMI demonstrated the lowest GMV. WMV ROIs in temporal regions had a linear relationship with moderate PA in. In

males, increased BMI was associated with lower WMV in frontal regions, they also showed a positive relationship with moderate PA and WMV in the hippocampus.

CONCLUSION: Males and females have unique relationships among GMV, PA and BMI, suggesting that sex-aggregated analyses may lead to biased or non-significant results due to the different relationships in both sexes. These results suggest that higher GMV is present in overweight to obese females, and those females with greater PA levels have enhanced structural integrity. Males demonstrated results unique to females, highlighting the importance creating models for each sex separately. Future work should include other imaging parameters, such as perfusion, to identify if these differences are co-occurring in the same regions as grey matter.

4.3 Introduction

Obesity has a high incidence in individuals in midlife and into aging, with 39.9% of middle age and older adult populations being overweight and 28.1% considered obese (Government of Canada, 2019). This has important health implications given that obesity is associated with a higher incidence of diabetes, cardiovascular disease, certain types of cancers, and increased risk of early mortality (Hruby & Hu, 2015). Furthermore, a recent Lancet dementia commission paper identified that greater body mass index (BMI), an indirect marker of obesity, is one of the 12 of the most influential modifiable factors in the risk of developing dementia (Livingston et al., 2020a). Notably, greater BMI earlier than 65 years old has been associated with a 1.6 increased relative risk of developing dementia (Pedditizi et al., 2016). Yet, this relationship is sometimes elusive, as some have found no relationship between BMI and dementia risk (Albanese et al., 2015).

These paradoxical findings also exist in the documented relationship between BMI and brain structure. For example, it has been identified that higher BMI may have deleterious impacts on the brain, including data showing an association between higher BMI and global grey matter (GM) atrophy, as well as atrophy of frontal, temporal, and hippocampal areas (Masouleh et al., 2016; Pannacciulli et al., 2007; Raji et al., 2009; Walther et al., 2010), regions associated with age-related cognitive decline (Moscovitch & Winocur, 1992b; R. West, 1996). However, others have identified that there is no relationship between BMI and GM volume (GMV) (Debette et al., 2014). Conversely, others showed that obesity may be protective in some GM regions indicated by a positive relationship between BMI and GMV (Huang et al., 2019; Taki et al., 2008). Given that obesity prevalence is generally higher in females than males (Cooper, Gupta, Moustafa, & Chao, 2021), and that fat distribution differs between them (Schorr et al., 2018), and over time in females (Isacco, Ennequin, & Boisseau, 2021; Rathnayake, Rathnayake, & Lekamwasam, 2022), it is possible that some of these contradictory relationships reflect sex-related differences. This could arise due to sex distribution imbalance in some studies, the age range included and how it relates to menopausal status, or the different ways sex is accounted for in studies (i.e., sex as an outcome versus a covariate). For example, Taki and colleagues identified that their results of negative and positive relationships in specific GMV regions with BMI were driven exclusively by males (Taki et al., 2008), which was later confirmed in a

separate longitudinal study investigating BMI and GMV (Arnoldussen et al., 2019). Finally, Huang and colleagues found that both males and females had positive and negative relationships with BMI and GMV, but *only* males experienced atrophy of the anterior cingulate cortex with increasing BMI (Huang et al., 2019), indicating that sex differences with structural brain outcomes could be region dependent.

The evidence on the direction of relationship between BMI and white matter volume (WMV) in aging is mixed, where some find that increased BMI is inversely associated with WMV (Ho et al., 2011; Raji et al., 2009), others found no relationship between BMI and WMV (Debette & Markus, 2010; Gunstad et al., 2008) and some report positive relationships (Pannacciulli et al., 2007). Taken together, the relationship between BMI and WM outcomes is variable, likely sex-dependent with males more negatively affected by greater BMI and potentially region specific.

Another important risk factor for late life disease, and more specifically dementia, is physical inactivity (Hersi et al., 2017; Livingston et al., 2020a). Furthermore, greater PA is consistently reported to be positively associated with structural outcomes (Colcombe et al., 2006;Hamer et al., 2018; Raichlen et al., 2020). Most research to date has shown a protective effect of PA with GMV within frontal (Arenaza-Urquijo et al., 2017; Halloway, Arfanakis, Wilbur, Schoeny, & Pressler, 2019; Rovio et al., 2005) and hippocampal region (Erickson, Leckie, & Weinstein, 2014b; K. I. Erickson et al., 2011; Halloway et al., 2019; Steffener et al., 2016). Recent reviews have extensively covered the relationship between GMV and PA in aging (Chieffi et al., 2017;Erickson et al., 2014b; Intzandt et al., 2021).

It has also been shown that the influence of PA on cerebral health is influenced by sex. In some instances, females benefit more from PA in terms of GMV than males (Varma et al., 2015), whereas Casaletto et al., 2020 identified that males, but not females, have a positive relationship between PA and GMV, particularly within the parahippocampal regions (Casaletto et al., 2020). The effect of sex on the relationship between PA and WMV, has not been extensively investigated, though one study reported that females benefited from higher PA levels but not males (Sanders et al., 2021).

Given the generally negative effect of obesity on brain health in aging, and the positive influence of PA, their interaction, alongside sex differences, could explain some of the

contradictory effects observed in the literature. For example, in instances where obesity has a seemingly positive or null effect on GMV, it could partially be due to higher PA levels. It is therefore important to investigate the sex-specific effects of obesity on cerebral macrostructure (GMV, WMV and WMH) and how PA might impact these relationships. We examined a group of older cognitively unimpaired females and males from the Pre-symptomatic Evaluation of Novel or Experimental Treatments for Alzheimer's Disease (PREVENT-AD) study across the BMI spectrum (i.e., BMI = 18.6 to 39.9 kg/m^2) (Breitner et al., 2016). The PREVENT-AD dataset includes *cognitively normal* older adults at baseline, that are at higher risk of developing Alzheimer's disease due to familial history of Alzheimer's dementia. Outcomes included GMV, WMV, WMH volume, PA as indicated by energy expenditure per week based on an in-depth adapted version of the Global Physical Activity Questionnaire (Friedenreich, Courneya, & Bryant, 1998). Polynomial regressions were employed in males and females separately, to investigate the relationship between GMV, WMV and WMH volume with i) BMI; ii) PA; and iii) the interaction of BMI and PA.

4.4 Methods

4.4.1 Participants

A total of 340 participants (247 females, average age of 62.6 years old for the whole sample) from the Pre-symptomatic Evaluation of Novel or Experimental Treatments for Alzheimer's Disease (PREVENT-AD) study were included here. The data used in preparation of this manuscript were obtained from the PREVENT-AD program data release 6.0. Briefly, the primary goal of PREVENT-AD is to investigate whether serial determination of multi-modal biomarkers of Alzheimer's disease may be measured and then used in pre-symptomatic individuals with a family history of dementia, to prospectively investigate disease progression and to measure effects of any potentially preventative treatments. The data used here is only from the baseline time-point in cognitively normal participants and is prior to any of the participants beginning the interventional component of this study.

Participants had to be above the age of 60, or above 55 if their own age was within 15 years of symptom onset of their youngest-affected first-degree relative. They all had a parent or a minimum of two siblings diagnosed with Alzheimer's disease dementia. Other inclusion criteria

included having no MRI contraindications, fluent in French and/or English, no evidence of cognitive impairment as determined by cognitive tests. Exclusion criteria included presence of neurological or psychiatric disorders or excessive drinking (more than two drinks per day on a basis). The Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) and the Clinical Dementia Rating Scale (Morris, 1993) were employed to screen for cognitive impairment, where a score of ≤ 26 out of 30 on the MoCA or greater than 0 on the CDR required further in depth neuropsychological screening assessed by a trained neuropsychologist to rule out mild cognitive impairment. All procedures were completed according to the Declaration of Helsinki and all participants provided written and informed consent. See (Breitner et al., 2016; Tremblay-Mercier et al., 2021) for more in-depth information.

4.4.2 Physical Health Outcomes

For all participants height was measured by asking participants to stand with their back against a wall and feet shoulder width apart, heels touching the wall. They were then asked to take in two large breaths followed by two exhalations and look straight ahead. Height was recorded to the nearest 0.01 m. Weight was measured with a standard clinical scale, and participants were asked to remove excess clothing and shoes for the measurement. Weight was recorded to the nearest 0.01 kg. Body mass index (BMI) was calculated for all participants according to the standard equation of BMI = (body weight [kg]/ height [m^2]). BMI Z-Scores were calculated for each sex separately.

Participants with a BMI of 18.5 or lower were removed from the analysis as they were considered underweight and therefore may represent a frail or soon to be frail population (0.39% of original female sample; 1.04% of original male sample). Given the reported relationship between being underweight and increased risk of dementia (Albanese et al., 2017), these participants may not be representative of a normal aging individual. Furthermore, those with class 3 obesity, as defined by BMI of greater than 40 were also excluded. Given the standard bore size of 60cm used in this study, only females of short stature could have class 3 obesity while still being able to participate in the study, making this obesity sample non-representative of the general population (2% of original female sample removed; 2.1% of original male sample).

The Framingham Risk Factor assessment (D'Agostino et al., 2008) was employed to take into account cardiovascular risk factors as a potential confound in statistical analyses, given its link with increased risk of dementia (Song et al., 2020). More specifically, sex-specific estimates are utilized, where higher risk is associated with greater points for each of the following: age, high-density lipoprotein cholesterol, total cholesterol, systolic blood pressure (treated vs untreated), smoking status and presence of diabetes.

4.4.3 Cardiovascular fitness and physical activity measures

All participants completed an adapted version of the Global Physical Activity Questionnaire (Friedenreich et al., 1998), an extensive PA questionnaire which inquired about the type of activities an individual participated in during the previous 12 months (e.g., skiing, running, cycling, walking, etc.), how often each activity was completed for : the number of months in a year (i.e. 1 to 12 months), the number of weeks out of a month (i.e., 1 to 4 weeks), the number of days the activity was completed on a weekly basis (i.e., 1 to 7 days a week), the intensity of each activity (e.g., ranked as light, moderate or intense – specific definitions were provided for each intensity), as well as the hours per session on a weekly basis. Rather than collected on a paper form in person, the questionnaire was completed in an online form, with the exact same questions as the original version. From here, the 2011 Compendium of Physical Activities was referenced for standardized metabolic equivalents (METs) for each type of activity. This allowed for an average of total weekly METs to be calculated for each participant, as well as to segregate activities by overall total METs, referred to as Total ZPA. Moreover, those that are considered moderate to high intensity activities (i.e., >3 METs), which will be referred to as moderate ZPA from here. It is important to note that as we were aiming to investigate the effects of engaging in PA on brain health, rather than the effects of PA vs no PA, and the interaction between PA and BMI, we excluded individuals within the PA analysis that reported engaging in no PA (27.2% of females and 31% of males did not participate in any PA). Sex disaggregated Z scores for total METs and moderate-high intensity METs were created.

4.4.4 MRI Acquisitions

All acquisitions were completed on a 3T Siemens TIM Trio machine (Siemens Medical Solutions, Erlangen, Germany). A 12- channel head coil was used for acquisitions. An

anatomical 1 mm^3 magnetization-prepared rapid gradient echo (MPRAGE) sequence (repetition time [TR] = 2300 ms; echo time [TE] = 30 ms; flip angle (FA) = 9°; matrix size = 256 x 256) was employed to quantify grey and white matter volume and for registration purposes. A fluid attenuated inversion recovery (FLAIR) (TR = 5000 ms; TE = 388 ms; inversion time (TI) = 1800 ms; resolution = 1 mm x 1mm; matrix size = 256 x 256), and T2-weighted sequences were also acquired (TR = 2500 ms; TE = 198 ms; resolution = 0.64 mm x 0.64 mm; matrix size = 320 x 320), alongside the MPRAGE, to estimate the presence and severity of white matter lesions.

4.4.5 Data Analysis

4.4.5.1 Gray Matter and White Matter Volume Quantification

The T1-weighted MPRAGE images were brain extracted using FSL's BET (M. Chappell et al., 2009) using standard parameters. All MPRAGE images were checked independently by two researchers to ensure the skull and neck were fully removed from all scans. These images were then further preprocessed using SPM's computational anatomy toolbox (CAT)12 to calculate voxel-based morphometry (Ashburner & Friston, 2000; Gaser & Dahnke, 2016), after the data were segmented into grey and white matter and cerebrospinal fluid (CSF). VBM calculates the difference in grey (GMV) or white matter volume (WMV) of each individual subject compared to the expected volume from a template. A statistical map is then created classifying each voxel type into GMV, WMV or CSF according to the highest probability of tissue type.

Registration matrices and warps were calculated to transform GM and WM maps from native T1 space into common MNI space using a non-linear rigid registration with ANTS (Avants, Epstein, Grossman, & Gee, 2008) with b-spline interpolation. The CAT12 internal template was then registered to the common MNI space template and the inverse matrices and warps were applied to each participant's VBM maps to bring them to the common MNI space. Data were smoothed with a Gaussian filter of 8 mm. We also created an average sex-specific GM and WM mask to restrict voxel-wise analyses to the grey and white matter, respectively.

4.4.5.2 Region of interest analysis

A hypothesis driven approach was taken to investigate sex-specific influences of ZBMI on regions in GM and WM that are known to decline in aging. More specifically, the LPBA40 atlas (Shattuck et al., 2008) was employed to extract GMV and WMV in regions of interest (ROI) in all participants from the following bilateral regions: superior frontal gyri, medial frontal gyri, inferior frontal gyri, superior parietal gyri, superior temporal gyri, medial temporal gyri and hippocampi. Additionally, GMV was extracted from the insular region. Prior to ROI extraction, the LPBA atlas was registered using ANTS, as described above, to the same common MNI space utilized throughout. This atlas was then multiplied by each individual's VBM map to create individual ROI's that were extracted using the weighted average for each participant with FSLmeants to correct for any potential GM or WM atrophy in GMV and WMV ROI's, respectively. The GMV and WMV for each participant from each hemispheric region was extracted to a spreadsheet and imported into R/RStudio (v.24) for further analysis.

4.4.6 Statistical analyses

Statistical analysis of the hypothesis driven data was completed in R and R studio to identify potential relationships between ROIs in GMV and WMV with i) Z-score of BMI; ii) Z-score of physical activity outcomes; iii) and the interaction of Z-score of BMI with the Z score of total physical activity and Z-score of moderate to intense physical activity. Each of these relationships were investigated separately for males and females. Age (in years), education (in years) and Framingham Risk Factor total score were used as covariates in all analyses. An independent samples t-test was employed to investigated differences between males and females for age, education, MoCA, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), and Framingham total points. Differences in APOE status and smoking status were investigated with a chi-square test. All relationships with each GMV and WMV ROI were investigated as a linear and quadratic relationship with the 'lm' package in R (Chambers, 1992; Wilkinson & Rogers, 1973). A p-value of 0.05 or less was considered significant. A Bayesian information criterion was then used to compare the goodness of fit of each type of regression. The regression with the lowest BIC value was the best fit (Raftery, 1995). Given the large sample size of each sex ($n > 50$), parametric tests were completed as normality assumptions with this sample should not introduce issues (Elliott & Woodward, 2007; Ghasemi & Zahediasl, 2012; Pallant, 2020). To correct for multiple comparisons in all analyses, a False Discovery Rate was employed using the

'FDRestimation' library in RStudio, to adjust p values for multiple comparisons (Murray & Blume, 2021).

4.5 Results

A total of 229 older adult females and 93 older adult males participated in this study. Demographics for both sexes can be found in Table 1. Male had lower global cognitive scores as assessed by the MoCA (t = -2.86; p = 0.004); greater ZBMI (t = 2.86; p = 0.0045); higher SBP (t = 3.13; p = 0.0019) and higher DBP (t = 2.34; p = 0.020). No differences were present between the sexes for age, education, smoking status, total Framingham points or presence of APOE ε4 alleles.

Table 4-1: Sex Specific Demographics

	Females (n = 229)	**Males (n = 93)**
Age (*years)*	62.6 ± 4.9	62.8 ± 4.9
Education (*years)*	15.2 ± 3.3	15.9 ± 3.7
MoCA (*out of 30)*	28.2 ± 1.4 *	27.6 ± 1.8
SBP (*mmHg)*	125.9 ± 17.4 *	134.8 ± 34.1
DBP (*mmHg)*	73.3 ± 9.3 *	75.9 ± 8.8
BMI (*kg/m^2)*	26.1 ± 4.1 *	27.5 ± 3.8
Smoker (*current; ex; never) [%]*	7; 44; 49	6; 47; 46
Total Framingham	11.3 ± 3.5	13.5 ± 2.8
APOE Status (*0; 1; 2****) [%]***	64; 33; 3	61; 37;2
BMI status (*NW; OW: OB****) [%]***	46; 36; 19	27; 53; 20
Moderate METs (*weekly MET minutes)*	1751.2 ± 1510.8	1708.6 ± 1266.6

Note: all outcomes reported are in mean ± standard deviation or in percentage; *denotes significant differences between males and females with $p < 0.05$

4.5.1 Grey matter volume regions of interest

4.5.1.1 Females

4.5.1.1.1 ZBMI Score

Results of both linear and quadratic regressions demonstrating relationships between ROI-average GMV and ZBMI can be found in Table 2. GMV in numerous ROIs had linear relationships with ZBMI in females (see Figure 1). More specifically, linear relationships were identified in the right superior temporal gyrus (adjusted-$R^2 = 0.153$; $p = 1.16 \times 10^{-6}$), the right medial temporal gyrus (adjusted-$R^2 = 0.151$; $p = 0.036$), the left medial temporal gyrus (adjusted-$R^2 = 0.162$; $p = 5.17 \times 10^{-7}$) and the right insula (adjusted-$R^2 = 0.060$; $p = 0.024$), where increased BMI was associated with greater GMV in these ROIs.

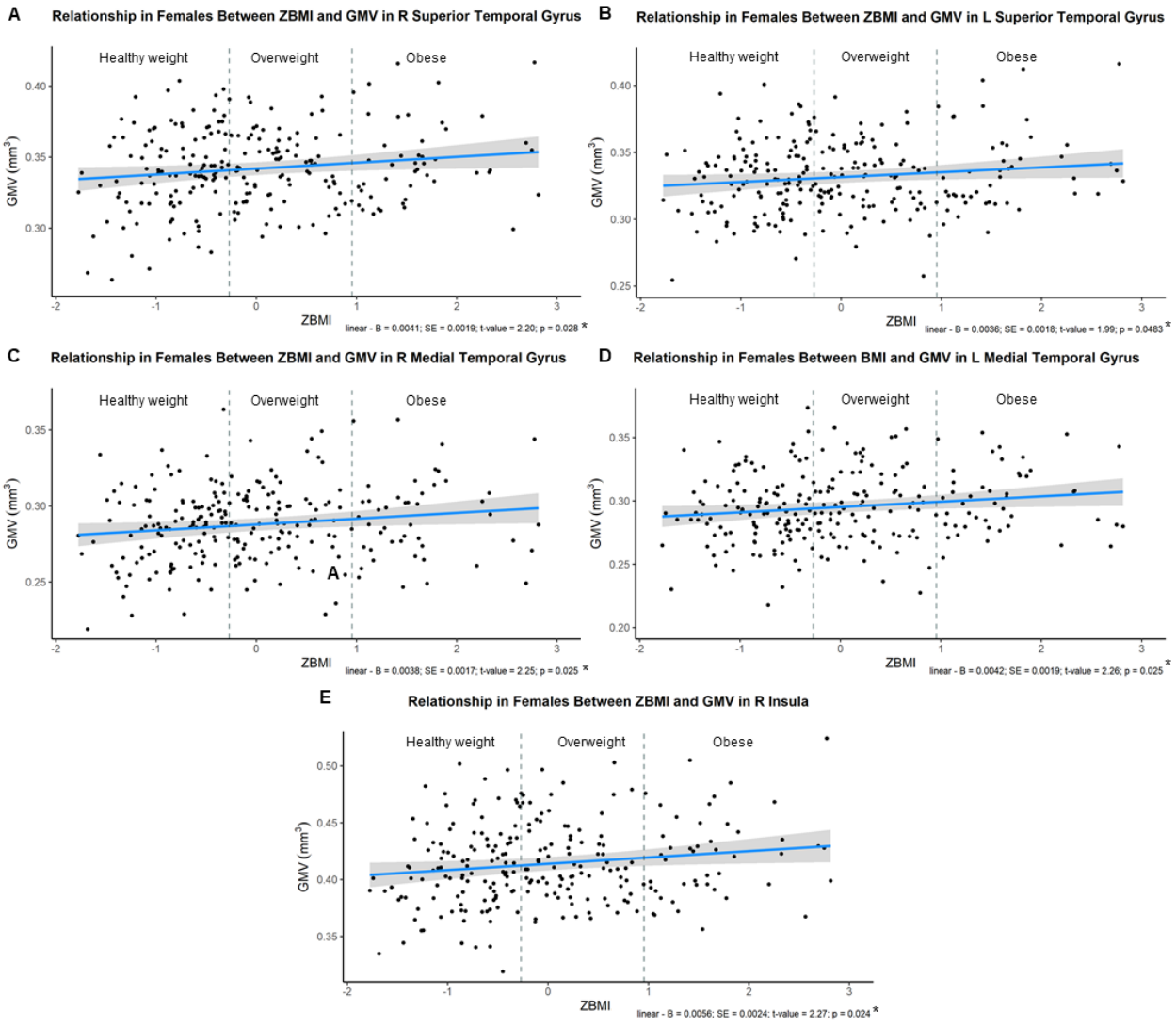

Figure 4—1 Relationships Between ZBMI in Females and GMV ROIs; A - relationship in right superior temporal gyrus; B – in the left superior temporal gyrus; C – right medial temporal gyrus; D – left medial temporal gyrus; E – right insular gyrus. From the y axis to the first dashed vertical grey line are individuals considered healthy weight (BMI = 18.6 – 24.99 kg/m^2; those data points between the two dashed vertical grey line are those considered to be overweight (BMI = 25.0 – 29.99 kg/m^2); individuals to the right of the second vertical dashed line were those with obesity (BMI = 30.0 – 39.99 kg/m^2)

4.5.1.1.2 Moderate ZPA

The moderate to vigorous METs physical activity z-score, Moderate ZPA, was associated with a few GMV ROIs (Table 3). More specifically, the linear component of the quadratic regression was significant in the right medial frontal gyrus (adjusted-R^2= 0.076; p = 0.012), and the left superior frontal gyrus (adjusted- R^2= 0.045; p = 0.038), indicating higher moderate PA amounts corresponded to greater GMV. The left medial frontal gyrus had an inverse quadratic

relationship, demonstrating an inverse U shape, (adjusted-R^2 = 0.113; p = 0.0027), as did the left superior temporal gyrus (adjusted- R^2= 0.150; p =0.036. Lastly, greater GMV in the left medial temporal gyrus was associated with increased Moderate ZPA (adjusted- R^2 = 0.128; p = 0.044) (see Table 3; Figure 2A-G).

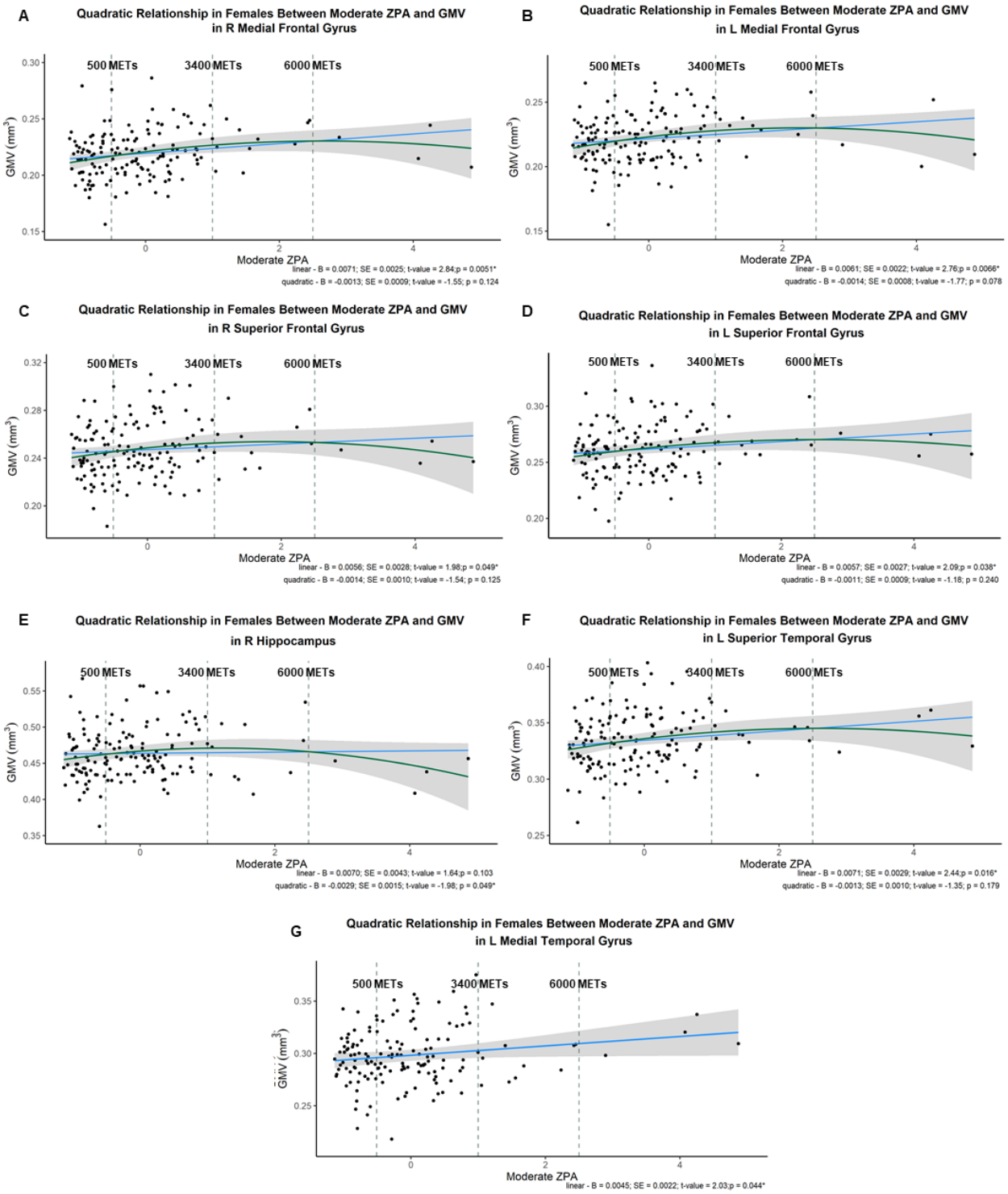

Figure 4—2A:G: Significant relationships between GMV ROIs and Moderate physical activity (ZPA) in females. A: Quadratic relationship between moderate ZPA and the right middle frontal gyrus; B: quadratic relationship between moderate ZPA and the left middle frontal gyrus; C: quadratic relationship between moderate ZPA and the right superior frontal gyrus; D: quadratic relationship between moderate ZPA and the left superior frontal gyrus; E quadratic relationship between moderate ZPA and the right hippocampus; F: quadratic relationship between moderate ZPA and the let superior temporal gyrus; G: linear relationship

*between moderate ZPA and the left medial temporal gyrus. From the y axis to the first dashed vertical grey line are individuals considered under the recommended PA guidelines (METs minutes per week < 500); those data points between the two dashed vertical grey line are those completing 501 to 3400 METs minutes per week; and individuals to the right of the second vertical dashed line were those completing excess of 6000 METs minutes per week. * Denotes p-value < 0.05*

4.5.1.1.3 ZBMI and Moderate ZPA Interactions

An inverse quadratic relationship was identified between ZBMI and moderate ZPA in two regions: the left medial frontal gyrus (adjusted-$R^2 = 0.098$; $p = 0.047$), and the left superior temporal gyrus (adjusted-$R^2 = 0.159$; $p = 0.007$) (see Figure 3 and table 4).

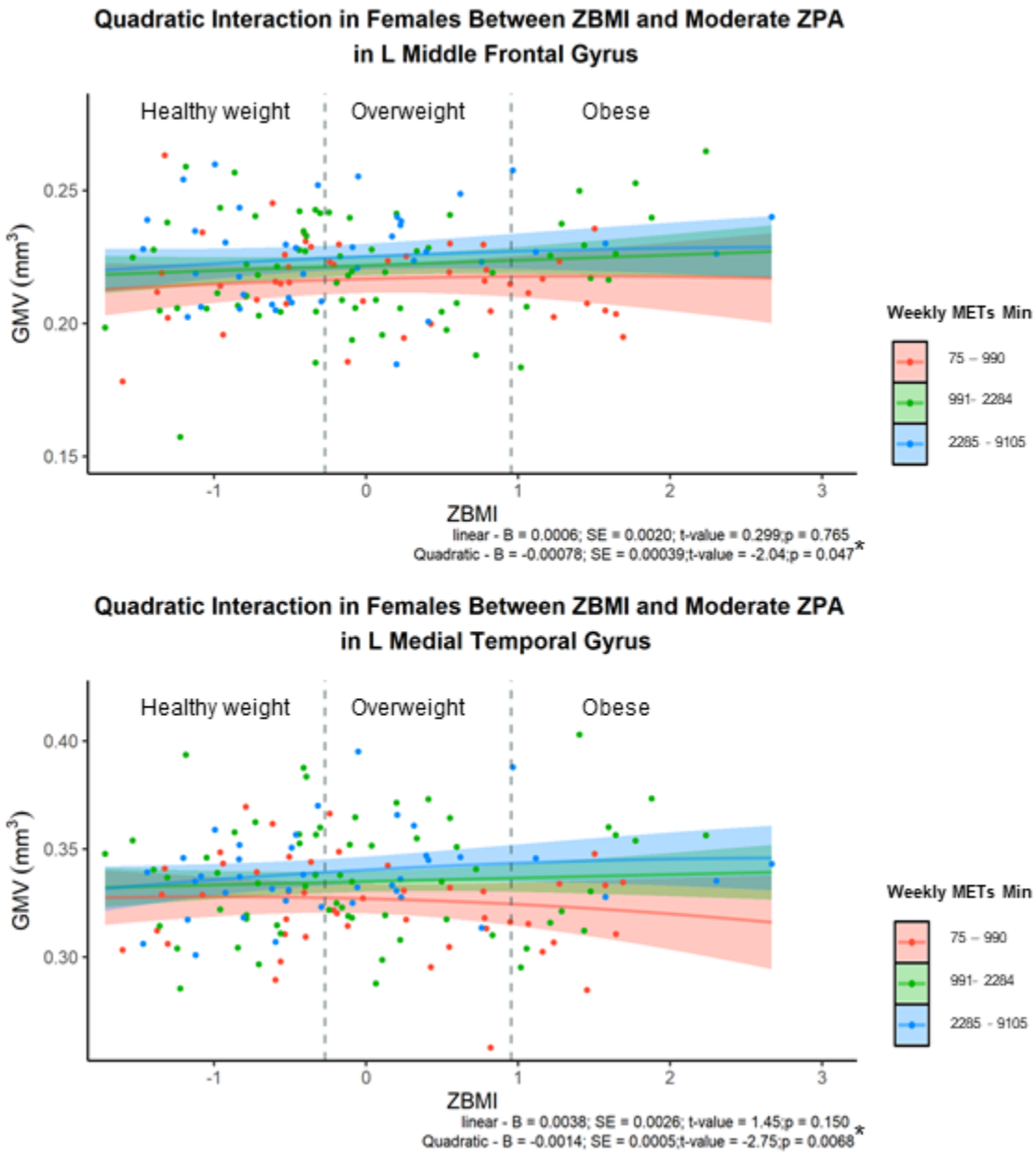

*Figure 4—3 (top figure) significant interaction with ZBMI and moderate ZPA in the left middle frontal gyrus. Bottom figure demonstrates the significant interaction of ZBMI with moderate ZPA in the left medial temporal gyrus. For both figures the red line indicates those with the least amount of reported moderate PA; the green were those females reporting the median amount, and finally the blue line indicates those with higher levels of PA. The number of weekly METs minutes are also indicated to provide the actual METs ranges completed for each line. Moreover, the two vertical grey dotted lines provide the healthy weight range (BMI: 18.6 – 24.99 kg/m^2), the overweight range is in between the two vertical lines (BMI: 25-29.99 kg/m^2) and those who were considered to be obese to the right of the second vertical line (BMI: 30-39.99 kg/m^2). * Denotes significant p-value < 0.05*

4.5.1.2 Males

4.5.1.2.1 ZBMI Score

Several GMV ROIs showed an inverse quadratic relationship (inverse U relationship) between GMV and ZBMI in males, including bilateral superior frontal gyri (*right:* adjusted-R^2 = 0.053; p = 0.0292; *left*: adjusted-R^2 = 0.090; p = 0.022), left superior parietal gyrus (adjusted-R^2 = 0.0545; p = 0.040), and the left superior temporal gyrus (adjusted- R^2 = 0.150; p = 0.028) (see Table 5 and Figure 4A-D).

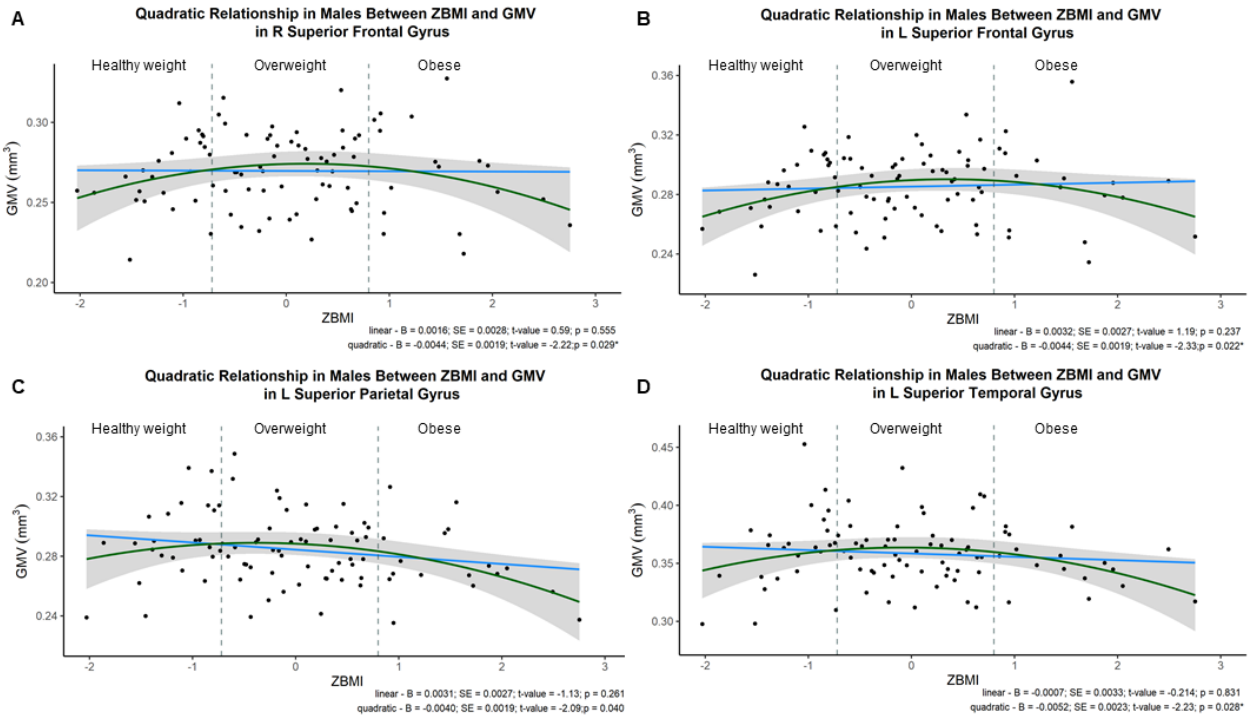

*Figure 4—4A:D: Relationships Between ZBMI in Males and GMV ROIs; A – inverse quadratic relationship in right superior frontal gyrus; B – inverse quadratic relationship in the left superior frontal gyrus; C – inverse quadratic relationship in the left superior parietal gyrus; D – inverse quadratic relationship left superior temporal gyrus. From the y axis to the first dashed vertical grey line are individuals considered healthy weight (BMI = 18.6 – 24.99 kg/m^2; those data points between the two dashed vertical grey line are those considered to be overweight (BMI = 25.0 – 29.99 kg/m^2); individuals to the right of the second vertical dashed line were those with obesity (BMI = 30.0 – 39.99 kg/m^2). * Denotes significant p-value < 0.05.*

4.5.1.2.2 Moderate ZPA

There were no relationships between GMV ROIs and Moderate ZPA for males. (p > 0.05)

4.5.1.2.3 Interaction for ZBMI and Moderate ZPA

An interaction between Total ZPA and ZBMI was identified in one region, the left hippocampus, showing a negative interaction (adjusted-R^2 = 0.261 p = 0.017) (see Table 6; Figure 5). A Johnson Neyman test revealed that this interaction was driven by the healthy weight males with the highest moderate PA levels having the greatest GMV in the left hippocampus compared to the healthy weight males with the lowest weekly moderate PA (p = 0.01).

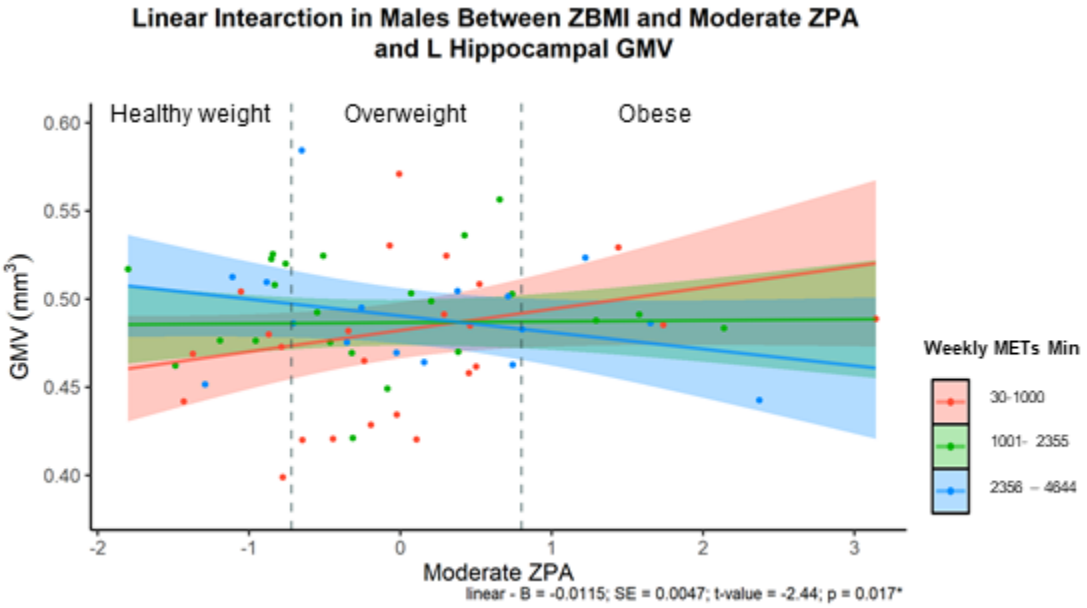

*Figure 4—5: significant interaction with ZBMI and total ZPA in the left hippocampus. The red line indicates those with the least amount of reported total PA; the green were those males reporting the median amount, and finally the blue line indicates those with higher levels of PA. The number of weekly METs minutes are also indicated to provide the actual METs ranges completed for each line. Moreover, the two vertical grey dotted lines provide the healthy weight range (BMI: 18.6 – 24.99 kg/m^2), the overweight range is in between the two vertical lines (BMI: 25-29.99 kg/m^2) and those who were considered to be obese to the right of the second vertical line (BMI: 30-39.99 kg/m^2). * Denotes significant p-value < 0.05*

4.5.2 White matter volume regions of interest

4.5.2.1 Females

4.5.2.1.1 ZBMI Score

There were no ROI in the WMV that demonstrated a significant relationship with ZBMI in females ($p > 0.05$).

4.5.2.1.2 Moderate ZPA

Moderate ZPA demonstrated a positive linear relationship with the left middle frontal gyrus (adjusted- $R^2 = 0.081$; $p = 0.049$), the left medial temporal gyrus (adjusted- $R^2 = 0.103$; $p = 0.0139$) and the left superior temporal gyri (adjusted- $R^2 = 0.049$; $p = 0.035$) (see Table 7; Figure 6A-C).

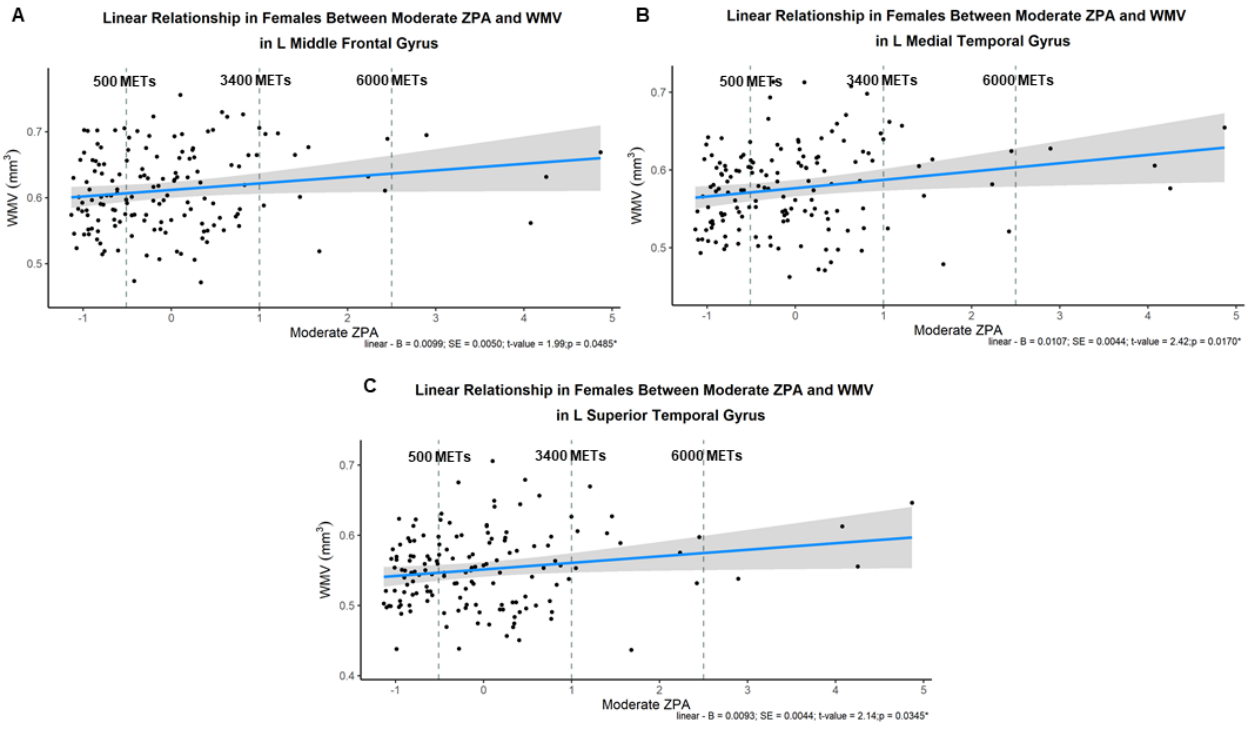

*Figure 4—6A:C Significant relationships between WMV ROIs and Moderate ZPA in females. A: linear relationship between moderate ZPA and the left middle frontal gyrus; B: linear relationship between moderate ZPA and the left medial temporal gyrus; C: linear relationship between moderate ZPA and the left superior frontal gyrus. From the y axis to the first dashed vertical grey line are individuals considered under the recommended PA guidelines (METs minutes per week < 500); those data points between the two dashed vertical grey line are those completing 501 to 3400 METs minutes per week; and individuals to the right of the second vertical dashed line were those completing excess of 6000 METs minutes per week. * Denotes p-value < 0.05*

4.5.2.1.3 ZBMI and Moderate ZPA Interactions

There were no significant interactions between ZBMI and moderate ZPA in any white matter ROIs ($p > 0.05$).

4.5.2.2 Males

4.5.2.2.1 ZBMI Score

In males there were significantly inverse linear relationships between ZBMI and the right medial frontal gyrus (adjusted- $R^2 = 0.131$; $p = 0.041$) and the left inferior frontal gyrus (adjusted- $R^2 = 0.051$; $p = 0.020$) (see table 8 and figure 7A-B).

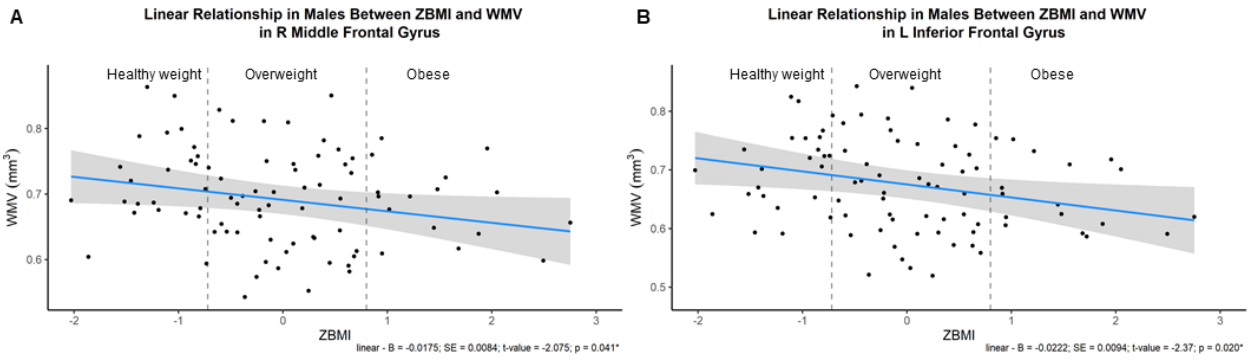

*Figure 4—7A:B Relationships Between ZBMI in Males and WMV ROIs; A – inverse linear relationship in right middle frontal gyrus; B – inverse linear relationship in the left inferior frontal gyrus. From the y axis to the first dashed vertical grey line are individuals considered healthy weight (BMI = 18.6 – 24.99 kg/m^2; those dots between the two dashed vertical grey line are those considered to be overweight (BMI = 25.0 – 29.99 kg/m^2); individuals to the right of the second vertical dashed line were those with obesity (BMI = 30.0 – 39.99 kg/m^2). * Denotes significant p-value < 0.05.*

4.5.2.2.2 Moderate ZPA

The linear component of the quadratic regression between moderate ZPA and right hippocampal WMV demonstrated a significant relationship (adjusted- $R^2 = 0.085$; $p = 0.048$) (see figure 8 and table 9).

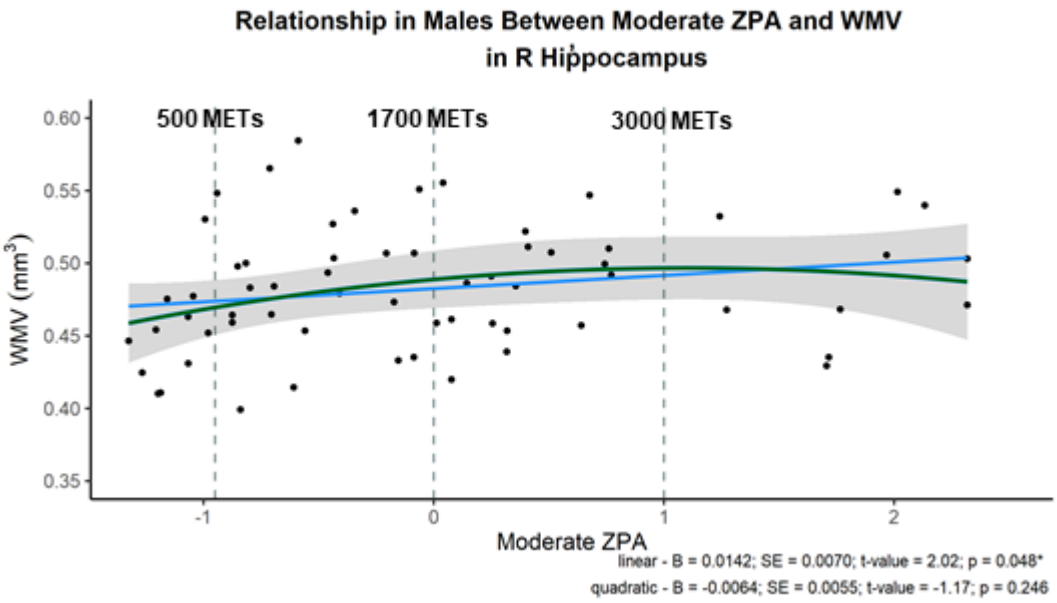

*Figure 4—8 Significant relationships between WMV ROIs and Moderate ZPA in males the right hippocampus. From the y axis to the first dashed vertical grey line are individuals considered under the recommended PA guidelines (METs minutes per week < 500); those data points between the two dashed vertical grey line are those completing 501 to 1700 METs minutes per week; and individuals to the right of the second vertical dashed line were those completing excess of 3000 METs minutes per week. *Denotes significant p-value < 0.05.*

4.5.2.2.3 ZBMI and Total ZPA Interactions

There were no interactions between ZBMI and ZPA moderate in any white matter ROIs for the males ($p > 0.05$).

4.6 Discussion

We examined the sex-specific relationships between cerebral macrostructural outcomes (GMV and WMV), BMI and PA in older adults of moderate level of BMI (~ 26 kg/m^2) and PA (~1751 weekly METs minutes). In females, our data demonstrated that with higher BMI, GMV was increased in several regions showing a benefit of higher BMI. Conversely, in males, an inverse U shape was revealed, indicating those males who were overweight had the largest GMV in ROIs compared to the normal or obese individuals. For moderate ZPA, most regions in females demonstrated an inverse U relationship with GMV suggesting a ceiling effects of PA for females, whereas males had no relationships. The interaction in females between moderate to vigorous PA and ZBMI revealed that those with the highest levels of moderate to vigorous PA

across the BMI spectrum had significantly higher GMV in all significant ROIs compared to those with the lowest amounts of PA. In opposition to females, the interaction between ZPA and ZBMI indicates that normal weight males with the highest levels of PA have the greatest GMV compared to those normal weight individuals completing the least amount of moderate PA. Though, it is worth noting, that a post-hoc power analysis of this interaction revealed a power of 15%, thus, a much larger sample of males across the BMI and PA spectrum, and especially in the obese category, which was sparse in this sample, is necessary to confirm these results.

In females there were no relationships between ZBMI, ZPA and WMV ROIs, except in a few regions where higher moderate ZPA was associated with greater WMV. Conversely males demonstrated a negative relationship between ZBMI and WMV regions, and a positive relationship between moderate ZPA and WMV.

4.6.1 Sex-Specific Relationships in BMI and Structural Outcomes

The results presented here in both males and females, separately, are consistent with the existence of the obesity paradox, whereby weight beyond the normal range is found to be protective for brain structure in aging (Pedditizi et al., 2016; Pegueroles et al., 2018). However, males and females may experience these benefits within a different weight range. In females, our data is consistent with the obesity paradox as observed by (Pedditizi et al., 2016; Taki et al., 2008), with a positive relationship between BMI and GMV so that those with the highest BMI had the largest GMV within temporal regions. On the other hand, data in males indicated an optimal BMI range, with an inverse U relationship where overweight BMI is most protective for GMV. This more closely resembles the original obesity paradox in (Pegueroles et al., 2018). It is therefore possible that some of these discrepancies in the literature reflect sex differences and are biased by the distribution of both sex and weight ranges for each sex. For example, while Taki et al. identified a similar linear relationship as ours in their mixed sample (Taki et al., 2008), only 2% of their sample were considered obese, as opposed to approximately 20% in ours, making detection of an inverse U relationship more challenging.

To date there have been very few studies investigating the sex-specific relationships between obesity and brain health, rather introducing sex as a covariate, revealing a significant gap to the current literature. The existing data is mixed, with some work suggesting that females

are more likely to experience atrophy or cognitive decline as a consequence of obesity than males (Hayden et al., 2006; Kim et al., 2019) whereas others found the opposite, where males were more negatively affected by obesity (Espeland et al., 2020). Our results of females seemingly being protected by overweight on grey matter atrophy could be related to the fact that obesity in isolation may not be uniquely detrimental to health. It may be that obesity contributes to poor vascular and metabolic health through adipose tissue inflammatory signaling (Koenen, Hill, Cohen, & Sowers, 2021), but not when obesity is not associated with chronic low grade inflammation. Therefore, taking these downstream effects into account through the Framingham risk score in statistical analyses isolates the effects of obesity and shows that it is not in fact an independent contributor to decreased structural brain health in this aging sample. Thus, it is possible that as males develop cardiovascular risk factors earlier in life than females (due to protective effects of estrogen in females), males' levels of inflammation could have been higher here. Indeed, females in our sample had lower Framingham Risk Factor scores than males, indicating a more limited number of cardiovascular risk factors. Future research should more carefully investigate the impact of cardiovascular risk factors in the relationship between BMI and cerebral structure in males and females. In addition, exploring the role of inflammatory markers may help understand further these sex-specific relationships in GMV.

Interestingly, no significant relationships were identified between ZBMI and WMV for females, though males with greater BMI had lower WMV. Previous work has also found this lack of relationship (Debette et al., 2014; Gunstad et al., 2008), likely due to the unspecific nature of BMI as a marker of obesity. Central adiposity and visceral fat may be more likely to demonstrate a relationship with WMV and WMH lesions (Debette & Markus, 2010). Moreover, a stronger relationship with GMV than WMV, has been somewhat consistently found, and been hypothesized a greater sensitivity of GMV over WMV to the low-grade chronic inflammation associated with obesity (Vachharajani & Granger, 2009). However, obesity is consistently reported to affect white matter microstructure (Alfaro et al., 2018; Dekkers, Jansen, & Lamb, 2019), indicating early changes to white matter since it is documented that microstructure declines about two decades before white matter macrostructure (Irimia, 2021). Taken together, it is possible that our sample is too young to capture volume changes in white matter. Thus, future work should not only investigate the sex differences in BMI on microstructure utilizing

acquisitions like diffusion weighted imaging or magnetization transfer, but also explore these relationships in a larger age range.

4.6.2 Sex- Specific Relationships with Physical activity and Macrostructural outcomes

Females in this sample showed that with increased moderate ZPA and the GMV in the left medial temporal gyrus was greater. Yet, other frontal and temporal regions demonstrated an inverse U shape, indicating that there was likely a ceiling for moderate-vigorous activity possessing beneficial effects. However, it should be noted that few females in our sample completed a high amount of PA and are likely not representative of the overall sample trends. Conversely, total ZPA demonstrated only linear positive relationships with GMV ROIs. The discrepancy between the two intensities of PA is especially notable in females, as it suggests the presence of a dose response upper limit for the gains of moderate to vigorous activities on overall brain health. In fact, previous work found that, although increasing PA was associated with increased GMV, there was no additional benefit once activity guidelines were met (Wood, Nikolov, & Shoemaker, 2016). Here, the ceiling effect of PA occurred above the recommended guidelines of 500 MET minutes/week (Lauer, Jackson, Martin, & Morrow, 2017). Our data suggests this ceiling may occur at around 3000 MET minutes per week, corresponding to about 8.5 hours of moderate to vigorous PA. Interestingly, Wood et al. (2016) found that master athletes who were engaged in > 15 hours of weekly activity showed no significant differences in WMH, or subcortical gray matter compared to active older adults (Wood et al., 2016). Indeed, the data indicated diminishing returns, or a ceiling effect, on cortical decline, as the master athletes had the same decline as the active older adults. Our work and previous studies therefore strongly suggest the presence indicate that there could be diminishing returns of increasing moderate-vigorous PA past a certain dosage, with a ceiling effect in the preservation of GMV.

Males demonstrated a significant positive linear relationship in the left hippocampus for moderate PA. This was not bilaterally evident, though the right hippocampus approached significance, so is likely due to insufficient power. In any case, this finding in the hippocampus confirms previous work by Barha and colleagues (2020) who revealed that only older males who spent a greater amount of time walking in the previous 1 to 10 years had greater hippocampal volume (Barha et al., 2020). No other regions had a significant relationship with PA, in stark

contrast to a recent paper showing that males are more likely to benefit from the exact same amounts of PA as females for GMV, as a function of PA lowering inflammatory markers more in males (Casaletto et al., 2020). The authors suggested that this may be attributable to differences in immune function between males and females. Males tend to have a lower immune functioning (Klein & Flanagan, 2016) and may therefore benefit more from the immune-enhancing properties of PA than females, who already have a more active immune system (Casaletto et al., 2020).

A comparison of the amount of PA reported by each sex can also shed light on potential dose-response effects and how this may interact with sex. In our sample, females participated in a greater amount of total and moderate to vigorous PA than males. Therefore, our sampling of the dose-response relationship is not identical between sexes, potentially explaining the lack of relationship between PA and GMV across most regions in males. It is possible that males might require *more* PA to see the effects detected in females, perhaps due to the higher number of cardiovascular risk factors and lower immune function in males.

4.6.3 Interaction of BMI and PA on Macrostructural Health

Early work identified that fit obese males were no more likely to die of a cardiovascular event compared to their lean and equally fit counterparts (Wei et al., 1999). This led to the "fat but fit" hypothesis, whereby the positive effects of cardiovascular fitness, or greater PA levels, can attenuate the negative consequences associated with obesity. Other work has observed a similar effect in cognitive health, where those who were obese but fit performed significantly better on cognitive tests compared to their unfit obese counterparts. In fact, high fit obese individuals demonstrated the same cognitive functioning as their non-obese fit counterparts (Boidin et al., 2020). To our knowledge, only one study to date has investigated the presence of these effects using neuroimaging. Knight and colleagues (Knight et al., 2021) identified that, regardless of sex, individuals who were overweight to obese had significantly decreased cerebral blood flow, but that this reduction in blood flow was attenuated in those *overweight* individuals who reported higher levels of PA. Individuals who were obese did not seemingly gain this benefit to cerebral blood flow. These results by Knight et al. are somewhat in contrast to our findings of high PA levels having beneficial effects regardless of BMI for females, but are

consistent with our results in males(Knight et al., 2021). As Knight et al did not complete sex-disaggregated analyses, it may be that their results are biased by the relationship between obesity and PA in the male portion of their sample.

4.7 Limitations

This study has a few limitations that should be noted when interpreting these results. Firstly, the major limitation to this study is the use of self-reported PA rather than a more objective measure. However, the Global Physical Activity Questionnaire is comprehensive, incorporating seasonality, numerous activities and was completed anonymously online, likely reducing the extent of over reporting.

Secondly, the data utilized here were cross-sectional and thus, cannot be used to investigate the temporality of the relationships among PA, obesity, and macrostructural outcomes. Future work employing longitudinal studies, including additional information about past weight and PA patterns could provide more clarity on these interactions and sex-distinctions.

Thirdly, our sample contained a greater proportion of females and is thus not equivalently powered for looking at these relationships in males. A future study utilizing sex and age matched individuals is warranted.

Moreover, BMI is known to have important limitations as a marker of adiposity since is not overly representative of where adipose tissue is stored or the type of adipose tissue present in individuals. For example, males possess more abdominal visceral fat compared to females (Grauer et al., 1984), whereas females are known to accumulate more subcutaneous fat in the femoral and gluteal regions (Karastergiou, Smith, Greenberg, & Fried, 2012). Visceral fat is known to have more inflammatory and toxic consequences for the body (Chait & den Hartigh, 2020), as well as the brain (Debette & Markus, 2010). Thus, future work should aim to include markers of adiposity that can provide further insight into form of adipose tissue, from something as simple as waist circumference to more advanced measures like dual-energy x-ray absorptiometry or a computed tomography scan to define the amount of subcutaneous versus visceral fat tissue present in each area of the body. Notably, it has recently been proposed it is likely the number of years that an individual has been overweight/obese that is the critical

element, ‘obesity-years’, rather than at certain time points (Abdullah et al., 2011). For example, those who maintain a stable weight and BMI into aging have the lowest incidence of dementia (Power et al., 2013), and another group demonstrated that those who were overweight and had great cardiovascular risk at midlife, *but* had significant weight decrease into later life, had the highest risk of poor outcomes in late life (Strandberg et al., 2009). Thus, future studies should aim to collect more data on years of obesity, and lifespan weight changes, to further understand the influence of the timing of obesity.

Moreover, given the role those inflammatory markers have in causing the cascade of vascular changes due to obesity, future work should also investigate the potential modulatory role that inflammatory markers likely have on this interaction between BMI and PA. This is of particular relevance given that there are known differences in inflammatory markers due to sexual dimorphisms (Rathod et al., 2017); obesity (Cohen, Margalit, Shochat, Goldberg, & Krause, 2021) as previously stated, and PA (Hamer et al., 2012).

Finally, the macrostructural outcomes investigated, have been shown to be sensitive but physiologically ambiguous in isolation (Tardif et al., 2017). Future work should also employ sequences that can investigate combinations of microstructural outcomes, such as diffusion-weighted imaging or magnetic transfer MRI sequences to better understand the underlying changes in brain health related to obesity and PA.

4.8 Conclusion

Overall, we identified that males and females demonstrate distinct relationships among GMV, WMV, BMI and PA. Overall, females demonstrated that increasing BMI was related to greater GMV ROIs, whereas males demonstrated that overweight individuals had the most GM Females had an inverse U relationship between moderate to intense PA levels and GMV, indicating saturation effect for the beneficial effects of increasing moderate PA levels, whereas males demonstrated no relationships with GMV ROIs and moderate PA. Finally, across the BMI spectrum, females with the higher levels of PA were found to have more GMV than those with the least amount of PA. Males seemed to reveal the opposite relationship where greater PA was associated with decreased GMV as BMI rose, though this should be interpreted with caution due to the small number of obese males. Taken together, this work highlights the need to investigate females and males separately, rather than using sex as a covariate. Future work, in a larger

sample, employing more objective measures of PA and more accurate measure of adiposity and body composition are necessary to validate these findings. Additionally, future studies should examine inflammatory markers to further elucidate underlying mechanisms for the relationships identified here, as aging, obesity and PA all have a unique influence on inflammation.

Table 4-2: Significant regressions between ZBMI and GMV ROI in females

	LINEAR				**QUADRATIC**					
	First Order				Second Order				Whole Model	
	Estimate (SE)	p	BIC	Adjusted R^2	Estimate (SE)	p	Estimate (SE)	p	BIC	Adjusted R^2
RSTG	***0.0041 (0.0019)***	***0.039***	***-1019.2***	***0.153***	0.0050 (0.0021)	0.0019	-0.0014 (0.0015)	0.354	-1014.6	0.153
RMTG	***0.0038 (0.0017)***	***0.0073***	***-1068.71***	0.151	0.0053 (0.0019)	0.0066	-0.0021 (0.0013)	0.113	-1065.8	0.173
LMTG	***0.0042 (0.0019)***	***0.0075***	***-1023.8***	***0.162***	0.0049 (0.0021)	0.020	-0.0012 (0.0015)	0.456	-1018.9	0.161
RInsula	***0.0056 (0.0024)***	***0.0355***	***-896.27***	***0.060***	0.0063 (0.0028)	0.024	-0.0011 (0.0019)	0.362	-891.1	0.057

Table 4-3: Significant regressions between Moderate ZPA and GMV ROIs in Females

	LINEAR				**QUADRATIC**					
	First Order				Second Order				Whole Model	
	Estimate (SE)	p	BIC	Adjusted R^2	Estimate (SE)	p	Estimate (SE)	p	BIC	Adjusted R^2
RMFG	0.0043 (0.0017)	0.014	-706.3	0.067	***0.0071 (0.0025)***	***0.0122***	-0.0013 (8.6×10^{-4})	0.124	**-708.9**	**0.076**
LMFG	0.0029 (0.0016)	0.060	-739.8	0.082	***0.0067 (0.0025)***	***0.008***	***-0.0011 (4.2×10^{-4})***	***0.006***	***-742.2***	***0.113***
LSFG	0.0032 (0.0019)	0.086	-685.0	0.041	***0.0057 (0.0027)***	***0.049***	-0.0011 (9.4×10^{-4})	0.240	***-688.4***	***0.045***
LMTG	***0.0045 (0.0022)***	***0.044***	***-632.5***	***0.128***	0.0050 (0.0033)	0.129	-2.2×10^{-4} (0.0011)	0.840	-627.6	0.123
LSTG	0.0049 (0.0021)	0.021	-649.7	0.154	***0.0083 (0.0031)***	***0.0078***	***-0.0016 (0.0011)***	***0.035***	***-652.3***	***0.150***

Table 4-4: Significant regression interactions GMV ROIs between Moderate ZPA ZBMI in Females

	LINEAR				**QUADRATIC**					
	First Order				Second Order				Whole Model	
	Estimate (SE)	p	BIC	Adjusted R^2	Estimate (SE)	p	Estimate (SE)	p	BIC	Adjusted R^2
LMFG	0.0012 (0.0019)	0.508	-731.4	0.097	6.0×10^{-4} (0.0022)	0.765	***-7.8×10^{-4} (3.9×10^{-4})***	***0.035***	***-734.7***	***0.098***
LSTG	0.0037 (0.0023)	0.110	-656.0	0.153	0.0038 (0.0026)	0.150	***-0.0014 (5.0×10^{-4})***	***0.0153***	***-658.8***	***0.159***

Table 4-5: Significant regressions between ZBMI and GMV ROI in males

	LINEAR				**QUADRATIC**					
	First Order				Second Order				Whole Model	
	Estimate (SE)	p	BIC	Adjusted R^2	Estimate (SE)	p	Estimate (SE)	p	BIC	Adjusted R^2
RSFG	-3.2×10^{-4} (0.0027)	0.907	-386.8	0.008	0.0016 (0.0028)	0.555	***-0.0044 (0.0020)***	***0.0292***	***-387.5***	***0.053***
LSFG	0.0012 (0.0026)	0.645	-393.9	0.041	00032 (0.0027)	0.237	***-0.0044 (0.019)***	***0.022***	***-395.1***	***0.090***
LSPG	-0.0049 (0.0026)	0.067	-391.1	0.016	-0.0030 (0.0027)	0.261	***-0.0040 (0.0019)***	***0.040***	***-391.1***	***0.054***
LSTG	-0.0030 (0.0032)	0.343	-358.1	0.110	-7.0×10^{-4} (0.0033)	0.831	***-0.0052 (0.0023)***	***0.028***	***-359.0***	***0.150***

Table 4-6: Significant regression interactions in GMV ROIs between Moderate ZPA and ZBMI in Males

ROI	LINEAR				QUADRATIC					
	First Order				Second Order				Whole Model	
	Estimate (SE)	p	BIC	Adjusted R^2	Estimate (SE)	p	Estimate (SE)	p	BIC	Adjusted R^2
LHippo	***-0.0115 (0.0047)***	***0.018***	***-207.6***	***0.254***	-0.0106 (0.0046)	0.026	-0.0036 (0.0020)	0.080	-207.1	0.282

Table 4-7: Moderate ZPA and WMV ROI Regression Results in Females

ROI	LINEAR				QUADRATIC					
	First Order				Second Order				Whole Model	
	Estimate (Std Error)	p	BIC	Adjusted R^2	Estimate (Std Error)	p	Estimate (Std Error)	p	BIC	Adjusted R^2
LMFG	***0.0099 (0.0050)***	***0.049***	***-390.8***	***0.081***	0.0126 (0.0073)	0.088	-0.0015 (0.0025)	0.545	-384.6	0.069
LMTG	***0.0110 (0.0044)***	***0.0139***	***-427.2***	***0.103***	0.0144 (0.0065)	0.0288	-0.0017 (0.0022)	0.442	-419.5	0.095
LSTG	***0.0093 (0.0044)***	***0.0345***	***-428.0***	***0.049***	0.0077 (0.0064)	0.231	7.5×10^{-4} (0.0022)	0.731	-423.1	0.043

Table 4-8: ZBMI and WMV ROI Regression Results in Males

ROI	LINEAR				QUADRATIC					
	First Order				Second Order				Whole Model	
	Estimate (Std Error)	p	BIC	Adjusted R^2	Estimate (Std Error)	p	Estimate (Std Error)	p	BIC	Adjusted R^2
RMFG	***-0.0175 (0.0084)***	***0.041***	***-181.5***	***0.132***	-00.0178 (0.0090)	0.049	7.4×10^{-4} (0.0063)	0.908	-177.1	0.121
LIFG	***-0.0222 (0.0094)***	***0.020***	***-162.7***	***0.051***	-0.023 (0.0099)	0.023	0.0018 (0.0070)	0.799	-158.3	0.406

Table 4-9: Moderate ZPA and WMV ROI Regression Results in Males

ROI	LINEAR				QUADRATIC					
	First Order				Second Order				Whole Model	
	Estimate (Std Error)	p	BIC	Adjusted R^2	Estimate (Std Error)	p	Estimate (Std Error)	p	BIC	Adjusted R^2
LHippo	0.0092 (0.0056)	0.106	-190.9	0.079	***0.0142 (0.0070)***	***0.048***	-0.0064 (0.0055)	0.246	***-193.5***	***0.085***

4.9 Supplementary Material

4.9.1 Females

4.9.1.1 GMV ROIs

4.9.1.1.1 Total ZPA

Females demonstrated significant positive linear relationships between the total METs physical activity Z-Score (Total ZPA) and GMV ROIs (see table 3a for more information). More specifically, the following regions were significantly associated with Total ZPA (see figure 2a): the bilateral medial frontal gyri (*right:* adjusted-R^2 = 0.063; p= 0.020, *left*: adjusted-R^2 = 0.042; p = 0.009), the left superior temporal gyrus (adjusted-R^2= 0.153; p = 0.019) and the left medial temporal gyrus (adjusted- R^2= 0.133; p = 0.030).

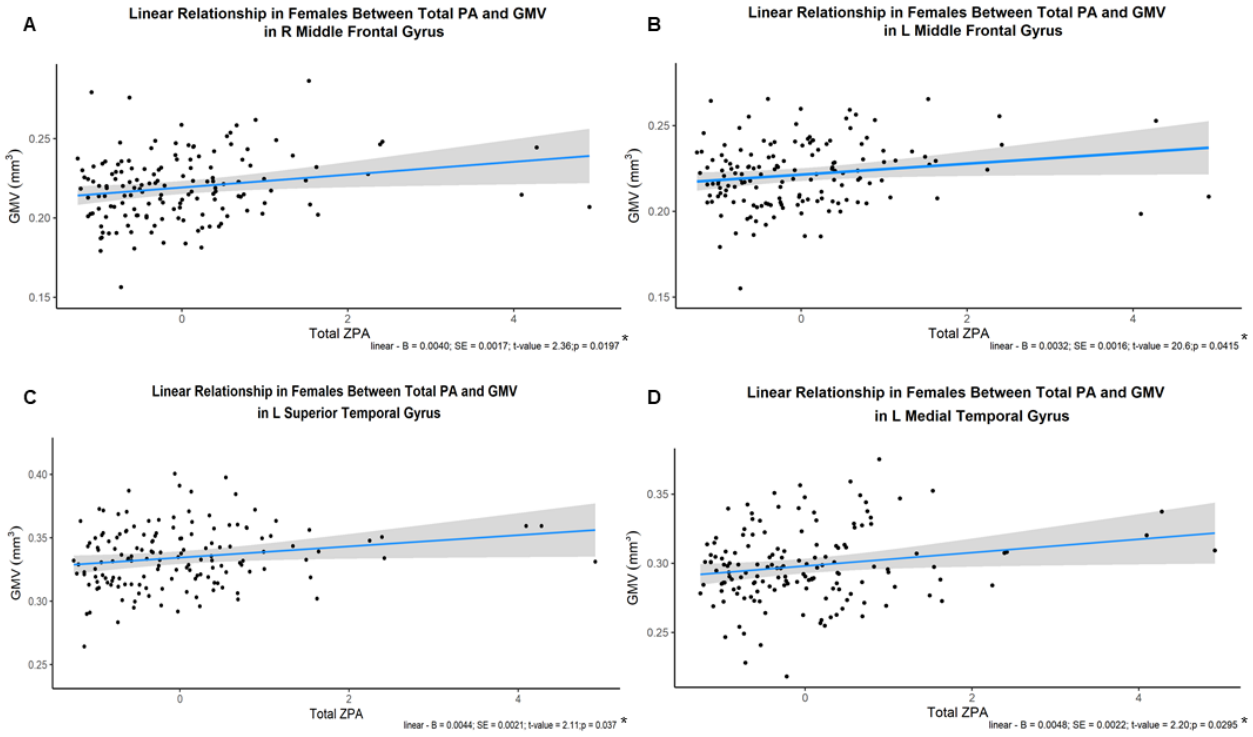

*Figure 4—9A-E: Significant relationships between Total ZPA and GMV ROI; A : significant linear relationship in the right middle frontal gyrus and Total ZPA; B: significant linear relationship between left middle frontal gyrus and Total ZPA; C: significant linear relationship between left superior temporal gyrus and Total ZPA; D: significant linear relationship between left medial temporal gyrus and Total ZPA. * denotes significant p-value < 0.05*

4.9.1.1.2 ZBMI by ZPA Total Interaction`

A significant positively linear interaction was identified in the left superior parietal gyrus for females (adjusted- $R^2 = 0.080$; $p = 0.037$) between ZBMI and Total ZPA (Table 4a). No other regions demonstrated a significant interaction ($p > 0.05$). (Table 4a; figure 4)

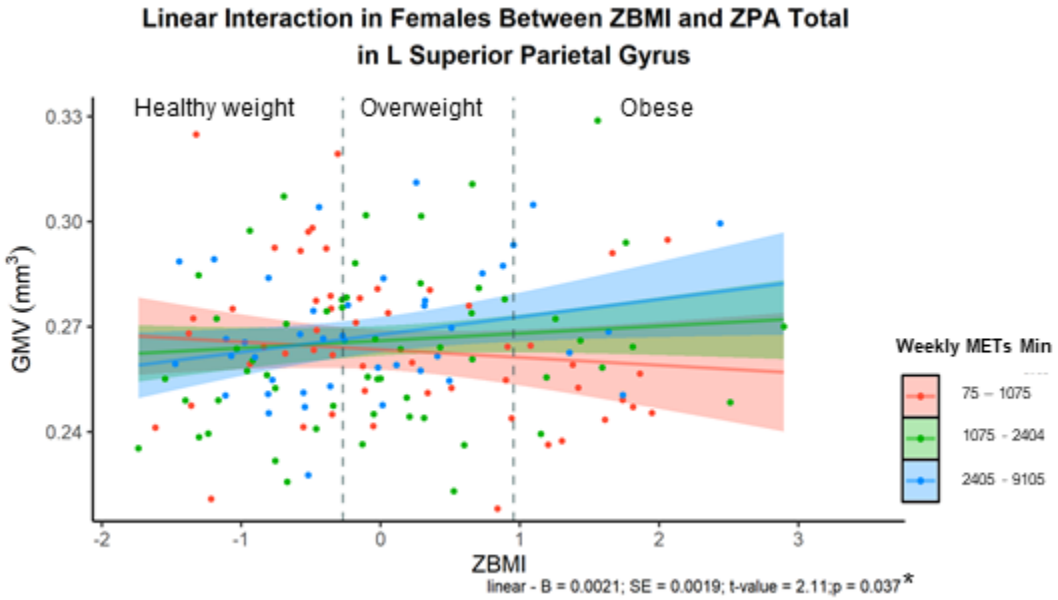

*Figure 4—10: significant interaction with ZBMI and Total ZPA in the left superior parietal gyrus. The red line indicates those with the least amount of reported total PA; the green were those females reporting the median amount, and finally the blue line indicates those with the higher levels of PA. The number of weekly METs minutes are also indicated to provide the actual METs ranges completed for each line. Moreover, the two vertical grey dotted lines provide the healthy weight range (BMI: 18.6 – 24.99 kg/m^2), the overweight range is in between the two vertical lines (BMI: 25-29.99 kg/m^2) and those who were considered to be obese to the right of the second vertical line (BMI: 30-39.99 kg/m^2). * denotes significant p-value < 0.05*

4.9.2 Males

4.9.2.1 GMV ROIs

4.9.2.1.1 ZPA Total

There was a significant linear relationship between the right hippocampus and Total ZPA in males (adjusted- $R^2 = 0.302$; $p = 0.002$) and significant inverse quadratic relationship with the left hippocampus (adjusted- $R^2 = 0.285$; $p = 0.041$) (Table 6a; Figures 7A-B). These were the only two GMV ROIs that demonstrated a significant relationship with Total ZPA. (See Figure 7). There were no significant relationships between ROIs and moderate ZPA ($p > 0.05$).

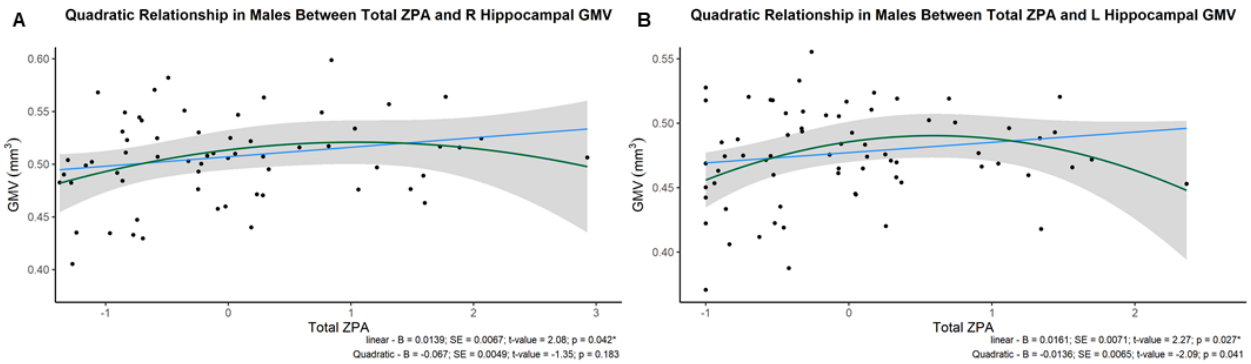

*Figure 4—11A-B: Significant relationships between Total ZPA and GMV ROI in males; A : significant quadratic relationship in the right hippocampus; B: significant quadratic relationship in the left hippocampus. * denotes significant p-value < 0.05*

4.9.2.1.2 ZBMI and ZPA Total Interaction

For the interactions between Total ZPA and ZBMI, left hippocampus was found to have a significant negative interaction (adjusted-R^2 = 0.261 p = 0.018) (see Table 7a; Figure 8). No other ROIs demonstrated a significant interaction (p > 0.05).

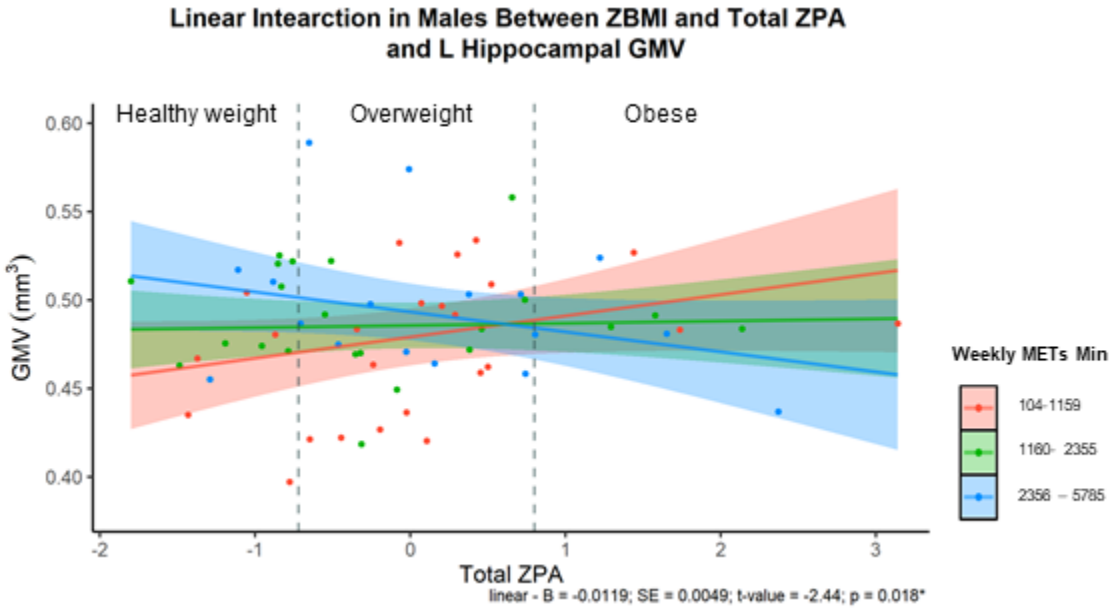

Figure 4—12 significant interaction with ZBMI and total ZPA in the left hippocampus. The red line indicates those with the least amount of reported total PA; the green were those males reporting the median amount, and finally the blue line indicates those with higher levels of PA. The number of weekly METs minutes are also indicated to provide the actual METs ranges completed for each line. Moreover, the two vertical grey dotted

*lines provide the healthy weight range (BMI: 18.6 – 24.99 kg/m^2), the overweight range is in between the two vertical lines (BMI: 25-29.99 kg/m^2) and those who were considered to be obese to the right of the second vertical line (BMI: 30-39.99 kg/m^2). * denotes significant p-value < 0.05*

4.10 WMV Regions of Interest

4.10.1 Females

4.10.1.1 Total ZPA

Total ZPA revealed a significantly positive relationship with the WMV in the left medial temporal gyrus (adjusted- $R^2 = 0.096$; $p = 0.0253$) (Table 8a: figure 10). No other WMV regions had a significant relationship with Total ZPA ($p > 0.05$).

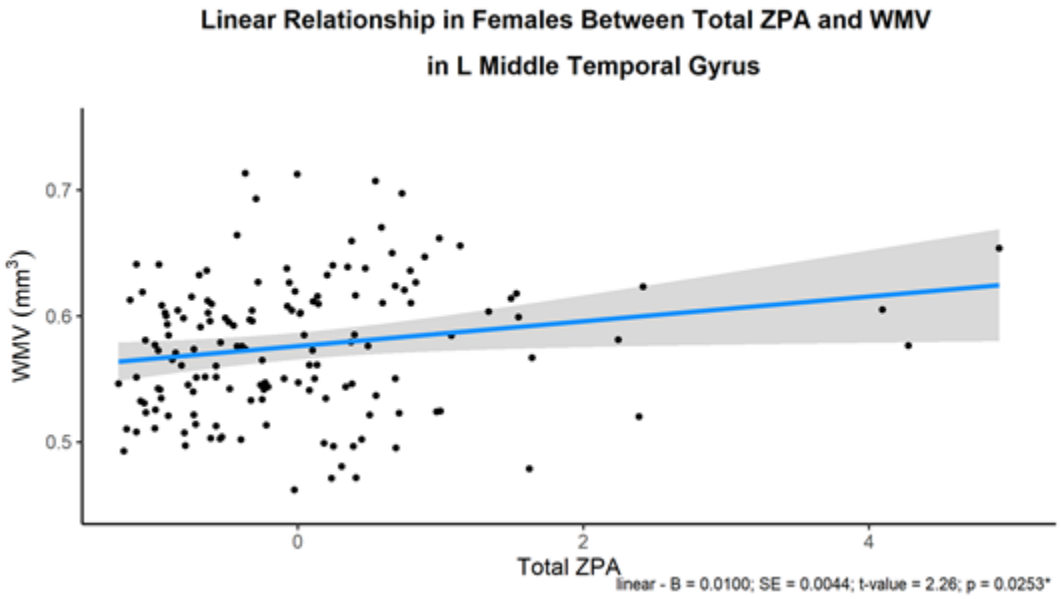

*Figure 4—13 Significant relationships between WMV ROIs and Total ZPA in females the left medial temporal gyrus. * denote significant p-value < 0.05.*

4.10.1.2 ZBMI and Total ZPA Interactions

There were no significant interactions between ZBMI and Total ZPA or moderate in any white matter ROIs ($p > 0.05$).

4.10.2 Males

4.10.2.1 Total ZPA

No WMV ROIs were significantly associated with Total ZPA ($p > 0.05$)

4.10.2.2 ZBMI and Total ZPA Interactions

There were no significant interactions between ZBMI and ZPA moderate in any white matter ROIs for the males ($p > 0.05$).

Table 4-10: Significant regressions between Total ZPA and GMV ROIs in Females

	LINEAR				**QUADRATIC**					
	First Order				Second Order				Whole Model	
	Estimate (SE)	p	BIC	Adjusted R^2	Estimate (SE)	p	Estimate (SE)	p	BIC	Adjusted R^2
RMFG	***0.0040 (0.0017)***	***0.020***	***-708.2***	***0.063***	0.0061 (0.0024)	0.012	-0.0010 (0.0008)	0.222	-704.7	0.058
LMFG	***0.0032 (0.0016)***	***0.0088***	***-742.9***	***0.042***	0.0052 (0.0021)	0.016	-0.0010	0.174	-739.8	0.091
LSTG	***0.0048 (0.0020)***	***0.019***	***-651.3***	***0.153***	0.0076 (0.0030)	0.0127	-0.0022 (0.0017)	0.206	-647.1	0.157
LMTG	***0.0048 (0.0022)***	***0.030***	***-633.3***	***0.133***	0.0050 (0.0031)	0.106	-7.21×10^{-5} (0.0011)	0.946	-628.3	0.127

Table 4-11: Significant regression interactions in GMV ROI between Total ZPA and ZBMI in Females

	LINEAR				**QUADRATIC**					
	First Order				Second Order				Whole Model	
	Estimate (SE)	p	BIC	Adjusted R^2	Estimate (SE)	p	Estimate (SE)	p	BIC	Adjusted R^2
LSPG	***0.0039 (0.0019)***	***0.037***	***-692.7***	***0.080***	0.0045 (0.0020)	0.025	6.3×10^{-4} (7.5×10^{-4})	0.401	-688.4	0.078

Table 4-12: Significant regressions between Total ZPA and GMV ROIs in Males

	LINEAR				**QUADRATIC**					
	First Order				Second Order				Whole Model	
	Estimate (SE)	p	BIC	Adjusted R^2	Estimate (SE)	p	Estimate (SE)	p	BIC	Adjusted R^2
RHippo	0.0090 (0.0056)	0.118	-191.2	0.175	***0.0139 (0.0067)***	***0.0425***	-0.0066 (0.0049)	0.183	***193.3***	***0.187***
LHippo	0.0079 (0.0061)	0.197	-235.7	0.249	***0.0161 (0.001)***	***0.0269***	***-0.0136 (0.0065)***	***0.041***	***-236.1***	***0.285***

Table 4-13: Significant regression interactions in GMV ROIs between Total ZPA and ZBMI for Males

	LINEAR				QUADRATIC					
	First Order				Second Order				Whole Model	
	Estimate (SE)	p	BIC	Adjusted R^2	Estimate (SE)	p	Estimate (SE)	p	BIC	Adjusted R^2
LHippo	***-0.0119 (0.0049)***	***0.018***	***-207.6***	***0.261***	-0.0123 (0.0048)	0.0126	-0.0044 (0.0022)	0.045	-206.1	0.302

Table 4-14: Total ZPA and WMV ROI Regression Results in Females

ROI	LINEAR				QUADRATIC					
	First Order				Second Order				Whole Model	
	Estimate (Std Error)	p	BIC	Adjusted R^2	Estimate (Std Error)	p	Estimate (Std Error)	p	BIC	Adjusted R^2
LMTG	***0.0100 (0.0044)***	***0.0253***	***-426.1***	***0.096***	0.0125 (0.0062)	0.044	0.0013 (0.0022)	0.531	-418.3	0.088

5 Manuscript 4: Sex differences in the beneficial effects of physical activity on cerebral blood flow in aging

Authors: Brittany Intzandt, Safa Sanami, Louis Bherer and Claudine J Gauthier

5.1 Preface

Age-related vascular decline also extends to the cerebral vasculature, resulting in an assortment of changes and declines, but one of the earliest changes quantifiable changes is a reduction to CBF. This hypoperfusion occurs beginning in mid life and continues to decline well into aging (Lu et al., 2011). Notably though, sex differences have been consistently implicated, where females have greater CBF across the lifespan (Juttukonda et al., 2021; Rodriguez, Warkentin, Risberg, & Rosadini, 1988), and the rate at which the CBF declines is also sex dependent (Chen et al., 2011; Lu et al., 2011). Conversely, PA is an important factor in maintaining or enhancing vascular health and tis has been identified to translate to CBF. For example, those who participated in greater PA levels over a four year time period had significantly greater CBF at the follow up (Rogers, Meyer, & Mortel, 1990), and since then this work has been replicated in cross-sectional studies (Boraxbekk et al., 2016; Zlatar et al., 2019). Recent work has indicated that females might gain more benefit from PA on CBF than males in aging (Gonneaud et al., 2022), however given that midlife is a crucial stage for vascular decline, this is an imperative time point to investigate as well.

Here, in manuscript four, we included a sample of almost 500 participants from the human connectome project, aging subsample (Bookheimer et al., 2019; Harms et al., 2018), where males and females were separated, and further subsamples were created dependent upon age. More specifically a middle aged (those less than 55 years) and an older aged group (55 or older) were categorized for males and females separately. This dataset also included the collection of a PA questionnaire that was employed to gain information about PA participation in METs/ week like in manuscript three, and further incorporated more information about intensity types (e.g., total METs, walking METs, vigorous METs, etc.) A multi-band pCASL was also acquired in all individuals to allow for quantification of CBF across the lifespan. Though of great interest to this thesis, BMI was not included in this chapter, however it is noted that it will be in future versions

of this manuscript to further understand and hopefully extend the findings of manuscript three, in a larger sample.

5.2 Abstract

In aging, CBF is consistently observed to decline. Understanding the vascular changes and risk factors that can influence CBF in *normal* aging, prior to any pathological changes is crucial. One important factor may be sex since females have greater CBF across the lifespan and a different rate of decline. Another factor that influences vascular health is physical activity (PA). PA is beneficial for CBF in both males and females, though recent work has revealed that older females may benefit more from the effect of PA on CBF than older males and younger females. Further bringing into question if there is an ideal window of opportunity to maximize the beneficial impacts of PA on CBF. Here we examined how CBF, and PA relate according to sex and if an individual was in middle age (35-55 years) or older age (greater than 55 years). A total of 496 participants aged 36 to 100 were included from the Human Connectome Lifespan Aging study. PA was quantified based on the METs for each activity into Total PA, Walking PA, Moderate PA, Moderate-vigorous PA, and vigorous PA. Structural, white matter vascular lesion and cerebral blood flow data were collected. Polynomial regressions were used to investigate the relationship between CBF and each intensity of PA for males and females separately for midlife and older age. Results revealed that middle aged males had an inverse U shape between CBF and vigorous PA, whereas older aged males showed an inverse U relationship between moderate-vigorous and moderate PA and CBF. Finally, older aged females demonstrated a linear relationship between CBF and both Total PA and walking PA, yet middle aged females had no relationships between CBF and any intensity of PA. Overall, this work shows a predominantly positive relationship between PA and CBF across the lifespan, with males benefitting mainly in midlife and females in older age. Therefore, this work highlights the importance of utilizing sex-disaggregated analysis to understand the relationship between CBF and PA. Future work should incorporate sex hormones to further elucidate the potential mediation effect that sex hormones have on the relationships between CBF and PA in pre to post-menopausal females.

5.3 Introduction

Maintenance of cerebral health requires constant cerebral blood flow (CBF) to provide tissue with sufficient oxygen, nutrients, energy metabolites, and for cellular waste and carbon dioxide to be removed. Thus, chronic hypoperfusion is associated with a range of deleterious vascular and metabolic consequences (Hoge et al., 1999), including damage to surrounding tissue which can manifest as pathological conditions, such as cognitive impairment (Liu & Zhang, 2012; Sarti, Pantoni, Bartolini, & Inzitari, 2002) or Alzheimer's disease (AD)(Girouard & Iadecola, 2006). Furthermore, CBF has been consistently observed to decline with age (Amen, Egan, Meysami, Raji, & George, 2018; Chen et al., 2011; Juttukonda et al., 2021; Lu et al., 2011). These age-related hypoperfusion patterns are typically observed to occur within temporal (Chen et al., 2011; Martin, Friston, Colebatch, & Frackowiak, 1991), frontal (Chen et al., 2011; De Vis et al., 2018; Martin et al., 1991), parietal (Amen et al., 2018; Martin et al., 1991) and parahippocampal regions (De Vis et al., 2018; Martin et al., 1991), which are also regions known to be associated with cognitive decline and AD. Therefore, understanding the vascular changes that can potentiate or rescue CBF changes in *normal* aging, prior to any pathological manifestations is a crucial step in harnessing all the preventative tools at our disposal to reduce the development of pathological perfusion declines across the adult lifespan.

Sex differences have been reported in overall vascular health (Chrissobolis & Sobey, 2004), as well as cerebrovascular health (Krause, Duckles, & Pelligrino, 2006). Females have been shown to have greater CBF across the lifespan after accounting for brain volume differences (Juttukonda et al., 2021). Furthermore, females and males differ in the rate at which CBF declines across the lifespan (Chen et al., 2011; Lu et al., 2011). Some of these CBF differences are likely linked to disparities in the cerebral vasculature between sexes, which are hypothesized to be primarily influenced by sex hormones (Robison, Gannon, Salinero, & Zuloaga, 2019). In fact, these differences have been shown to lead to an approximate 11% higher global CBF in females than in males throughout the lifespan (Rodriguez et al., 1988), and in younger adults, this greater CBF in females has been reported to be as high as 15% (Gur et al., 1982). Indeed, higher CBF has been consistently linked to estrogen, which is known to promote vasodilation and overall vascular health (Pelligrino et al., 2000; Skarsgard, Van Breemen, & Laher, 1997). This is consistent with the observation that CBF is significantly decreased in post-menopausal females compared to pre-menopausal(Liu, Lou, & Ma, 2016). Therefore, sex-related

differences have a considerable influence on the trajectory of cerebral perfusion across the lifespan and should be taken into consideration when investigating CBF modulation by lifestyle factors.

Beyond sex-related influences, a crucial factor in determining vascular health during aging is physical activity (PA). In fact, the 2020 Lancet dementia commission identified that physical inactivity is an important risk factor in the development of dementia (Livingston et al., 2020b). Early work identified that over a four-year period, those individuals who participated in PA showed a significantly higher CBF over time compared to those who chose to remain inactive after retirement (Rogers et al., 1990). Follow up studies have confirmed that consistent participation in PA has multifactorial beneficial effects on cerebral functions (Barnes, 2015), but in particular an association with greater CBF (Bailey et al., 2013). More specifically, increased PA levels have been associated with greater CBF in posterior cingulate cortex (Boraxbekk et al., 2016) and frontal regions (Zlatar et al., 2019), while others have found that after 10 days of cessation of a PA program in Master Athletes, significant CBF declines occurred in temporal, parietal, and hippocampal regions (Alfini et al., 2016). PA is thought to help maintain or improve brain vascularization, the health of vessels and metabolic processes (Ainslie et al., 2008; Steventon et al., 2020). The underlying protective mechanisms of PA are thought to include reduction of oxidative stress (Colcombe & Kramer, 2003), changes in hormonal responses (Weuve et al., 2004) and the elevation of neurotrophic factors (van Praag, Christie, Sejnowski, & Gage, 1999). Notably, recent work has revealed that older females may benefit more from the effect of PA on CBF than males (Gonneaud et al., 2022). Moreover, *when* in the lifespan PA occurs seems to be an important factor and numerous studies have identified that midlife PA participation is more beneficial for cognition than later life than later life PA (Rovio et al., 2005; Tolppanen et al., 2015).

Overall, the literature shows that there are reductions to CBF in aging due to vascular changes, and that sex differences are present throughout the lifespan, whereby females have higher CBF, likely related to hormone levels. Moreover, PA has been observed to have a beneficial role on CBF in aging, especially in females. Yet to date, it is unclear how PA levels might influence CBF in males versus females across the lifespan, and if PA might have more influential role on CBF in middle aged versus older age depending on sex. Here, we aimed to

investigate how the relationship between PA and CBF changes depending upon if individuals are in middle age (36 to 55 years old) compared to older adult (older than 55 years) and how sex influenced these relationships in a sample of almost 500 males and females between the ages of 36 and 100.

5.4 Methods

5.4.1 Participants

A total of 496 participants from the Human Connectome Project Aging Lifespan (HCP-A) dataset were used here (females n = 278, age 60.7 ± 16.1 years). The HCP-A dataset is a large, normative data set that includes a range of brain, biometric and cognitive data associated with changes across the lifespan. More specifically participants were included if they were between the ages of 36 to 100 years old, and 'typically' aging, defined as exhibiting typical health for their age, while having an absence of pathological causes of cognitive decline, such as stroke or clinical dementia (Bookheimer et al., 2019; Harms et al., 2018). Participants were excluded from HCP-A if they had been diagnosed or treated for neurological disorders (e.g., Parkinson's disease, stroke), major psychiatric disorders (e.g., bipolar disorder, schizophrenia), and those who had severe depression requiring treatment for 12 months or longer in the previous five years (Bookheimer et al., 2019; Harms et al., 2018). Furthermore, individuals over the age of 60 were screened using the Telephone Interview for Cognitive Status modified (TICS-M) (Brandt, Specter, & Folstein, 1988), and participants with a score of 30 or greater were included.

An age specific MoCA threshold was used as exclusion criteria (e.g., less than 80, >19/30, 80-89 >17/30 and 90+ 16/30). All participants were also assessed for their capacity to give informed consent based on (Appelbaum & Gutheil, 2007). More information on exclusion and inclusion criteria can be found in (Bookheimer et al., 2019). Data collection for all of the following components were completed at four sites across the United States of America, including: Massachusetts General Hospital, University of California – Los Angeles, University of Minnesota, and Washington University in St Louis. All data collection, including behavioral, biological, cognitive, and imaging, had identical protocols at all four sites. All participants provided informed written consent prior to the baseline data collection, according to local ethics boards and the declaration of Helsinki. See Bookheimer et al., for a more in-depth description of methods (2019).

5.4.2 Physical Health Outcomes

Data on current and history of smoking status, systolic blood pressure (SBP), diastolic blood pressure (DBP) and current body mass index (BMI) as measured according to the standard equation of BMI = (body weight [kg]/ height [m^2]) were collected.

5.4.3 Physical Activity Measurement

The international physical activity questionnaire (IPAQ) (condensed version) was utilized to document the overall background of each participant's involvement in physical activities. Activities were categorized into walking (METs), moderate (3 to 6 METs) moderate-vigorous (greater than 3.0 METs), vigorous METs (greater than 6.0 METs) and their overall, or total PA participation levels. The IPAQ has been found to be a valid and reliable questionnaire (van Poppel, Chinapaw, Mokkink, van Mechelen, & Terwee, 2010).

As the primary aim here was to investigate the effects of participating in PA on CBF, rather than the effects of participating in PA versus no participation in PA, those individuals in this study that did not report engaging in any overall PA were excluded from the final analysis (14 females: 11 males)

5.4.4 MRI acquisitions

At all four sites, a Siemens 3T Prisma machine (Siemens Medical Solutions, Erlangen, Germany), with 32-channel head coils were utilized. The full imaging protocol can be found here (Harms et al., 2018), however only a portion of sequences was used in this study. Moreover, approximately 68 individuals were excluded since they did not have pCASL scans available, and 16 individuals were excluded since they were missing either T1-weighted or T2-weighted images or both.

5.4.4.1 Structural Scans

A multi-echo 0.8 mm^3 T1 weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence (repetition time [TR] = 2500 ms; inversion time [TI]; 1000 ms; echo time [TE] = 1.8/3.6/5.4/7.2 ms; flip angle (FA) = 8°; matrix size = 320 x 300 x 208; field of view [FOV] = 256 x 240 x 166 mm) was employed to collect anatomical information for registration purposes and for partial volume correction of the final perfusion maps estimated with the pseudo-continuous arterial spin labelling sequence (pCASL). A T2 weighted scan (TR = 3200

ms; TE = 564 ms; turbo factor = 314; matrix size = 320 x 300 x 208; FOV = 256 x 240 x 166 mm) was used to estimate white matter lesions by FreeSurfer as described in Fischl (Fischl, 2012).

5.4.4.2 Pseudo-continuous Arterial Spin Labeling

A multi-band 2D echo planar imaging pseudo-continuous arterial spin labeling (pCASL) sequence was collected to quantify cerebral blood flow (CBF) for all participants (TR = 3580 ms; TE = 19 ms; SMS acceleration factors = 6; total slices = 60; resolution = 2.5 mm^3; acquisition time = 5.5 minutes). Two equilibrium magnetization (M_0) images were also acquired. Since arterial transit time (ATT), the time taken for the labeled blood to travel from the labeling site to the cerebral tissue being imaged, generally increases with age, a sequence with multiple post-labeling delays was employed to allow for more accurate CBF quantification across the lifespan. This sequence included five post-labeling delays (PLDs): 200 ms (control/labeled pairs =6); 700 ms (pairs = 6); 1200 ms (pairs = 6); 1700 ms (pairs = 10) and 2200 ms (pairs = 15) with a labeling duration of 1500 ms throughout.

5.4.5 Data Analysis

5.4.5.1 T1-w MPRAGE

T1-weighted MPRAGE images were processed using FSL's brain extraction tool (BET) to remove the non-brain tissue from all participants (Smith, 2002, p. 200) with a fractional intensity threshold ranging from 0.15 to 0.3. All MPRAGE extracted images were independently verified by two researchers to ensure the skull and neck were completely removed from the final extracted images. These raw MPRAGE images were also pre-processed with SPM's computational anatomy toolbox (CAT) 12 to segment the images into grey matter, white matter, and cerebrospinal fluid (CSF) for each participant, compared to the expected volume of a template (Ashburner & Friston, 2000; Gaser & Dahnke, 2016; Penny et al., 2011). From here, a statistical parametric map was created, classifying each voxel type into GMV, WMV or CSF according to the highest probability of voxel type for partial-volume correction (PVC) of CBF maps to account for atrophy.

5.4.5.2 T2-w

The T2-weighted images were all processed in the same way as the T1-w images, where FSL's BET tool was employed, and all extracted images were independently verified by two independent researchers. These T2 images were then used for registrations purposes.

5.4.5.3 pCASL resting CBF

All pCASL time series also had FSL BET employed to each individual volume of the whole time series. The time series was then motion corrected using the statistical parametric mapping (SPM)12 run in Matlab/R2020a ((Ashburner & Friston, 2005)). The motion parameters in the x, y, and z directions were output for both rotation and translation to allow for visual inspection of movement, where volumes with movement that was equal to or greater than 2 mm were removed from the time series. The output motion parameters were also used in a general linear model (GLM) to regress out the motion parameters from the time series. The first pair of tag control volumes were removed to reduce risk of motion contamination unrepresentative of the remaining volumes in the time series.

From here, the remainder of the paired tag-control volumes were surround-subtracted. CSF masks were also created for all participants to be used as the CSF M0 in the final perfusion quantification as competed in (Intzandt et al., 2020). Briefly, 10 voxels were chosen in the same axial slice for all participants, where possible, in the slice that the lateral ventricles were clearly present. In some cases, it was necessary to take a more superior or a more inferior slice to clearly identify the ventricles. Two independent researchers then individually inspected all masks to ensure that the extracted masks were located within the ventricles. Individual masks were required to be created given the varying anatomical structures in our age range of participants.

We then utilized FSL's BASIL toolkit (Chappell, Groves, Whitcher, & Woolrich, 2009), to quantify and create perfusion maps in native pCASL space with the following standardized parameters: labeling: cASL/pCASL; bolus duration: constant (1.5s), inversion times [PLDs + labeling delay): 1.7s, 2.2s, 2.7s, 3.2s, 3.7s; repeats: 6, 6, 6, 10, 15; calibration image: M0 collected during pCASL sequence; reference tissue type: CSF; mask: CSF masks for each participant; slice timing: 0.059s; slice band: 10; echo time: 19 ms; CSF T1: 4.3 s ; T2: 750 ms ; T1: 1.3s ; T1 blood: 1.65 s ; inversion efficiency: 0.85.

An in-house Matlab script was then employed which corrected for partial volume differences in the perfusion maps utilizing each participant's own individual GM, WM and CSF maps produced from the T1-w images. These T1-w had previously been projected to native pCASL space employing the inverse matrices utilized to get the perfusion maps from ASL to T1 space (discussed below). The partial volume correction employed incorporated the method described by Asllani and colleagues (2008) in order to correct for voxel intensities corresponding to GM, WM, and CSF(Asllani, Borogovac, & Brown, 2008).

5.4.5.4 Registration

The registration pipeline began with a 3 degree of freedom translation of the mean and extracted pCASL image to the native T2-weighted image, followed by a 6 degree of freedom linear registration to the same native T2-weighted image. The T2-w image was incorporated in our registration pipeline prior to registration to the T1-w image as it was the only structural image collected on the same day as the pCASL image. The T1-w image was collected on a separate day. We then utilized a 6 degree of freedom linear registration from the T2-w native space to the T1-w native space. Finally, the native T1-w image was registered to the standard MNI space employing a uniform non-linear registration with 12 degrees of freedom. Matrices and the warp were applied to the native pCASL perfusion weighted image to project them to a standard MNI space. All registrations were completed utilizing ANTS (Avants et al., 2008).

5.4.5.5 Region of interest analysis

A hypothesis driven approach was taken to investigate the sex and age specific relationships between PA and regions of CBF that are known to decline in aging, and that were used in our previous work demonstrating sex-specific PA relationships with structural outcomes (Intzandt et al., 2022- submitted to GeroScience). More specifically, the LPBA40 atlas (Shattuck et al., 2008) was utilized to extract CBF in regions of interest in all participants from the following bilateral regions: superior frontal gyri, medial frontal gyri, inferior frontal gyri, superior parietal gyri, superior temporal gyri, medial temporal gyri, insular cortices, and hippocampi. Prior to ROI extraction, the LPBA atlas was registered using ANTS, as described above, to the same common MNI space utilized throughout. This atlas was then multiplied by each individual's perfusion map in order to create individual ROI's that were extracted using the

weighted GM average for each participant with FSLmeants to correct for any potential GM atrophy (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). CBF for each participant from each hemispheric region was extracted to a spreadsheet and imported into R/RStudio (v.24) for further analysis .

5.4.6 Statistical Analysis

Each sex was separated into two age groups, middle aged, defined as those participants between the ages of 36 and 55 years old, and older aged, defined as those participants who were above the age of 55 years. After all the CBF ROIs were extracted including global GM CBF the hypothesis driven data was analyzed statistically in R and R studio. T-tests were used to test group differences in age, education, SBP, DBP, BMI, volume of white matter hyperintensities, MoCA score, PA outcomes (vigorous, moderate-vigorous, moderate, walking, total) between: i) all males versus all females; ii) young males versus older males; iii) young females versus older females; iv) young males versus young females; and v) old males versus old females. In order to examine if sex differences were present in the relationships between CBF ROIs and volume of each intensity of PA, linear regression interactions were utilized where the CBF ROI was the dependent variable, intensity of PA was the independent variable, and sex was the interaction term.

To further comprehend the sex and age specific relationships between CBF ROI and intensities of PA, the relationships between CBF ROI and each of the four groups were individually examined with quadratic regressions, as our previous work demonstrated some regions revealed inverse quadratic relationships with PA and brain health (Intzandt et al., 2022 submitted). In all analyses, systolic blood pressure, education in years, age in years and volume of white matter hyperintensities were included as covariates. All linear and quadratic relationships were explored using the 'lm' package in R (Chambers, 1992; Wilkinson & Rogers, 1973). A p-value of 0.05 or less was considered to be significant a priori. If both a linear and quadratic regression were significant, Bayesian Information criterion was used to compare the goodness of fit of each regression, and that with the lowest BIC value was considered to be the best regression fit (Raftery, 1995). Given the large sample size of each of the four groups (>75), parametric tests were always employed as normality assumptions with this sample have been shown to be reliable (Elliott & Woodward, 2007; Ghasemi & Zahediasl, 2012; Pallant, 2020). To

investigate the presence of sex interactions between CBF and any of the PA intensities, 'emmeans' and 'emtrends' were employed in RStudio, while correcting for covariates, to run post-hoc analyses correcting for multiple comparisons within the post-hoc with Tukey's test. Finally, to correct for multiple comparisons in all analyses, not just the post-hoc tests, a False Discovery Rate was employed using "FDRestimation" a library employed in Rstudio, to adjust p values for multiple comparisons (Murray & Blume, 2021).

5.5 Results

5.5.1 Overall Sex Differences

There were no significant differences between males and females as revealed by t-tests for age ($p > 0.05$); BMI ($p > 0.05$); MoCA ($p > 0.05$); systolic blood pressure ($p > 0.05$); white matter hyperintensity volume ($t = 1.73$; $p = 0.084$), amount of vigorous PA ($t = -1.13$; $p = 0.26$), volume of time spent in walking PA ($t = 1.72$; $p = 0.087$); total volume of PA ($t = 0.94$; $p = 0.35$). Males had higher education ($t = -1.10$; $p = 0.0002$) and diastolic blood pressure ($t = -4.47$; $p = 9.77 \times 10\text{-}6$) than females, while females participated in a greater amount of moderate PA ($t = 2.09$; $p = 0.037$) and had more CBF in gray matter ($t= 3.86$; $p = 0.00013$).

Table 5-1: Demographics of Females and Males

	Females (n = 278)	**Males (n = 218)**
Age (years)	60.7 ± 14.9 (36.2 – 89.8)	60.2 ±15.1 (36 – 89.8)
Education (years)	17.1 ± 2.2 (8 – 21)**	17.9 ± 2.0 (9 – 21)
BMI (kg/m^2)	26.5 ± 4.7 (18.7 – 39.7)	27.2 ± 3.9 (18.6 – 38.4)
SBP (mmHg)	130 ± 17 (85 – 183)	133 ± 17 (96 – 199)
DBP (mmHg)	80 ± 10 (41 – 113)**	85 ± 10 (53 – 123)**
WMH Volume (mm^3)	2056.8 ± 2456.4 (401.4 – 21987.1)	2582.2 ± 3302.6 (413.2 – 32206.5)
MoCA (out of 30)	26.3 ± 2.4 (19 – 30)	26.3 ± 2.7 (19 – 30)
Vigorous PA (METs)	685.7 ± 1073.8 (0 – 8640)	822.26 ± 1442.8 (0 – 16800)
Moderate PA (METs)	533.4 ± 720.1 (0 – 3840)**	416.0 ± 493.0 (0 – 3360)**
Walking PA (METs)	1131.5 ± 1619.1 (0 – 13860)	909.0 ± 1153.1 (0 – 8316)
Total PA (METs)	2350.3 ± 2443.7 (33 – 19728)	2147.3 ± 1960.0 (49.5 – 20106)
Mod-Vig PA (METs)	1219.1 ± 1451.0 (0 – 8640)	1238.3 ± 1622.4 (0 – 18720)

CBF (ml/100g GM/min)	67.1 ± 21.4 (18.6 – 134.3)**	56.3 ± 19.7 (16.8 – 136.1)

**Statistically differences between all females and all males $p < 0.05$. BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; WMH – white matter hyperintensities; MoCA – Montreal Cognitive Assessment; PA – physical activity; Mod-Vig – moderate-vigorous PA; CBF – cerebral blood flow

5.5.2 Sex by Age Group Differences

5.5.2.1 Older Males versus Older Females

T-tests identified differences between older males and females for the following outcomes: males had significantly greater years of education than females ($t = -2.89$, $p = 0.004$) as well as DBP ($t = -3.33$; $p = 0.0010$), whereas older females had greater moderate PA ($t = 2.3$; $p = 0.022$) and CBF in the right and left superior parietal gyrus (right $t = 2.89$; $p = 0.004$; left $t = 2.93$; $p = 0.0037$)[See Table 1].

Linear interactions of sex with moderate PA were identified for global CBF in GM (adjusted-$R^2 = 0.032$, $p = 0.032$, Fig. 1A); the right superior parietal gyrus (adjusted-$R^2 = 0.045$; $p = 0.008$, Fig. 1B) and the left hippocampus (adjusted-$R^2 = 0.04$; $p = 0.019$, Fig. 1C). A linear sex interaction was also present between walking PA and the right inferior frontal gyrus (adjusted-$R^2 = 0.030$; $p = 0.048$) [See Fig. 1D]. Post-hoc analyses were employed to further investigate which sex was responsible for the statistically significant relationship, while correcting for covariates. The post-hoc analyses revealed no significant sex interaction with moderate PA for global CBF ($p = 0.158$). Post-hoc analyses identified a significant effect due to males in the right superior parietal gyrus where older aged males had increased CBF in the RSPG with greater amounts of moderate PA (estimate = 0.0116; $p = 0.0395$, Fig. 1B), which was also observed for the left hippocampus CBF and moderate PA in males (estimate = 0.0058; $p = 0.028$, Fig. 1C). Conversely, the post-hoc analysis between walking PA and CBF in the RIFG revealed that females with larger volumes of walking PA had significant greater RIFG CBF (estimate = 0.00278; $p = 0.0414$, Fig. 1D).

Table 5-2: Significant differences between middle-aged males and older-aged males

	Middle-Aged Males	Older-Aged Males
Age (years)	46.1 ± 6.4 (36-54) **	70.1 ± 10.2 (55-100)
Education (years)	17.9 ± 2.0 (12-21)	17.9 ± 2.1 (9-21)
BMI (kg/m^2)	27.8 ± 4.1 (20.1 – 38.4	26.8 ± 3.6 (19.3- 36.9)
SBP (mmHg)	129.4 ± 14.3 (100-169)**	136.4 ± 138.1 (96-177)
DBP (mmHg)	85.1 ± 10.6 (61-123)	84.3 ± 10.7 (53 – 123)
WMH Volume (mm^3)	1123.6 ± 608.2 (470.5-5356.8)**	3667.6 ± 4875.4 (413.2-32206.5)
MoCA (out of 30)	28.3 ± 1.6 (24-30)	26.0 ± 2.6 (18-30)
Vigorous PA (METs)	1012.6 ± 1935.5 (0-16800)	714.5 ± 876.1 (0 – 3360)
Moderate PA (METs)	460.6 ± 555.07 (0 – 3360)	400.2 ± 439.2 (0 – 1960)
Walking PA (METs)	981.3 ± 1288.2 (0-8316)	911.3 ± 1040.4 (0-6930)
Total PA (METs)	2454.6 ± 2441.4 (160-20106)	2020.8 ± 1465.2 (49.5 – 8010)
Mod-Vig PA (METs)	1473.3 ± 2155.7 (0-18720)	1117.5 ± 1016.2 (0-4320)
CBF (ml/100g GM/min)	61.7 ±18.0 (22.2-130.7)**	51.9 ± 20.1 (16.8 – 136.1)

**Statistically differences between middle-aged males and older-aged males $p < 0.05$. BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; WMH – white matter hyperintensities; MoCA – Montreal Cognitive Assessment; PA – physical activity; Mod-Vig – moderate-vigorous PA; CBF – cerebral blood flow

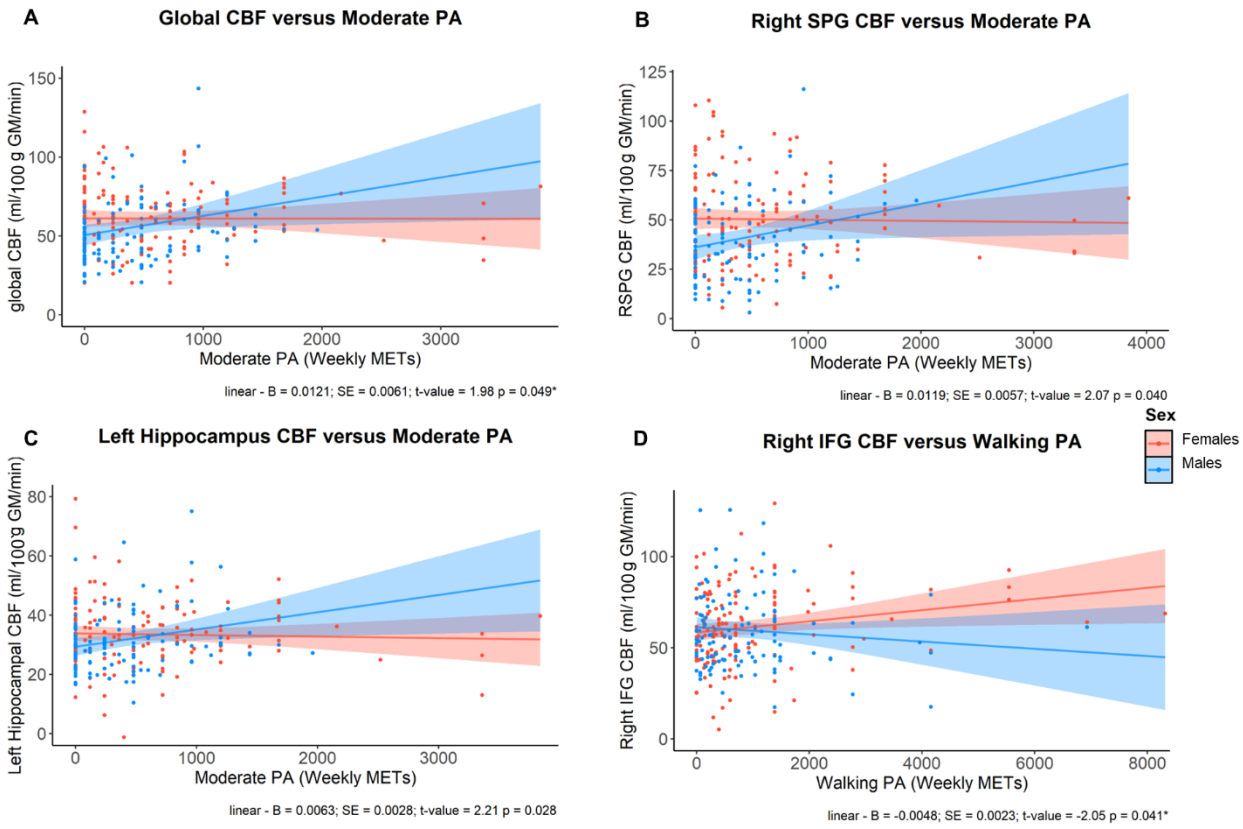

Figure 5—1 – Sex interactions in older aged adults and A) global CBF and moderate PA; B) Right Superior Parietal Gyrus CBF and Moderate PA; C) Left Hippocampal CBF and Moderate PA; D) Right Inferior Frontal Gyrus and Walking PA. Corrected p-values for multiple comparisons ($p < 0.05$).

5.5.2.2 Middle-Aged Males versus Middle-Aged Females

Significant differences in the middle-aged males and females were found, where males had significantly higher education (t = -2.35; p = 0.019); systolic blood pressure (t = -3.03; p = 0.0028), diastolic blood pressure (t =-3.29; p = 0.0012) and white matter hyperintensities (t = -3.78; p = 0.00020). CBF was higher in females than males in all ROI's.

A linear sex interaction was identified between total PA and the right superior temporal gyrus CBF (r = 0.062; p = 0.0045, Fig. 2A); as well as with the bilateral superior parietal gyrus CBF (*right: adjusted-R^2* = 0.117; p= 1.43 x 10-4, Fig. 2B, *left: adjusted-R^2* = 0.093; p = 9.7 x 10 -4, Fig. 2C). Post hoc analyses revealed that greater Total PA was associated with higher CBF in the right superior temporal gyrus in both males and females, but males had a marginal advantage over females by 0.00253 (p = 0.0247). [See Figure 2].

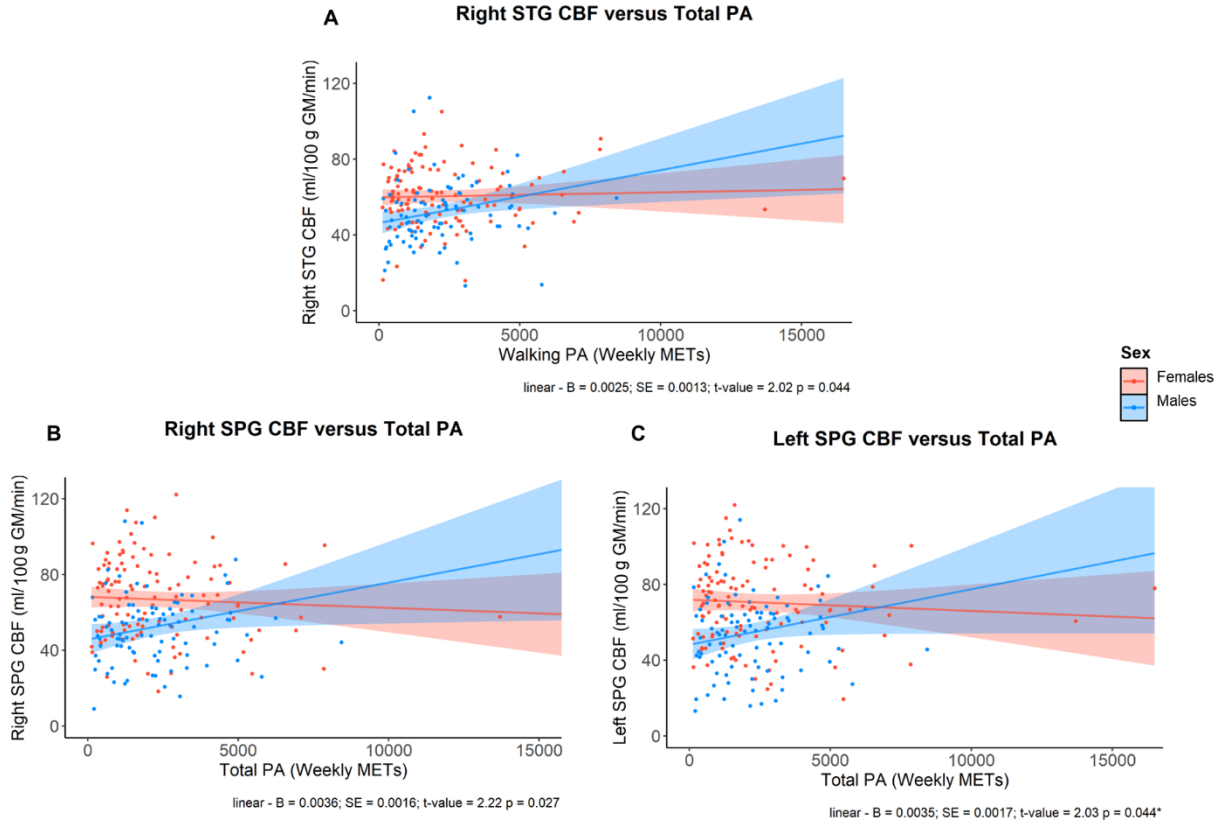

Figure 5—2- Sex interactions in middle-aged adults and A) Right Superior Temporal Gyrus CBF and Total PA; B) Right Superior Parietal Gyrus CBF and Total PA; C) Left Superior Parietal Gyrus CBF and Total PA. All interactions were statistically significant, even after multiple comparison corrections.

5.5.3 Males: Age Outcomes

Overall, the middle aged and older aged males were statistically different for age ($t = -20.8$, $p < 0.05$), SBP ($t = -2.96$, $p = 0.003$) and volume of white matter hyperintensities ($t = -5.04$; $p = 9.85 \times 10^{-7}$). There were no statistical differences for global CBF, MoCA, DBP, or any intensity of PA ($p > 0.05$). All CBF ROIs were statistically different between middle and older aged males except bilateral medial temporal gyri, left superior temporal gyrus, right insula, and bilateral hippocampi ($p > 0.05$). [see Table 2]

5.5.3.1 Middle Aged Males

There were no significant regressions between age and global CBF or CBF in any of the regions for the middle-aged sample of males ($p > 0.05$). Middle-aged males had an inverse quadratic relationship with vigorous PA and CBF in the following regions: the left medial frontal

gyrus (adjusted-R^2 = 0.097; p = 0.024, Fig. 3A);the left inferior frontal gyrus (adjusted-R^2 = 0.085, p = 0.036, Fig. 3B), bilateral medial temporal gyri (*right: adjusted-R^2* =0.113; p = 0.013, Fig. 3C; *left* adjusted-R^2 = 0.111; p = 0.014, Fig. 3D) as well as the left superior temporal gyrus (adjusted-R^2 = 0.099; p = 0.022, Fig. 3E), indicating that the highest CBF was observed in the range of 2000-3000 METs in these regions.[See Figure 3 A-E]

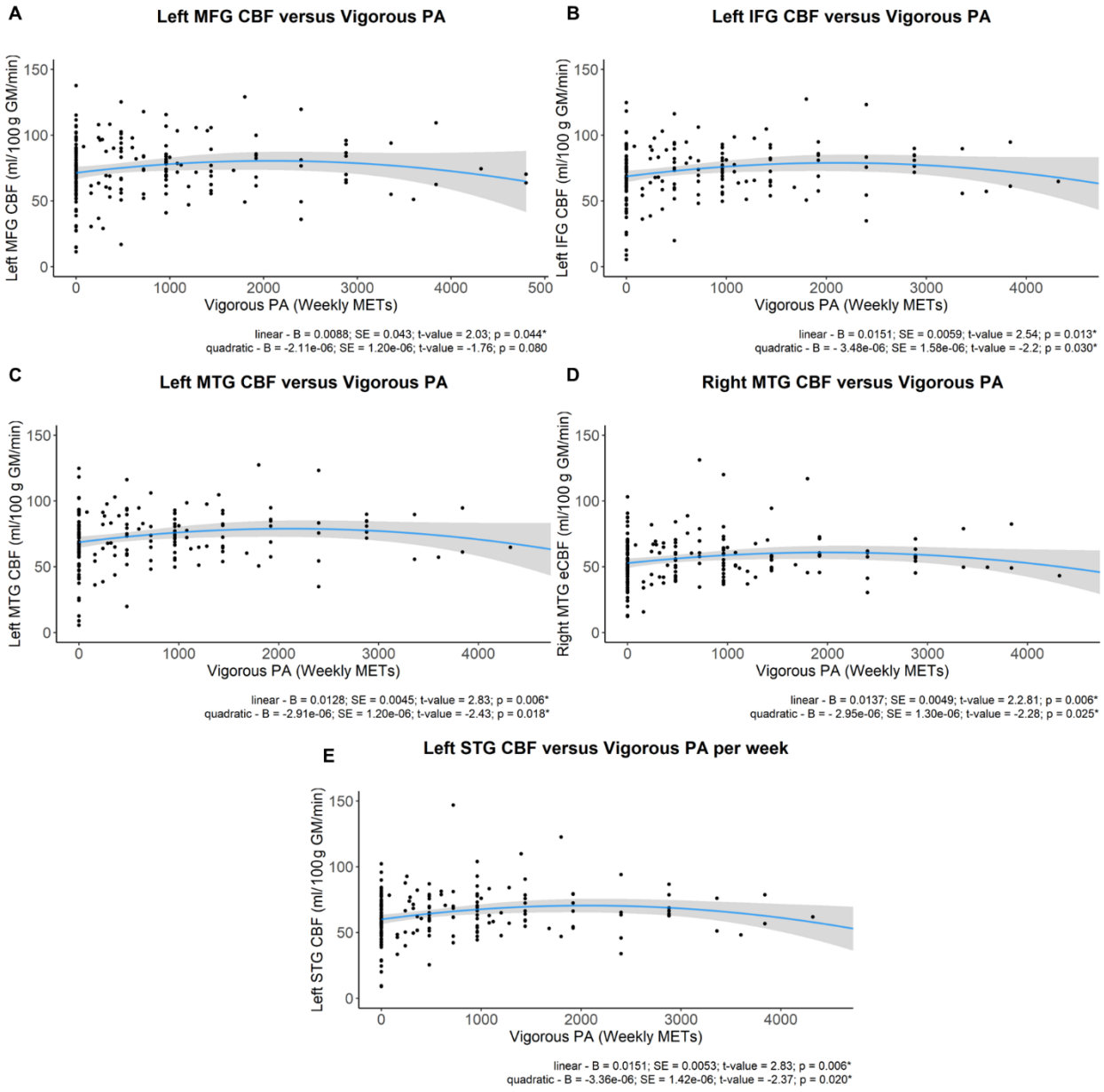

Figure 5—3: Significant Regions of Interest in CBF for Middle-Aged Males and Vigorous PA: A) Left Medial Frontal Gyrus; B) Left Inferior Frontal Gyrus; C) Left Medial Temporal Gyrus; D) Right Medial Temporal Gyrus; E) Left Superior Temporal Gyrus. All relationships were statistically significant, even after multiple comparison corrections ($p < 0.05$).

*5.5.3.2 **Older aged males***

The older aged males did not demonstrate a significant relationship in the regressions between age and global or regional CBFs ($p > 0.05$). A significant inverse quadratic relationship was present for CBF in the right medial frontal gyrus (adjusted-$R^2 = 0.050$; $p = 0.050$, Fig. 4A), as well as the left medial frontal gyrus (adjusted-$R^2 = 0.047$; $p = 0.046$, Fig. 4B) with moderate-vigorous PA, indicating highest CBF in the range of 1900 -2100 weekly METs. The linear component of the quadratic relationship between CBF and moderate PA was also significant for the left inferior frontal gyrus (adjusted-$R^2 = 0.053$; $p = 0.053$, Fig. 4C) and the right medial temporal gyrus (adjusted-$R^2 = 0.058$; $p = 0.043$, Fig. 4D). Finally, the left hippocampus CBF had a linear relationship with moderate PA (adjusted-$R^2 = 0.053$; $p = 0.043$, Figure 4E). [See Figure 4A-E].

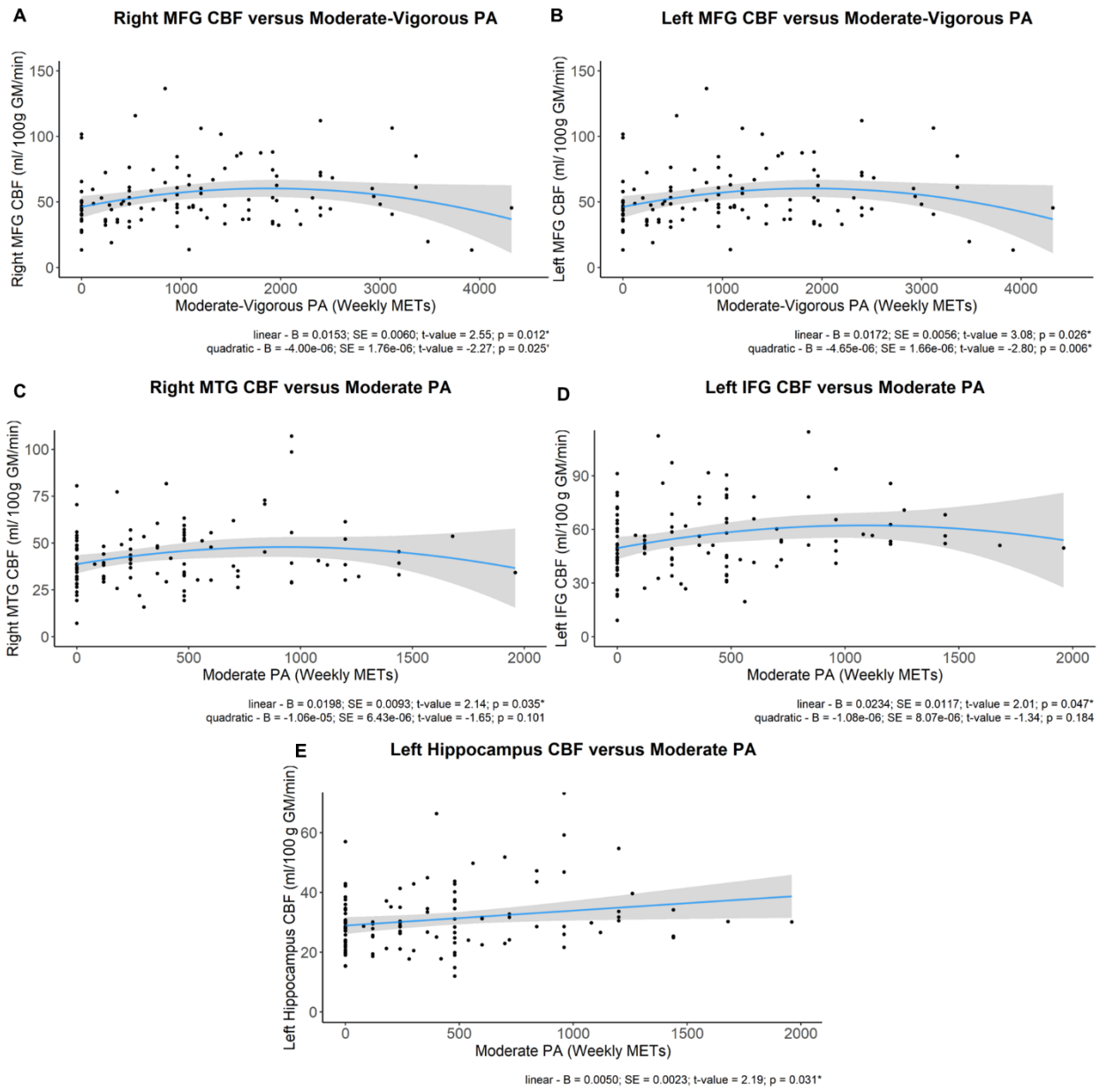

Figure 5—4: Significant Regions of Interest in CBF for Older-Aged Males: A) Right Medial Frontal Gyrus and Moderate-Vigorous PA; B) Left Medial Frontal Gyrus and Moderate-Vigorous PA; C) Right Medial Temporal Gyrus and Moderate PA; D) Left Inferior Frontal Gyrus and Moderate PA; E) Left Hippocampus and Moderate PA. All relationships were statistically significant, even after multiple comparison corrections ($p < 0.05$).

5.5.4 Females: Age Outcomes

Middle aged females and older aged females were statistically different for age (t = -23.25; p = 2.2 x 10-16), global CBF in gray matter (t = 6.95; p = 2.5 x10-11); SBP (t = -5.9, p

=1.01 x 10 -8) and the volume of WMH (t= -6.1, p =3.3 x10 -9). There were no statistically significant differences for MoCA, education, BMI, DBP, or the amount of METs spent for any of the intensities of PA (p > 0.05). [See Table 3]

Table 5-3: Significant differences between middle-aged and older-aged females

	Middle-Aged Females	Older-Aged Females
Age (years)	45.4 ± 5.5 (36.2 – 54.3)**	71.9 ± 20.4 (55.3 – 100)
Education (years)	17.2 ± 2.3 (8 -21)	17.1 ± 2.2 (10 -21)
BMI (kg/m^2)	27.0 ± 4.9 (18.7 – 39.7)	26.0 ± 4.8 (18.7 – 39.5)
SBP (mmHg)	122.6 ± 16.4 (85-183)**	135.8 ± 18.4 (98 - 182)
DBP (mmHg)	79.7	80.1
WMH Volume (mm^3)	875.9**	2947.6
MoCA (out of 30)	27.2**	26.1
Vigorous PA (METs)	653.1	744.0
Moderate PA (METs)	518.5	571.1
Walking PA (METs)	1265.9	1088.4
Total PA (METs)	2437.4	2403.5
Mod-Vig PA (METs)	1171.6	1315.1
CBF (ml/100g GM/min)	76.4 ± 19.0 (28.9 – 134.3)**	60.1 ± 20.4 (18.6 – 134.3)

**.Statistically differences between middle-aged females and older-aged females p < 0.05. BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; WMH – white matter hyperintensities; MoCA – Montreal Cognitive Assessment; PA – physical activity; Mod-Vig – moderate-vigorous PA; CBF – cerebral blood flow

5.5.4.1 Middle Aged Females

Middle aged females demonstrated no relationships with global CBF or ROI CBF for age (p > 0.05) or any of the intensities of PA (p > 0.05).

5.5.4.2 Older Aged Females

Females in the older group demonstrated decreased CBF with increasing age (adjusted-R^2 = 0.057; p = 0.0152). A linear relationship between total PA and the right medial frontal gyrus CBF (adjusted-R^2 = 0.045; p = 0.022, Fig. 5A) was identified. Total PA and CBF analysis revealed that the linear component of the quadratic regression was significant in the right inferior frontal gyrus (adjusted-R^2 = 0.056; p= 0.022, Fig. 5B) and the left medial temporal gyrus (adjusted-R^2= 0.072; p = 0.0083, Fig. 5C). Finally, there was a quadratic relationship between the right hippocampus CBF and total PA (adjusted-R^2 = 0.0353; p = 0.044, Fig. 5D) with peak CBF in the range of 12,000 METs for the frontal and temporal region, and 8000 METs for the hippocampus. [See Figure 5A-D]

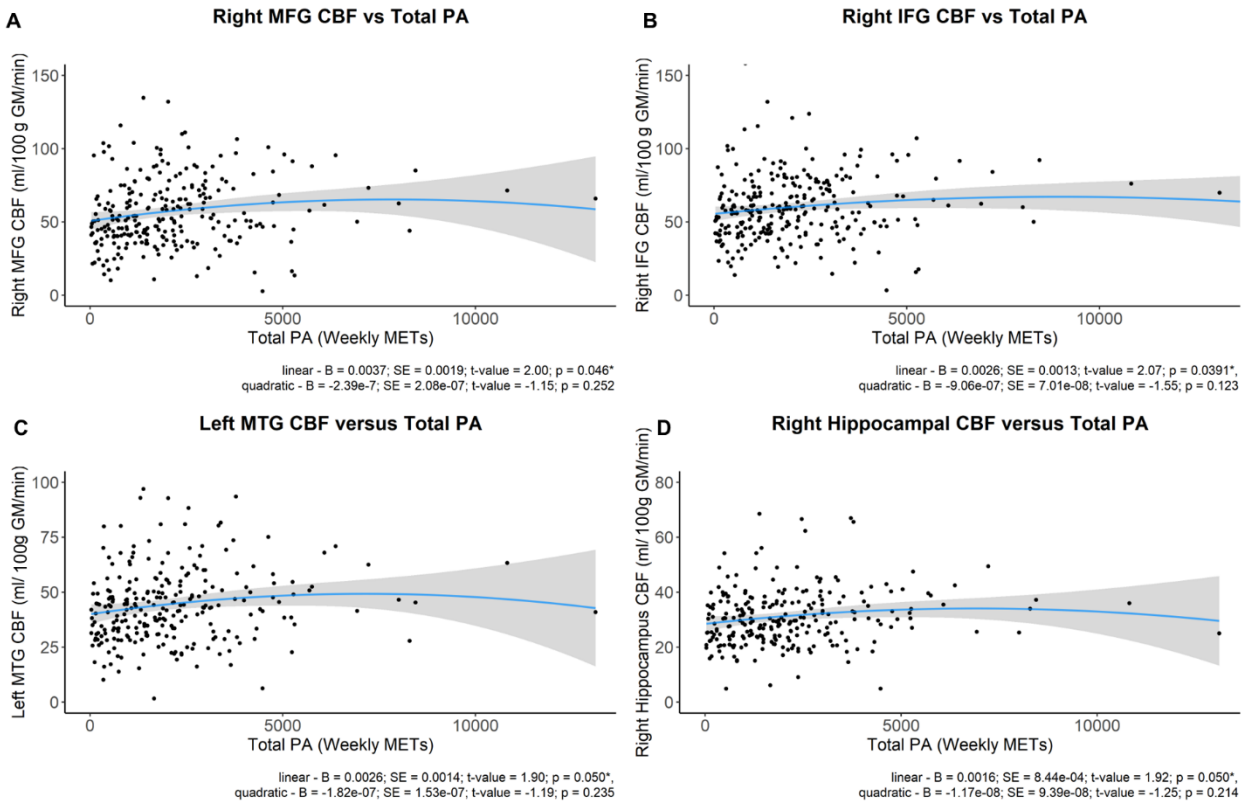

Figure 5—5 – Significant relationships between regions of interest in CBF and Total PA in Older Aged Females: A) Right Medial Frontal Gyrus ;B) Right Inferior Frontal Gyrus; C) Left Medial Frontal Gyrus; D) Right Hippocampus. All relationships were statistically significant, even after multiple comparison corrections ($p < 0.05$).

5.6 Discussion

In this study, we examined the sex and age specific relationships between CBF and PA across the lifespan, in a group of healthy older adults between the ages of 36 and 100 years. In general, CBF was found to significantly decline with age across the lifespan, confirming previous work (Chen et al., 2011; Lu et al., 2011), with strongest decline in older females. While PA was found to lead to higher CBF in many regions, our work identified important sex-specific linear interactions showing differential effects of PA on CBF in males and females. In the older aged group, moderate PA was associated with greater CBF in the right superior parietal gyrus and the hippocampus in the older aged males, whereas higher walking PA was associated with higher CBF in the right inferior frontal gyrus in the older aged females. In the middle-aged group, higher total PA was associated with higher CBF in the right superior temporal gyrus and the bilateral superior parietal gyri in males.

Investigation of these relationships in each group separately revealed beneficial effects of PA across all intensity for males, though middle-aged males benefitted only from vigorous PA. Notably, an inverse U quadratic relationship between PA and CBF was found in frontal and temporal regions in males, indicating a ceiling effect for the benefits of exercise both in middle-age and older age males. Interestingly however, hippocampal CBF showed a significantly linear relationship with moderate PA levels in older males, indicating there did not appear to be an upper threshold for moderate PA on hippocampal CBF. Given importance of the hippocampus in memory and cognitive decline (Bettio, Rajendran, & Gil-Mohapel, 2017), this linear relationship for CBF across the entire moderate PA range is consistent with a positive role of PA in maintaining cognitive health in aging.

Older females also demonstrated an overall beneficial effect of PA on CBF, with predominantly linear relationships in frontal and temporal regions indicating no ceiling effect. In contrast to males, the hippocampus demonstrated an inverse U relationship with total PA, consistent with a ceiling effect in this important structure. This ceiling effect may be dependent on PA type however, since analysis of walking PA revealed a linear relationship whereby walking PA was beneficial to hippocampal CBF across the entire range of walking METs in our sample.

5.6.1 Males, Perfusion and Physical Activity

In this work we revealed that older males benefitted from moderate, moderate-vigorous, and vigorous PA, whereas middle aged males benefitted only from vigorous PA and females benefitted from total and walking PA. This result of vigorous PA seemingly being predominantly beneficial in males follows the hypothesis that for high intensity PA, males experience high metabolic stress, which is thought to lead to large vascular changes (Ansdell et al., 2020). Some of these effects may also be due to the fact that middle-aged males in our sample completed significantly more vigorous PA on a weekly basis compared to the other three groups. Thus, on average, they were more likely to experience the putative positive associations between metabolic stress due to participation in high intensity PA and vascular health. However, the observation of an inverse U relationship between CBF and vigorous PA indicates that there is likely an upper limit in vigorous PA volume to have benefits for CBF. In this sample, this ceiling effect was observed in the range of 2000-2200 METs, corresponding to a maximum of 330 minutes of vigorous PA per week, which is well above the 75 minute minimum recommended by the American College of Sports Medicine and Canadian Society for Exercise Physiology (Garber et al., 2011; Ross et al., 2020). However, future work should explore this employing more objective measures of PA, like accelerometry.

Similarly to middle aged males, older aged males showed a ceiling effect for the benefits of PA, with peak CBF in the range of 2000 METs for moderate-vigorous PA, corresponding to approximately 250 minutes of moderate-vigorous PA in comparison to the recommended 150 minutes moderate-vigorous PA by ACSM and CSEP (Garber et al., 2011; Ross et al., 2020). The peak CBF for moderate PA occurred around 1000 METs, corresponding to 222 moderate minutes per week, again above the recommended 150 minutes. Interestingly, moderate PA showed the greatest benefits on CBF for the older aged males. This is somewhat surprising given that the older aged males participated in the least amount of moderate PA compared to the other three groups. Though to the authors' knowledge, there has yet to be a study systemically investigating the effects of intensity of PA on CBF in older adults, in particular with a focus on sex differences. This finding is however consistent with findings by Casaletto and colleagues showing that older aged males require less PA to experience benefits (Casaletto et al., 2020). This may be partly due to differences in immune function since Casaletto et al. identified that males had significantly less inflammatory markers when participating in the same amount of PA as females (Casaletto et al., 2020). This decreased inflammatory markers corresponded to better

cognition and greater GMV (Casaletto et al., 2020). They hypothesized that as females already have greater, faster, and more adaptive immune responses, the older males might benefit more from the enhanced immune effects of a given amount of PA. Though immune response was not measured in this study, it could be a reasonable explanation for why lower levels of moderate PA in our older aged male sample seemingly benefitted the most cerebral health. Thus, future work should include measures of immune function, to further investigate the mitigating role that it might have of exercise intensity on cerebral brain health and the sex-related differences that are present as a function of age.

5.6.2 Females, Perfusion and Physical Activity

Surprisingly, our results revealed that middle-aged females were the only group to not demonstrate any relationships between PA at any level of intensity and CBF. It is possible that females in this age range have not yet experienced significant CBF decline which can be mitigated by the beneficial effects of PA on the vasculature. This is consistent with work by Chen and colleagues showed that CBF is maintained in female midlife, with similar global CBF values in young and middle-aged females (average of 52 years in their middle age group)(Chen et al., 2011). This hypothesis is also consistent with the lower CBF measured in our middle age male sample, as well as their higher SBP and greater WMH volumes, which are known to be markers of vascular damage (Alber et al., 2019; Chutinet & Rost, 2014; Webb & Werring, 2022). This indicates a potential ceiling effect whereby PA leads to higher CBF only when vascular impairments or age-related CBF decline have already started to occur. Additional contributions from higher immune function could also contribute, with the beneficial effects of PA on immune function being dampened in this group by an already enhanced immune function (Nieman & Wentz, 2019).

Another important influential outcome in middle-aged females is menopausal status, particularly as the middle-age sample here was comprised of pre-menopausal, peri-menopausal, and likely some post-menopausal individuals (average age of 51 for menopause). Given the role that estrogen has as a signalling molecule within the brain (Brinton, 2008) and its vasoactive properties (Barton, 1999; Raz, 2014; Sarrel, 1999; White, 2002), incorporation of estrogen measurements is highly valuable in studies involving females who are not yet post-menopausal. Estrogen has been found to have an overall positive effect on health. It is linked with increased

CBF(Belfort et al., 1995; Ono et al., 2002), including in hormone replacement therapy in post-menopausal females (Ohkura et al., 1995; Resnick, Maki, Golski, Kraut, & Zonderman, 1998). Furthermore, greater amounts of PA have been found to be associated with increased estrogen levels in pre- and post-menopausal females (Razzak, Khan, & Farooqui, 2019; Smith, Phipps, Thomas, Schmitz, & Kurzer, 2013). Therefore, it is possible that these beneficial effects of estrogen on CBF contribute to the putative ceiling effect for CBF we observed in middle-aged females. Future work should aim to investigate these relationships, in particular with estrogen in both males and females, to understand its contribution to the link between PA and CBF at midlife.

In contrast to the middle-age group, the older female group showed relationships between PA and CBF, as well as being the only group with a clear relationship between CBF and age. This absence of relationship with age in the other sub-groups likely reflects the relatively narrow age range of sub-groups, as well as their more limited sample sizes. The larger age effect in older females may reflect their post-menopausal status. Vascular changes have been shown to accelerate post-menopause and while female vascular disease typically begins to increase about a decade after males, it follows a steeper trajectory post menopause (Moreau & Hildreth, 2014; Moreau, Hildreth, Meditz, Deane, & Kohrt, 2012). Importantly however, these older aged females did demonstrate linear beneficial effects of total PA on CBF in frontal regions. This is in agreement with work showing that older females participating in greater amounts of PA on a weekly basis, had significantly increased CBF within the precuneus and posterior cingulate cortex (Gonneaud et al., 2022). Conversely, in the medial temporal gyrus and the hippocampus an inverse U shape was identified, where the upper threshold of benefit of total PA seemingly appeared for these regions around 1000-1200 METs, corresponding to at least 150 minutes of PA, depending upon the intensity of PA completed (e.g., at moderate [4.5 METs} ~ 267 minutes/week; at vigorous [8 METs} ~ 150 minutes/week) (Garber et al., 2011; Ross et al., 2020). This level of PA is well above the recommendations and shows that exercise can be used to improve cerebrovascular health in females across a wide spectrum of PA. In agreement with our results showing the benefits of walking more specifically for older females, previous work has identified that older females showed higher hippocampal GMV with more walking (Varma et al., 2015). Taken together, our work and that of others provide robust evidence that PA is beneficial for CBF in older aged females in frontal, temporal, and hippocampal regions.

Overall, both males and females benefitted from participating in PA for CBF globally, though each sex demonstrated unique relationships between PA and CBF. Specifically, older aged females demonstrated mostly linear relationships with CBF and total PA, though in the hippocampus there did appear to be an upper threshold for PA being beneficial for CBF. Moreover, males, both middle aged and older aged, were observed to share an inverse U relationship with CBF and moderate, as well as moderate-vigorous PA, regardless of region, again indicating that there is likely an upper threshold to these intensities of PA for CBF in males. In this sample, though both males and females benefit from PA on CBF, males seemingly benefit across the lifespan, and from higher intensities compared to females.

Limitations

This study has some limitations that should be regarded when interpreting the results of the study. The primary limitation of this study was that the PA data was collected utilizing the results of a subjective PA questionnaire rather than using objective measure of PA, such as a VO_2max test. However, it is important to note that the IPAQ is a well-used and highly regarded method for quantifying PA in large scale studies. Secondly, due to the cross-sectional nature of this study, we cannot gain any causality information for the relationship between sex, age, CBF and PA at different intensities. Future work should aim to investigate longitudinally across the lifespan to gain further insight to when and what type of PA might be most beneficial for males and females to maintain or enhance cerebral vascular health at different ages. Moreover, future work should investigate these relationships in a larger sample of pre- to post-menopausal females understand how sex hormones, including but not limited to estrogen, and menopausal status influence the effects of PA on brain health.

Finally, one question not addressed in this work but of interest in the field is the idea that modality of exercise, for example aerobic training versus resistance training, might prove to be important rather than overall PA at various stages of life. For example, strength training has been identified to enhance estrogen levels in post-menopausal females (Razzak et al., 2019). Strength training has also been found to significantly enhance CBF in females compared to their counterparts participating in aerobic activities (Xu et al., 2014). Conversely, other work has suggested that aerobic exercise might be more beneficial for cognition in females than males (Barha et al., 2020, 2017; Barha, Hsu, ten Brinke, & Liu-Ambrose, 2019), though this was in

older adults. Therefore, future studies should investigate the interactions of modality on sex and age to further elucidate the potential of PA on cerebrovascular health across the lifespan.

5.1 Conclusion

Overall, this work in a large sample of middle and older age adults demonstrates the beneficial effects of PA on cerebrovascular health in temporal, frontal and hippocampal regions across the lifespan. While males benefitted from PA across all intensities in older age, only vigorous PA was found to lead to higher CBF in middle-age. Furthermore, males demonstrated an overall pattern consistent with a ceiling for the beneficial effects of PA on most brain regions, corresponding to a high PA dose well above recommended guidelines. However, the hippocampus demonstrated benefits across the entire PA spectrum, highlighting the potential of PA in mitigating the effects of cognitive decline and dementia in aging. In contrast to males, only older females seemed to benefit from PA, since CBF in middle-aged females was not influenced at any PA intensity. This may be due to the fact that females in middle-age exhibit few vascular risk factors and still largely benefit from the positive effects of estrogen on the vasculature. Future studies should investigate the effects of sex hormones and menopausal status on the relationship between PA and CBF. Finally, older females showed a predominantly linear relationship between total PA and walking PA with CBF, indicating that older females benefit from the effects of PA across all intensities, with walking representing an important source enhanced cerebrovascular health in this population.

6 General Discussion

The overall aim of this thesis was to understand the effects of PA and exercise on brain health in aging, and the mitigating influence of BMI and sex. Therefore, manuscript one provided an overarching framework for the remainder of the thesis by detailing comprehensively the current state of the literature on two common non-pharmacological interventions used to enhance cerebral health in aging individuals. Here, we were able to identify essential physiological outcomes that can be modified during aging (e.g., volumetric structural changes, microstructural, connectivity or hemodynamics), and key gaps in the literature to date were characterized (e.g., factors that should be influential on cerebral health like sex, but not currently well studied).

The subsequent manuscripts further investigated the relationship between cardiovascular fitness and PA with volumetrics and cerebral hemodynamics, to relate cross-sectional trends to some of the effects observed in shorter-term interventional studies included in manuscript one. In particular, manuscript 2 sought to quantify relationships that were understudied in the literature, such as between cardiovascular fitness and CVR as measured with MRI. In manuscript two, we hypothesized that in a group of very healthy older adults that we would be able to reproduce the findings of cardiovascular fitness being related to gray matter volume (GMV) from the intervention studies involved in manuscript one (Intzandt et al., 2021), but also from the overall cross-sectional literature (Arenaza-Urquijo et al., 2017; Erickson et al., 2014b). In terms of hemodynamics, it was expected that there would be a positive relationship between cardiovascular fitness and CBF as well as CVR, as all three are markers of vascular health and reserve (Brown, Clark, & Liu, 2007; Liu & Brown, 2007; Mandell et al., 2008; Nystoriak & Bhatnagar, 2018).

Notably, another crucial factor that was identified as a disparity in the literature in manuscript one, was that sex tended to be used as covariate in many studies rather than examined as an independent variable. Given the well documented physiological differences between females and males across the lifespan (Ji et al., 2022; Stanhewicz, Wenner, & Stachenfeld, 2018) it was hypothesized sex differences could underlie some of the inconsistencies observed in Manuscript one. This could be ascertained by performing sex-disaggregated analyses in larger samples. More specifically, in manuscript three we aimed to understand sex-specific

relationships between PA and volumetric outcomes. Based on the current literature, it was hypothesized that there would be differences between males and females' level of PA on GMV and WMV, as there is literature suggesting that perhaps females might benefit more (Sanders et al., 2021; Varma et al., 2015). We also examined how PA could mitigate the effects of modifiable lifestyle factors like obesity, which are also known to have sex specific differences, since males tend to have poorer brain health with increasing BMI (Huang et al., 2019; Taki et al., 2008). Taken together, in manuscript three we hypothesized that females would be observed to have greater GMV and WMV in relation to increased PA levels, yet the effects of PA as a mitigating factor for obesity would have a more substantial influential role on the relationship between volumetrics and BMI in the males.

Finally, in manuscript four we explored these sex differences in greater depth by incorporating a larger age range of participants to understand if there is a preferential window of opportunity when PA might be more beneficial for cerebral health for males and females. Recent studies have suggested that midlife may be a more influential timeline for risk factors as well as preventative strategies for the vascular system (El Khoudary et al., 2020; Gliemann & Hellsten, 2019) and cerebral health (Power et al., n.d.; Tian, Studenski, Resnick, Davatzikos, & Ferrucci, 2016). Moreover, this manuscript focuses on the effects of PA on cerebral blood flow (CBF) rather than volumetric outcome, since it is thought to be affected upstream of volumetrics in aging (de la Torre, 2000). In manuscript four it was expected that there would be sex differences between middle aged and older aged individuals' participation in PA on cerebral health. However, given this had yet to be investigated at all in the previous literature we hypothesized that based on the null relationships in manuscript three males between PA and cerebral health perhaps, middle age might be the most lucrative period for males, yet for females it was expected that PA would be most beneficial after the menopausal transition.

6.1 Contributions of this thesis

6.1.1 Current state of the literature, gaps and developing the thesis framework: a reflection on the systematic review

To fully appreciate the current literature, in manuscript one we completed a systematic review of the literature involving cerebral changes, measured by MRI, associated with two common lifestyle interventions in healthy older adults, cognitive and exercise training. We

revealed that cognitive training was more associated with benefits to the microstructure, and exercise training significantly enhanced GMV. Yet a major gap to the exercise training literature was that cerebrovascular health and hemodynamics were virtually unstudied, despite the fact that exercise is known to have beneficial impacts on the vasculature at the whole-body level. Only one study (Chapman, Aslan, Spence, Keebler, DeFina, et al., 2016) investigated this in our review and did not reveal many changes after exercise training. This could be due to insufficient volume or intensity of aerobic exercise, a sex-aggregated analysis, or that due to the inherently low SNR of ASL and low spatial resolution the subtle changes that could have occurred were unable to be captured. Another gap we identified was the lack of sex-specific investigations, as well as the discrepancies in studies examining the relationships between cardiovascular fitness and enhanced brain health. For example, some found that cardiovascular fitness was directly related to cerebral changes, whereas others found that it was not the change in fitness itself but rather the amount of time, mode and overall volume of time spent in participating in these interventions. Thus, leading us to hypothesize that perhaps some of the discrepancies were driven by sex-differences and the construct employed to measure physical health (i.e., PA, exercise, or cardiovascular fitness). Having identified some of these sources of discrepancies and gaps in the literature, we then sought to address them in the following original research manuscripts. The subsequent studies then aimed to further examine some of the key findings from manuscript one, in particular if the relationship between cardiovascular fitness and cerebral health in aging was present in cross-sectional samples reflecting the effects of PA and exercise participation on the brain over longer time scales across the lifespan. Moreover, based on the heterogeneity in the exercise and MRI literature it was determined that the employment of cross-sectional studies to further comprehend the underlying mechanism of action of PA for cerebral health was necessary to be able to control for multiple confounders of the relationships (i.e. obesity and sex), as well as provides the ability to investigate a larger sample of individuals with multiple outcomes (Thiese, 2014)

6.1.2 Cardiovascular fitness, cerebral hemodynamics, and a very healthy group of older adults

In this manuscript, we investigated if cardiovascular fitness was related to GMV and cerebral hemodynamics in a sample of very healthy older adults with no comorbidities and were

not taking any medications. Studies to date have largely focused on normal, rather than healthy aging. While this makes their conclusions representative, it does limit to some extent the inferences that can be drawn about the effects of exercise on the aging brain, rather than on a brain with pathological features that can be sensitive to the effects of exercise, such as common conditions like hypertension. Notably, we revealed that cardiovascular fitness was in fact related to increased gray matter volume, confirming previous work (Colcombe et al., 2006) and the findings of our systematic review that exercise training is associated with enhanced GMV (Intzandt et al., 2021). Conversely to what was expected however, we revealed that greater cardiovascular fitness was related to *decreased* CVR and shared no relationship with CBF. Albeit the opposite of our original hypothesis, these results confirmed findings by Thomas and colleagues who also found this negative relationship between fitness and CVR but in a sample of Master Athletes (B. P. Thomas et al., 2013). This suggests that in samples of very healthy and homogenous individuals, vascular health might be relatively unimpaired and therefore uninfluenced by the beneficial effects of exercise, while other physiological variables such as autoregulation or chemosensitivity could lead to changes in CVR. Unfortunately, we could not probe this hypothesis in the work presented here, but changes in autoregulation and chemosensitivity have previously been documented in highly active samples (Katayama et al., 1999; McConnell & Semple, 1996; Mikkel et al., 2011).

The results of manuscript two could also be partly attributable to the unbalanced sex distribution of this sample, which was comprised of almost 75% females. In another analysis of this sample, we found for example that sex was an important determinant of the relationship between arterial stiffness and CVR (Sabra et al., 2021), raising the possibility that some of the physiological effects of exercise could impact our CVR measurement differently according to sex.

Moreover, the previous two manuscripts brought into question the idea of cardiovascular fitness versus physical activity. Given the nature of conducting VO_2max testing, it can be difficult for all participants, especially older adults to attain their actual max and even a true peak. Additionally, VO_2peak tends to be related to physical activities that are moderate-vigorous in nature, rather than lesser levels of intensity, or even total PA completed in a week (Aadahl, Kjaer, Kristensen, Mollerup, & Jørgensen, 2007). This means that VO_2peak may not always be

representative in an older adult sample, since the amount of activities performed that are considered to be above the moderate-vigorous level significantly decline in aging, while lighter activities, such as walking, tend to be maintained (McPhee et al., 2016). Thus, this brings into question the universality of using VO_2peak as a marker of vascular health in aging if it does not represent the level of activity most older adults are participating in, at least in terms of how PA relates to cerebral health. Furthermore, the large sample sizes necessary for sex-disaggregated analyses are more typically compatible with questionnaire measures of PA, rather than VO_2peak measurements. Therefore, in the following manuscripts, these questions were addressed using large publicly available datasets which included PA questionnaires.

6.1.3 Involving sex-specific analyses on the relationship between cerebral volumetrics and physical activity in a large sample of normal aging individuals

In addition to the factors studied thus far, the third manuscript also focused on obesity. It is well documented that obesity is on the rise, particularly in older adults, and can be associated with a cascade of vascular and metabolic consequences extending to the cerebral vasculature. Previous studies have shown that obesity is associated with reduced GMV, CBF and increased WMH (Amen et al., 2020; Debette et al., 2014; García-García et al., 2022; Lampe et al., 2019) though the literature suffers from a large number of inconsistencies with studies reporting negative (Amen et al., 2018; Debette et al., 2014; Dekkers et al., 2019; Masouleh et al., 2016; Taki et al., 2008), null (Huang et al., 2019), and even positive (Pannacciulli et al., 2007; Silvah et al., 2020) effects. There are also clear sex differences in the vascular consequences of obesity (Lönnqvist, Thörne, Large, & Arner, 1997; Shi, Wong, & Brooks, 2020; Taylor & Sullivan, 2016). In manuscript three, we identified that higher BMI in females was associated with higher GMV, which had not been previously explored to our knowledge in a sample of older females. Our findings are however consistent with results from, the one study that has investigated the relationship between obesity and cerebral health in females, which identified numerous regions with *increased* CBF obese compared to lean females (Silvah et al., 2020). Conversely, males revealed opposite patterns, where they had an inversed U shape with BMI and GMV, where being overweight seemed to be associated with the most GMV, confirming previous work of a potential obesity paradox in aging males (Huang et al., 2019). Moreover, we confirmed that greater levels of total PA and moderate PA in females was associated with increased GMV and

WMV. These findings with PA were found to be present in conjunction with BMI, where regardless of where females were on the BMI spectrum, having higher moderate PA levels was always associated with higher GMV. Surprisingly, males shared no relationships between moderate PA and GMV or WMV. However, normal weight males who had the highest PA had enhanced GMV compared to males with the lowest PA levels with normal weight. Essentially these results indicate that in females, obesity is not as important as partaking in PA, whereas in males, it seems that being normal weight or overweight, but not obese, and participating in high levels of moderate PA is important for bulk GM health. This work highlighted the importance of utilizing sex-disaggregated statistical analyses as the patterns and relationships were unique to each sex.

Manuscript three brought into question the lack of relationships between PA and cerebral outcomes in males. Given that it is increasingly recognized that midlife is a perhaps more of a critical time period for physiological changes to occur, a time specificity might be present for PA to have the most beneficial effect for cerebral health. Moreover, given that CBF is known to decline prior to GMV and WMV (de la Torre, 2000; Farkas & Luiten, 2001), and that CBF is more directly reflective of vascular health, it was hypothesized that perhaps CBF might be a more sensitive marker of cerebral health in relation to PA for males, and generally speaking across the adult lifespan. introducing preventative strategies to reduce risk of future disease, mortality, and morbidity.

6.1.4 Extending sex-specific findings to address a larger age range and the role of intensity of physical activity on cerebral blood flow in normally aging individuals

In manuscript four, we addressed some of these gaps in the current literature and examined in a large sample of adults ranging from 36 to 100 years old, if the relationship between PA and CBF differed across the lifespan within each sex. This dataset, contrary to previous CBF quantifications in the thesis, involved a multi-delay rather than a single delay pCASL sequence, which with the age range of participants, allowed for greater confidence in the CBF quantified, given that multiple delays can capture the temporal profile of tag at each voxel for each participant (Buxton et al., 1998).

In manuscript four we also wanted to investigate different PA intensities within these groups to attempt to disentangle if there are a sex-specific intensities of PA that are more

beneficial for CBF, and if this differed by age group, given that we found no relationship between CBF and VO_2peak (directly related to participation in vigorous PA) in manuscript 2, but others identified positive relationships (Dougherty et al., 2021; Zimmerman et al., 2014). Importantly, manuscript four revealed that indeed sex and age both were important determinants of the relationship between CBF and PA. Older aged males experienced greater CBF in relation to increasing moderate PA levels. In the females, older aged individuals demonstrated positive linear relationships with CBF and total as well as walking PA, consistent with results of previous work demonstrating the positive effects of walking in females only (Varma et al., 2015) (Varma et al., 2015). Furthermore, this could help explain our absence of relationship between VO_2peak and CBF in manuscript two since VO_2peak measurements are less representative of walking PA and since our sample was predominantly female.

In middle age, greater amounts of Total PA were associated with higher CBF in males. Moreover, there were sex and intensity of PA specific relationships with CBF, where middle aged males shared an inverse U relationship with CBF and Vigorous PA, indicating the potential of a ceiling effect of benefits. It is important to note however that this ceiling effect, if confirmed, would be at PA participation well beyond current recommendations. Older aged males also shared an inverse U relationship, but with moderate and moderate-vigorous PA and CBF in most regions, but a positive linear relationship with CBF in the hippocampus. Higher CBF in the hippocampus has previously been demonstrated after an aerobic intervention in a sample of males and females (Maass, Düzel, Goerke, Becke, Lovden, et al., 2015). Interestingly, the ceiling effect observed in males, also well beyond current recommendations, could help explain the effects observed in Manuscript two and in the MA literature. MA may participate in PA levels well beyond the beneficial range, leading to other physiological adaptions which were captured by these studies. Notably, our middle-aged females demonstrated no relationship between any PA intensity and CBF, perhaps an indication that PA does not lead to higher CBF beyond the effects of sex hormones until vascular changes become entrenched post-menopause.

6.2 Future Directions

Taken together, it is apparent that exercise, cardiovascular fitness, and physical activity have numerous benefits to cerebral health for older adults. Moreover, these gains likely extend beyond the measures utilized here in the original studies. The results presented in this thesis also

highlight that there is a heavy influence of sex, age, and other modifiable factors like obesity in these relationships. Generally speaking, however, the findings of this thesis lead to many questions that remain unanswered. In manuscript two, the use of only extremely healthy, i.e., successfully aging individuals, limits the generalizability of the relations between VO_2peak and cerebral hemodynamics to those individuals who are highly fit for their age, taking no medications, and possessing no overt disease or disorders, and thus not a normal aging sample. Particularly given that recent work has highlighted that across a spectrum of cardiovascular fitness in aging, an inverse U shape between VO_2peak and CVR exists (DuBose et al., 2022). This highlights the fact that there might be underlying physiological differences that are influencing the relationships between cardiovascular fitness and CVR, depending upon an individual's fitness level, like chemosensitivity and/or autoregulation (Intzandt et al., 2020; Thomas et al., 2013). Therefore, future studies should aim to incorporate these physiological measures in a large sample of older adults with varying fitness levels to further understand how autoregulation and/or chemosensitivity, which are commonly reduced in highly fit individuals (Katayama et al., 1999; Mikkel et al., 2011), interact, and influence the relationship between CVR and cardiovascular fitness.

Importantly, in the latter half of this thesis, we also identified and highlighted the necessity in completing a priori sex-disaggregated analyses. Unfortunately, due to power constraints in manuscript two, this was not feasible. Though, it is worth noting that other work from our lab, employing this data set, did identify that sex moderated the relationship between pulse wave velocity (a marker of aortic stiffness and overall cardiovascular health, where higher is worse) and CVR (Sabra et al., 2021). More specifically, it was identified that males had a positive relationship with CVR and pulse wave velocity, where higher CVR was related to greater pulse wave velocity, opposite to what would be hypothesized. Conversely, females demonstrated the hypothesized relationship, where greater pulse wave velocity was associated with reduced CVR. Taken together, these results, along with what is already in the extant literature, create more questions regarding what is actually being measured with CVR from a physiological perspective, and does it potentially represent different physiology in males versus females, and older versus younger adults, and how might sex hormones contribute to these relationships. Future studies should investigate the underlying physiological components that

comprise CVR and how common physiological occurrences influence the meaning of the measure, like sex hormones, autoregulation and chemosensitivity.

Furthermore, the exclusion of sex hormones, such as estrogen, progesterone, testosterone, and luteinizing hormones, is a common limitation to this thesis and the current literature on PA and cerebral health in aging. Sex hormones likely play a significant role in these relationships, particularly given that estrogen has a role as a signaling molecule in the brain (Brinton, 2008), and is linked to significantly greater CBF in females (Ohkura et al., 1995; Resnick et al., 1998). Estrogen has also been demonstrated to be higher in post-menopausal females that participate in higher levels of PA (Razzak et al., 2019). This increase in sex hormones related to PA has also been demonstrated in pre-menopausal females, whereby greater PA is associated with larger concentrations of progesterone (Smith et al., 2013). Testosterone is also capable of converting to estrogen within the brain (MacLusky & Naftolin, 1981; Naftolin & Ryan, 1975), and in young male mice has been found to be increased in the hippocampus after a low intensity running intervention (Okamoto et al., 2012) Moreover, an increase in luteinizing hormone concentrations in post-menopausal females has been associated with an increased risk of developing Alzheimer's disease (Bowen, Isley, & Atkinson, 2000) as it promotes the metabolism and deposition of amyloid beta plaques in the hippocampus of mouse models (Casadesus et al., 2005). Notably, luteinizing hormone levels have been shown to be decreased in post-menopausal after participating in an aerobic exercise intervention (Tartibian, FitzGerald, Azadpour, & Maleki, 2015). Thus, taken together, there is an important gap in our knowledge of the effects of sex hormones on the brain and their interaction with PA or exercise in aging. Beyond the effects of single hormones, the interaction between their concentrations is likely an important determinant of their effects, yet at present unstudied in the literature. Furthermore, the influence of sex hormones on the interaction of PA and cerebral health is not only understudied in older adults, but in middle aged individuals and across the remainder of the lifespan, where sex hormones are likely even more pertinent to these associations. Therefore, future work should investigate the influence of these different sex hormones, how they affect relationships between sex, PA, and cerebral health. Future studies examining the menopausal transition and the importance of PA on maintaining cerebral vascular health is of upmost importance as this is a severely understudied population and since the risk of cardiovascular events significantly increases post-menopause. Thus, identifying *when* might be the most beneficial time period to

participate in PA and what type and intensity of PA is most effective for females in the menopausal transition is crucial for prevention in this population. Importantly, this work would greatly benefit from a longitudinal study design, given the high inter-individual differences in the menopausal transition and the rapid pace of changes.

This emphasizes the importance of completing longitudinal studies when investigating relationships between cerebral health and PA. Given how heterogenous the aging brain has been documented to be (Tucker-Drob, 2019), following the same individuals over an extended period of time, while capturing how PA and other lifestyle risk factors also change, would provide a comprehensive understanding of the interactions and mechanisms of action interact across the lifespan. Thus, the employment of longitudinal studies, although expensive and burdensome, would provide a viewpoint of lifelong changes associated with aging. When combined with sex hormone measurements, it would help reveal their relationships with cerebral brain health and to fully comprehend how hormones can influence each component of brain health (i.e., vascular, metabolic, microstructure, cerebral vessels, white matter, gray matter, etc.) to better target the hormone therapies with cerebral decline at specific times of the life course. This work also highlights the importance of collecting *and* reporting multiple MRI sequences within each study to capture different components of cerebral health, a fact that we identified was a major limitation of the literature in the systematic review (manuscript one). Multi-modality imaging strategies are needed including using CBF, GMV, white matter, microstructure etc. within the same study to further comprehend how each of these outcomes are influenced by PA, to obtain a more mechanistic understanding of the effects of PA on the brain.

Finally, only aerobic or overall PA according to intensity were investigated in the original research studies of this thesis. The systematic review however highlighted that PA modality might also influence cerebral health. This is particularly relevant when we incorporate the lens of sex-specificity given that there has been work to suggest that females in aging might benefit more from aerobic physical activity for cognition (Barha et al., 2019) but that in midlife females might benefit more from resistance training (Xu et al., 2014). Therefore, future studies should include more granular information about modality, in addition to intensity.

7 Conclusion

In this thesis we were able to confirm that cardiovascular fitness and physical activity are beneficial for cerebral health, especially bulk volumetrics, including gray and white matter volume, as well as cerebral blood flow. Notably, identified an inverse relationship between cardiovascular fitness and cerebrovascular reactivity in very healthy older adults. This extended similar findings in master athletes, showing evidence for physiological adaptations in autoregulation and chemosensitivity in highly active older adults. At the time, we were the first group to identify that this in fact the case outside of a group of highly endurance trained older adults and provided a unique physiological framework that could explain the counterintuitive findings. Furthermore, we were able to provide a rationale for seemingly paradoxical findings linking obesity and cerebral health, showing that these effects could be driven by sexual dimorphisms and mitigated by physical activity. This provides evidence that obesity may have different impacts on cerebral health depending on sex, and that PA recommendations should be tailored by sex to be most effective, Finally, our last manuscripts provides further evidence for the importance to employ sex-disaggregated analyses when investigating cerebral health and physical activity, particularly when examining these complex interactions across the lifespan. In this last manuscript, we provided evidence that higher intensity PA is most beneficial to males, while older females benefitted from overall PA and especially walking PA. Overall, this thesis involved contributed to the field by creating a highly pertinent knowledge base for our understanding of the sex-specific relationships between PA, brain health and obesity, and the impact of overall health status on these relationships. This knowledge base is an important step in tailoring PA and exercise trainings and guidelines to maximize their beneficial effects on the brain across the adult lifespan to reduce the burden of an aging population on health care systems and individuals alike.

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