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Midlife Cardiovascular Indicators of Cerebral White Matter Health and Cognitive Function

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Midlife Cardiovascular Indicators of Cerebral White Matter Health and Cognitive Function

by

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Dedication

For my family who has supported my every endeavor in life.

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Midlife Cardiovascular Indicators of Cerebral White Matter Health and Cognitive Function

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Recent evidence suggests that modifiable cardiovascular risk factors additionally play a causal role in the development of dementia and cognitive dysfunction. Currently, no cure for dementia exists making identification of early relationships in dementia pathophysiology critical for the purpose of primary prevention or remediation. As approximately 70% of adults in the United States are clinically overweight, the aim of Study 1 was to determine the anthropometric measures most strongly associated with early white matter disease and cognitive function at midlife. In this cross-sectional investigation of 126 middle-aged adults, waist circumference, body fat percentage, and visceral adiposity all significantly predicted white matter hyperintensities, indicating that midlife abdominal obesity is associated with the early development of white mater disease.

Midlife visceral adiposity is also associated with increased arterial stiffening. The aim of Study 2 was to determine if subclinical carotid artery stiffening is associated with lower cerebral white matter integrity at midlife in *a priori* regions of interest susceptible to vascular and cognitive aging. This study employed diffusion tensor imaging to gauge cerebral white matter integrity. In a middle-aged cohort of 143 adults, we determined that

arterial stiffening was associated with reduced integrity of multiple white matter regions independent of age, sex, and waist circumference. Arterial stiffness indirectly affected processing speed. These data suggest that arterial stiffening may negatively affect CWMI prior to clinically overt cognitive decline.

Individuals with metabolic syndrome are at increased risk of arterial stiffening and dementia. The purpose of Study 3 was to determine the role of physical activity on mitigating the adverse influence of metabolic syndrome on arterial stiffness and cerebral white matter integrity**.** In this cross-sectional investigation of 66 middle-aged adults, individuals with MetS who were physically active demonstrated lower arterial stiffness and more favorable CWM integrity than their sedentary peers, indicating that PA may be effective in mitigating the adverse effects of MetS on the vasculature and brain at midlife.

Taken together, these findings indicate that cardiometabolic risk factors negatively affect the vasculature, cerebral white matter health, and cognitive function at middle-age.

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CHAPTER 1: GENERAL INTRODUCTION

Dementia is defined as a major neurocognitive disorder due to its disruption of cognitive function and performance of activities of daily living (15). Alzheimer's disease and vascular dementia represent the two most common causes of dementia contributing to ~60-80% and ~10% of cases respectively. The rise in incidence of AD in the United States is staggering as the 4.7 millions of people with AD is expected to nearly triple by the year 2050 (15). With no curative treatment known for dementia, identification of early modifiable biomarkers is critical, especially given that AD pathophysiology takes years, if not decades, to progress (175). Although the causal mechanisms of AD are complex and multiple, vascular dysregulation has recently been identified as a key initiating event (143).

Because the brain's ability to store energy is limited, it is highly dependent on the cardiac output to receive energy substrate. Despite weighing just 2% of body weight, the brain receives 11% of the cardiac output and consumes 20% of the total oxygen of the body at rest (52). The tight delivery of cerebral blood flow is reliant on the perfusing vasculature that becomes vulnerable to malfunction with exposure to cardiovascular risk factors. In brief, cardiovascular risk factors that include obesity, hypertension, dyslipidemia, dysglycemia, and smoking contribute to arteriosclerosis and begin a cascade of events that results in breakdown of the blood brain barrier (BBB) and cerebral hypoperfusion (65, 153). The consequences of hypoperfusion are significant, leading to white matter injury, buildup of amyloid-β, and susceptibility to dementia (342). Mitigating the adverse effects that cardiovascular risk factors have on the vasculature

may prove valuable for maintaining cerebral autoregulation and healthy white matter while prolonging normal cognition.

Alterations of cerebral white matter are associated with vascular risk factors and ischemia and are considered an early pathological feature of dementia (40, 69, 175). Sensitive measures of white matter health can be assessed with magnetic resonance imaging (MRI). The two most common methods are capturing T2-weighted images to determine white matter hyperintensities (WMH), and performing diffusion tensor imaging (DTI), a sequence measuring in vivo water diffusion of white matter tracts reflective of structural integrity. Observing their associations in relation to cardiovascular risk factors, vascular function, and cognitive function at early stages of disease progress can be informative for identifying modifiable treatment targets for clinicians.

Purpose and Hypothesis

In recent years there has been considerable growth in the study of cardiovascular health in relation to brain structure and cognitive function. However, the relations of vascular dysfunction with early pathological alterations ultimately contributing to dementia, otherwise termed the vascular hypothesis, remain understudied at midlife (143). Therefore, the general and overall goal of this dissertation study is to further understand modifiable cardiovascular targets related to early neuroimaging biomarkers of dementia and cognitive dysfunction. This broad goal was addressed in three specific aims, each focused on different levels of the vascular hypothesis of dementia. Whole-body and abdominal adiposity, arterial stiffness, and physical activity was carefully analyzed in

relation to cerebral white matter health and cognitive function. The role of physical activity as a basic lifestyle modification to improve vascular health and ostensibly brain structure and function will be determined.

STUDY #1:

The purpose of Study #1 was to determine the strength of associations of body mass index (BMI), waist-to-hip ratio (WHR), waist circumference (WC), percent body fat (BF), and visceral adipose tissue (VAT) with white matter hyperintensity (WMH) and cognitive function at midlife. We hypothesized that dual-energy x-ray absorptiometry (DXA)-generated adiposity measures of BF and VAT would be more sensitive in predicting WMH and cognitive function at midlife than traditional anthropometric body composition measurements.

STUDY #2:

The purpose of Study #2 was to determine whether carotid artery stiffening impacts cerebral white matter microstructure at midlife. Secondly, we aimed to determine what white matter regions vascular stiffening would most likely hinder. We hypothesized that carotid artery stiffening would be negatively associated with *a priori* cerebral white matter regions that are closely related to executive function.

STUDY #3:

The purpose of Study #3 was to determine whether individuals with metabolic syndrome (MetS) who habitually perform physical activity demonstrate lower arterial stiffness and more favorable cerebral white matter integrity than their sedentary peers. Our working hypothesis was that MetS patients who habitually exercise do not demonstrate arterial stiffening and reduced cerebral white matter integrity.

CHAPTER 2: VISCERAL ADIPOSITY PREDICTS SUBCLINICAL WHITE MATTER HYPERINTENSITIES IN MIDDLE-AGED ADULTS[1]

Abstract

Objective: Growing prevalence of neuropathology and cognitive impairment are emerging consequences of the obesity epidemic. Adiposity indices used in examining the relationships between obesity, neuropathology, and cognition vary substantially in the literature leading to incongruent findings. Our aim was to determine the anthropometric measures most strongly associated with early white matter disease and cognitive function at midlife. **Method:** Multiple adiposity indices were measured in 126 adults aged 40-62 who also completed a magnetic resonance imaging (MRI) scan to quantify white matter disease and a cognitive test battery. Anthropometric indices of obesity were compared to image-based estimates of visceral adipose tissue with dual-energy x-ray absorptiometry (DEXA) as predictors of current white matter disease and cognitive function. We also explored sex as a potential moderator of these relationships. **Results:** Waist circumference (WC) was most strongly correlated with DEXA estimates of visceral adipose tissue (r=0.871, p<0.001). Increasing WC (β=0.231, p=0.034), percent body fat (β=0.230, p=0.045), and VAT (β=0.247, p=0.027) significantly predicted subclinical white matter hyperintensities in the absence of cognitive impairment after accounting for age, sex, years of education, and cardiovascular risk factors. Sex was not a significant

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[1]Pasha EP, Birdsill A, Parker P, Elmenshawy A, Tanaka H, Haley AP. Visceral adiposity predicts subclinical white matter hyperintensities in middle-aged adults. *Obes Res Clin Pract*. 2016.

Pasha EP designed the investigation, acquired data, performed statistics and wrote the manuscript.

moderator of any of the observed relationships. **Conclusions:** Of the anthropometric indices used in this study, WC, BF, and VAT successfully predicted subclinical white m atter disease in cognitively normal adults at midlife. Increasing VAT may independently insidiously affect cerebral white matter prior to detectable cognitive changes, necessitating early intervention.

Introduction

Obesity in the United States has become a pressing public health issue with 68.5% of adults over the age of 20 fulfilling criteria for overweight or obesity, and 34.9% classified as having obesity in 2011-2012 (211). Despite recent public health measures to curb the increase in the number of individuals with obesity, a recent study suggested obesity rates could rise until a steady state proportion of 42% by 2050 (131). An emerging consequence of having obesity is neurologic disease and cognitive deficit, independent of other cardiovascular comorbidities (267). Because the relationships between obesity measures and cognitive function and brain structure appear non-linear due to age related changes in body composition, determining the most robust adiposity measurements during midlife for estimating neurological vulnerability and cognitive function is critical (112).

Past work has suggested waist circumference (WC) as an ideal anthropometric measure of visceral adipose tissue (VAT) when investigating obesity in relation to cardiovascular comorbidities such as hypercholesterolemia and insulin resistance (230). VAT serves as an endocrine organ that secretes adipocytokines such as interleukins that can exacerbate inflammation and impair vascular function more than subcutaneous adipose tissue alone (17). VAT is a likely culprit behind observations linking higher body mass index (BMI) at midlife to increased risk of dementia in older age (114). Consequently, VAT could act to limit cerebral perfusion that can culminate in neuropathology and cognitive dysfunction (232) (62). In our own work with middle-aged adults, VAT has been linked to altered cortical thickness (157). Thus, anthropometric

measurements could be valuable indicators of early neurocognitive alterations if they accurately reflect visceral adipose tissue.

Currently, adiposity measures remain substantially varied in the literature in prospective studies examining obesity in relation to neurologic disease and cognitive decline with great reliance on BMI. However, BMI lacks specificity to appropriately quantify the deleterious VAT typically linked to adverse health outcomes (230). One study examined differences in the associations between obesity indices and cognitive function cross-sectionally and longitudinally at middle age (109). This group determined BMI and abdominal obesity measures including WC and waist-to-hip ratio (WHR) were all similarly associated with cognitive function tests in the global, executive and memory domains. (109). Nonetheless, these simple anthropometric indices have rarely been compared with an image-based estimate of VAT such as dual-energy x-ray absorptiometry (DEXA) in their associations to both neuropathology and cognitive function. Such a comparison can further elucidate the relative strength of relationships of obesity indices to neuropathology and cognitive function in younger adults.

A well-founded neuropathological marker seen in dementia and Alzheimer's disease is the volume of white matter hyperintensities (WMH) (40). WMH are usually denoted by areas of high intensity on T_2 weighted magnetic-resonance imaging (MRI) scans that are believed to be the result of chronic hypoperfusion and correlated with myelin and axonal loss (41, 299). Prior studies have observed associations between body composition and WMH in the elderly (146), but reports of said relationship at midlife are scarce. One study reported no significant associations between anthropometric measures and computed tomography (CT)-based measurements of VAT with WMH volume three

years later in older middle age (mean age at CT = 64; mean age at MRI = 67 years) (68). This study also did not investigate the relationships between anthropometric measures and cognitive function. The purpose of our study was to determine the strength of associations of concurrently obtained BMI, WHR, WC, percent body fat (BF), and VAT with WMH and cognitive function in a younger middle-aged population (ages 40-60 years). We hypothesized that DEXA generated adiposity measures of BF and VAT would be more sensitive in predicting WMH and cognitive function at midlife than traditional anthropometric body composition measurements.

Methods

Participants

Recruitment through local newspaper and online advertisements generated a multi-racial sample of 126 community dwelling men and women aged 40-62 years representative of the Austin, Texas area. To be admitted to the study, participants had to have no pre-existing cardiovascular disease (e.g., coronary artery disease, angina pectoris, myocardial infarction, heart failure, and cardiac surgery), overt neurological disease (e.g., stroke, Parkinson's disease, and clinically significant traumatic brain injury), or contraindications to MRI assessed through self-report on a health history questionnaire. Additionally, participants were non-depressed and cognitively normal as determined by scoring <29 on the Beck Depression Inventory-II and >84 on the Wechsler Abbreviated scale of Intelligence-II (WASI-II) Full Scale Intelligence Quotient (FSIQ). The local institutional review board approved the study and all participants gave informed consent.

Health Assessment

Following an overnight fast of at least 8 hours, blood was collected from the antecubital vein via venipucture. Glucose and total cholesterol levels were determined using standard enzymatic technique. Brachial systolic and diastolic blood pressure was assessed in the supine position after a 15-min period of rest (VP-2000; Omron Healthcare, Bannockburn, IL). Participants completed a detailed health history questionnaire outlining medication use and current physical activity behavior.

Obesity Indices

Height and weight were measured with a stadiometer and digital scale respectively for the calculation of BMI as kg/m^2. WC was measured with a measuring tape at the top of the iliac crest as measurement at the level of the navel may underestimate WC (60). The measuring tape was level to the floor and softly tightened without compressing tissues in accordance with National Heart, Lung and Blood Institute clinical guidelines (1). Hip circumference (HC) was measured in an identical method to WC but at the level of the greatest protrusion of the hips. Both WC and HC were recorded in centimeters to the nearest millimeter. WHR was then calculated as WC/HC. Estimates of BF and VAT were ascertained non-invasively with a lunar DXA DPX (General Electric Medical Systems, Fairfield, CT). Although DEXA is typically used to measure bone mineral density, it has been validated for body fat and visceral fat mass estimation with results similar to computed tomography (156, 326). BF was calculated as estimated total fat mass expressed as a percentage of whole body mass. To obtain an estimation of VAT, a region of interest with a caudal limit placed atop the iliac crest with its height set to 20% of the distance from the caudal limit to the base of the skull is automatically defined. Within this region, subcutaneous fat estimates are subtracted from total fat estimates to yield a

VAT estimate. During a separate visit, participants underwent a comprehensive cognitive function assessment and a MRI scan.

Clinical Assessment

The Beck Depression Inventory-II (BDI-II) was first used as a screening measure for depression, followed by a cognitive function battery that has been described in previous work (99). In short, administered tests included the Mini Mental State Examination (MMSE) to assess overall mental health status. Additionally, the Trail Making Test A and B, Wechsler Adult Intelligence Scale III (WAIS-III) Digit Span subtest, and Stroop interference subtest were used to characterize executive function. The California verbal learning test (CVLT)-II short delay free recall, long delay free recall, and recognition discriminability tasks characterized memory function. Domain specific Z-scores were created with timed tasks for directional congruity. Z-scores from tasks within each domain were averaged to create the executive function and memory domain score. Altogether, this procedure constituted a one hour testing battery. Each of the chosen clinical instruments has established reliability and validity. Trained research assistants administered cognitive testing in the morning, irrespective of menstrual cycle for female participants. The same assistants performed all scoring, enabling standardization of administration.

MRI Acquisition and Analysis

MRI data was acquired on a 3T Siemens Skyra MRI scanner and included a T_1 image of the entire brain acquired in the sagittal plane using a high-resolution ultrafast Gradient Echo 3D (MPRAGE) sequence (256×256 matrix, flip angle=7°, field of view (FOV)=24×24 cm^2, 1 mm slice thickness, 0 gap). A T_2 image was acquired using a fluid-

attenuated inversion-recovery (FLAIR) sequence (axial plane, TE=75 ms, TR=9500 ms, FOV=24x24 cm^2, 42 slices, 3 mm slice thickness, 0.3 gap).

WMH volume was quantified by Lesion Segmentation Tool version 1.2.3 (http://www.applied-statistics.de/lst.html), an automated algorithm implemented in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). A detailed description of The Lesion Segmentation Tool algorithm can be found elsewhere (249). Briefly, voxels were assigned to tissue probability maps and given a probability of being a white matter lesion based on spatial and intensity probabilities from T_1 images and hyperintensity outliers on T_2 FLAIR images. A conservative lesion belief map containing gray and white matter voxels was created and an initial threshold of 0.30 was applied to create lesion seeds. A growth algorithm then grew these seeds toward a liberal lesion belief map containing gray, white, and CSF lesion belief maps. A final threshold of 0.99 was applied to the resulting lesion belief map to remove any voxels with a lower probability of being a lesion. The resulting total volume of WMH was divided by intracranial volume, obtained through Freesurfer (https://surfer.nmr.mgh.harvard.edu/), and multiplied by 100 to give a white matter hyperintensity ratio (WMHr) in units of percentage of intracranial volume.

Statistical analyses. Sample means and standard deviations for physiological and cognitive variables were assessed with descriptive statistics. All descriptive variables passed Shapiro-Wilk tests for normality except for VAT (Shapiro-Wilk Statistic=0.911, $p<0.001$) and WMHr (Shapiro-Wilk Statistic=0.520, $p<0.001$). Consequently, a square root transformation was performed on VAT and a natural log transformation was utilized on WMHr resulting in normality of both variables. To avoid multiple comparisons in the cognitive realm, domain scores for executive function and memory were created and used

as primary outcome variables. An average of the Trails A, Trails B, WAIS-III Digit Span, and Stroop interference sample based z-scores constructed the executive function domain score. The z scores for timed tests were inverted, so that a higher score indicates better performance, consistent with the scoring of the tests where total correct responses was the outcome variable of interest. An average of the sample-based z-scores for CVLT-II short delay free recall, long delay free recall and recognition discriminability tests formed the domain score for memory.

To evaluate the relation between body composition measures, WMH, and cognitive function, two linear regression models were constructed for each outcome variable (WMH, executive domain score, and memory domain score). The first model statistically adjusted for age, sex, and education. The second model adjusted for age, sex, education, systolic blood pressure, total cholesterol and fasting glucose. Covariates were selected based on their existing relations to body composition and WMH within the literature (39, 147). Because of known sex differences in the distribution of adiposity, sex differences in obesity indices, white matter disease, and domain cognitive function were compared with independent samples t-tests (155). Sex was also investigated as a moderating variable between body composition measures, white matter disease, and cognitive function using non-parametric bootstrapping (the MODPROBE macro for SPSS) (126). An alpha level of 0.05 was used as the criterion for statistical significance in parametric analyses; 95% confidence interval (CI) not containing zero was used as the criterion for statistical significance in the non-parametric analyses. Statistical analyses were performed with SPSS version 22.0 (IBM SPSS Inc, Chicago, IL).

Results

Descriptive Statistics. Of the 126 participants recruited for this study, 57 (45.2%) were male and 69 (54.8%) were female. The sample was highly educated (16.3 ± 2.3 years) and ethnically diverse with 74 (58.7%) participants identifying as Caucasian, 8 (6.3%) as African American, 26 (20.6%) as Hispanic, 5 (4.0%) as Asian, and 10 (7.9%) as other or did not respond. Participants were middle aged (49.1 ± 6.6 years) and displayed overweight (28.5 ± 6.5 kg/m^2) BMI, but presented with healthy blood pressure, fasting lipids, and glucose on average. Remaining participant descriptive characteristics are presented in **Table 2.1**. WMHr was 0.17% ± 0.26 reflecting a pathologically subclinical subject population (231).

Obesity Indices. All anthropometric obesity indices as well as BF were significantly correlated with VAT. WC (r=0.871, p<0.001), had the strongest relation to VAT followed by BMI (r=0.693, p<0.001), WHR (r=0.574, p<0.001) and BF (r=0.473, p<0.001). Other significant relations existed between obesity indices and are enumerated in **Table 2.2**. T-tests revealed significant differences between sexes for all body composition measures (p<0.05) except BMI as shown in **Table 2.3**.

Body Composition Indices and White Matter Hyperintensities. Correlation results of linear regression models of body composition indices and WMH are displayed in **Table 2.4**. In the first model, adjusting for age, sex and years of education, WC (β=0.184, p=0.049) and VAT (β=0.218, p=0.021) significantly predicted WMH whereas BMI (β=0.100, p=0.274), WHR (β=0.048, p=0.646), and BF (β=0.195, p=0.054) did not. The second model included clinically pertinent parameters of systolic blood pressure, total cholesterol and glucose that potentially influence white matter disease. After accounting

for these contributions, WC (β=0.231, p=0.034), BF (β=0.230, p=0.045), and VAT (β=0.247, p=0.027) remained as significant predictors of WMH. BMI (β=0.129, p=0.198) and WHR (β=0.034, p=0.767) remained statistically insignificant. All model residuals were normally distributed (Shapiro-Wilk, p>0.05). Significant relations from this final model are displayed in **Figure 2.1a-c**. Sex was not a significant moderator of the relationship between obesity indices and WMH with 95% CIs straddling zero for all predictors.

Obesity Indices and Cognitive Function. Raw scores for individual cognitive function assessments are outlined in **Table 2.5**. Linear regression models relating obesity measures to executive function and memory domain scores are summarized in **Table 2.6**. Again, the first model accounted for age, sex, and years of education, with the second adding systolic blood pressure, total cholesterol and fasting glucose. Although most of these models were statistically significant, none of the obesity measures significantly contributed to any model (p>0.05). In these models, residuals were normally distributed when predicting executive function domain scores (Shapiro-Wilk, p>0.05). However, models predicting memory domain scores were not normally distributed (Shapiro-Wilk, p<0.05) despite transformations. Nonetheless, in memory domain models, the residual skewness range was -0.558 to -0.447 with a standard error of 0.225. Sex differences were observed in domain z-scores for memory (p=0.001) but not executive function (p>0.05). However, sex did not significantly moderate the relationships between obesity indices and cognitive function in either domain, as 95% CIs for the executive and memory domains straddled zero in both models.

Discussion

The principal findings from the present study are as follows. Congruent with our hypothesis, estimated VAT consistently related to WMH. Of the anthropometric obesity measures typically employed to evaluate the associations of obesity, neuropathology and cognition, only WC was as robust as VAT in predicting subclinical white matter disease. WC also predicted early WMH independent of the influence of other cardiovascular risk factors. This finding indicates WC as a proxy measure of VAT is sensitive to early white matter vulnerability and possibly independently contributes to WMH. None of the observed adiposity measures significantly related to executive function or memory domain scores. WC appears to be the closest anthropometric reflection of abdominal fat, having the strongest correlation with VAT and corroborates visceral fat as a culprit behind obesity related WMH. WC was sensitive enough to predict early WMH prior to the precipitation of cognitive abnormalities middle-aged subjects with low WMH volume. This study supports the use of WC as a more robust measure of early white matter vulnerability at midlife than the oft-used BMI and WHR. WC is also a safe, inexpensive alternative to DEXA. Lastly, the observed relationships were similar in both men and women.

Our findings are largely consistent with previous investigations relating obesity to neuropathology and cognitive function. Our group and others have demonstrated that many of these body composition indices are individually correlated with neuropathology, but investigations of obesity and WMH at middle age are few. In a sample of community dwelling Latinos with mean age of 70 years, 1-SD increase in WHR corresponded to a 27% increase in WMH after accounting for sex, cholesterol, blood pressure, and other

covariates (146). Similarly, a prospective study of Swedish women determined a 1 kg/m^2 increase in BMI at age 70 doubled the risk of obtaining WMH later in life (116). In the present study, only WC, BF, and VAT predicted WMH while BMI and WHR did not. This finding leads to the possibility that proxy measures of VAT are more sensitive measures for detecting associations between obesity and WMH.

In contrast to our results, a previous investigation observed no significant associations between BMI, WC, WHR, and computed tomography-based estimates of subcutaneous adipose tissue and VAT with WMH (68). In this study, statistical adjustments were made for age, sex, systolic blood pressure, smoking, diabetes mellitus, history of cardiovascular disease, physical activity, and BMI to their models and still no relation was found in their cohort with mean age 64 years for the CT evaluation and 67 years for the MRI valuation. While both methodological (e.g., CT vs. DEXA estimates of VAT; 1.5T vs. 3T MRI, consecutive vs. concurrent measurements of VAT and WMH) and study population differences (older vs. younger adults; lower vs. higher average WC) could have contributed to these result discrepancies, one cannot discount the possibility of a complex, non-linear relationship between adiposity and neuropathology throughout the lifespan.

Contrary to our hypothesis, we did not find any significant relationships between obesity measures and cognitive function domain z-scores. Our sample was young and highly educated, which may have provided these individuals greater cognitive reserve and rendered them more tolerant to the adverse effects of obesity related cognitive decline (279). The subject population also presented with minimal white matter disease volume. A study examining leuokaraiosis and phenotypic expression of dementia

suggested working memory performance was negatively affected when it involved at least 3% of the white matter (231). The amount of white matter present in the subject population of the current study was well under this threshold suggesting subjects have yet to accumulate sufficient disease to alter cognitive function. What is striking is that WC, BF, and VAT were related to seemingly trivial amounts of white matter disease that if left unidentified could silently accumulate and eventually precipitate in cognitive impairment. Prior evidence has established an association between obesity and impaired cognitive function. For example, our group showed that higher WC corresponded to a worse working memory related brain hemodynamic response in middle-aged adults. This impairment corresponded with poorer working memory task performance (99). We also demonstrated that DEXA measured VAT can alter cortical thickness in midlife (157). Further evidence entails a study where men and women with elevated WC scored lower on the Grooved Pegboard Test and Stroop test (316). A separate study using BMI showed men and women with overweight or obesity performed worse on executive function tests (111). In a similar investigation of older women, individuals with obesity determined by BMI performed more poorly on executive function tasks compared to normal weight individuals and this decrement was associated with reduced gray matter volume in the orbitofrontal cortex (317).

There are many mechanisms potentially responsible for visceral adipose tissue inducing white matter disease and subsequent cognitive dysfunction. One major pathophysiological antecedent to the occurrence of white matter hyperintensities is chronic ischemia (106). Cardiovascular risk factors such as hypertension and dyslipidemia are often comorbid with obesity and at subclinical levels can negatively

affect cerebral perfusion (65). These risk factors may reduce cerebral perfusion through damaging the vascular endothelium resulting in impaired cerebral vasodilatory capacity (162). Adipose tissue is considered the largest endocrine organ in the body and secretes deleterious adipocytokines including interleukin-1, interleukin 6, tumor necrosis factor, leptin, and adiponectin, among others (232). It is well established that these adipocytokines exacerbate inflammation that disrupt the function of the vascular endothelium (11). Endothelial function aids in maintaining a sound blood-brain barrier and protecting small cerebral vessels from pulsatility and blocking toxic metabolites from entering the brain (30). Making matters worse, these adipocytokines can cross the blood-brain barrier and affect the central nervous system (48, 322). Cross-sectional studies have shown proinflammatory cytokines are elevated in individuals with obesity, and play a role in dementia related neurodegeneration (105, 265). Further, in a cross-sectional study observing the role of inflammation and cognition in an elderly sample, increased IL-6 and C reactive protein correlated to increased cognitive decline (330). Although these outcomes may be distal to the population observed in the present study, the cumulative effects of adiposity at midlife, if untreated, may eventually surface as neuropathology and cognitive impairment through an inflammatory mechanism.

Despite accomplishing the goal of our investigation, the present study is not without limitations. While there were many significant relations between body composition indices and WMH, the cross-sectional nature of this study means a causal link between obesity and WMH cannot be established. Other physiological markers and social factors may influence having obesity, neuropathology, and cognitive function independently or synergistically that we did not consider in this analysis. The role of pro-

inflammatory cytokines that are typically elevated in individuals with overweight and obesity, and related to neuropathology, was not taken into account (322). Environmental factors such as socioeconomic status and social network strength, which may help stave off neuropathology and maintain cognitive function, were also not considered in this study (90, 96). While we did not consider these other factors in our analyses, their role in influencing the relations of obesity, neuropathology, and cognitive function should be considered in future work. Another potential limitation we encountered was a highly educated sample. Having a highly educated sample could ostensibly mask significant associations between neuropathology and current cognitive function through increased cognitive reserve. Finally, statistical adjustments for multiple comparisons were not employed.

This study greatly benefited from the characteristics of the observed sample. The sample was racially diverse, and included an equal number of men and women, permitting for generalizability of our findings. Importantly, participants were relatively young, without major comorbidities, and had minimal white matter disease, emphasizing the utility of WC and DEXA body composition measures as early markers of white matter disease preceding deterioration of cognitive function. This study also benefited by being one of the first to compare traditional and imaging body composition indices in their predictive value of early white matter disease and cognitive function.

Conclusions

In summary, after contrasting popular anthropometric obesity indices to image-based estimates of visceral adiposity, only WC was as successful in predicting obesity related subclinical white matter disease at midlife as BF and VAT. WC had the strongest

correlation with VAT. These results are congruent with and buttress literature that identifies WC as the ideal anthropometric measure when studying body composition in relation to neurocognitive vulnerability. This finding held true even after statistical adjustment for cardiovascular influences on WMH, suggesting increasing visceral adiposity independently negatively affects cerebral white matter at midlife prior to disruptions of cognitive function. While these findings need further replication and validation in large cross-sectional and prospective studies at midlife, we assert that future investigations relating obesity to brain structure and function should employ WC rather than BMI or WHR.

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Table 2.1. Selected participant characteristics

	Variable	Mean ± SD
Descriptive	Male/Female	57/69
	Age, y	49.1 ± 6.7
	Caucasian, n (%)	74 (58.7)
	African American, n (%)	8 (6.3)
	Hispanic, n (%)	26 (20.6)
	Asian, n (%)	5 (4.0)
	Other, n (%)	8 (6.3)
	Did not respond, n (%)	2 (1.6)
	Education, y	16.3 ± 2.3
	Systolic Blood Pressure, mmHg	120 ± 12
	Diastolic Blood Pressure, mmHg	72 ± 9
	Total Cholesterol, mg/dL	199 ± 37
	High Density Lipoprotein, mg/dL	52 ± 16
	Low Density Lipoproteins, mg/dL	125 ± 33
	Triglycerides, mg/dL	112 ± 58
	Glucose, mg/dL	99 ± 29
	Body Mass Index, kg/m^2	28 ± 7
	Waist Circumference, cm	94.8 ± 15.4
	Waist to Hip Ratio	0.89 ± 0.10
	Body Fat, %	34.1 ± 10.9
	Visceral Adipose, g	1121 ± 883
	White Matter Hyperintensity, %	0.17 ± 0.26
Physical Activity	Moderate to Vigorous Exercise, hours/week	2.1 ± 6.5
	Moderate to Vigorous Exercise, bouts/week	3.7 ± 3.0
	Sitting, hours/day	8.3 ± 4.0
Medications	Anti-Hypertensive Medication, n (%)	21 (16.7)
	Lipid Lowering, n (%)	14 (11.1)
	Anti-Diabetic Medication, n (%)	5 (4)
	Hormone Replacement Therapy, n (%)	8 (6.3)
	Birth Control, n (%)	3 (2.4)

Table 2.2. Pearson's correlation coefficients between adiposity indices

Index	BMI	WHR	WC	BF	VAT
BMI	1	.324**	.850**	.630**	.693**
WHR	-	1	.643**	.061	.574**
WC	-	-	1	.560**	.871**
BF	-	-	-	1	.473**
VAT	-	-	-	-	1

VAT, square root visceral adipose tissue; WC, waist circumference; BMI, body mass index; WHR, waist to hip ratio; BF, body fat percent
**$p < 0.01$

Table 2.3. Cognitive function assessment raw scores

Measure	Mean ± SD
Global Cognition	
Mini Mental State Exam	28.7 ± 1.4
WASI-II	
FSIQ-2 Subtests	114.1 ± 12.5
BDI-II	6.6 ± 5.3
Memory	
CVLT-II	
Short delay free recall	11.0 ± 3.1
Long delay free recall	11.6 ± 2.7
Recognition discriminability	3.0 ± 0.7
Executive Function	
Trail making test A, s	29.1 ± 9.8
Trail making test B, s	65.0 ± 29.1
WAIS-III digit span subtest, total	20.3 ± 4.2
Stroop interference	41.7 ± 10.6

WASI-II, Wechsler Abbreviated scale of Intelligence II; CVLT-II, California Verbal Learning Test II; WAIS-III, Wechsler Adult Intelligence Scale III

Table 2.4. Linear regression models depicting the association between body composition indices and white matter hyperintensities

	Predictor	Model *p*	β	S.E.	Predictor *p*
Model 1	BMI	0.045*	0.100	0.014	0.274
	WHR	0.072	0.048	1.058	0.646
	WC	0.015*	0.184	0.006	0.049*
	BF	0.015*	0.195	0.009	0.054
	VAT	0.008*	0.218	0.007	0.021*
Model 2	BMI	0.109	0.129	0.016	0.198
	WHR	0.214	0.034	1.130	0.767
	WC	0.050*	0.231	0.007	0.034*
	BF	0.048*	0.230	0.010	0.045*
	VAT	0.035*	0.247	0.008	0.027*

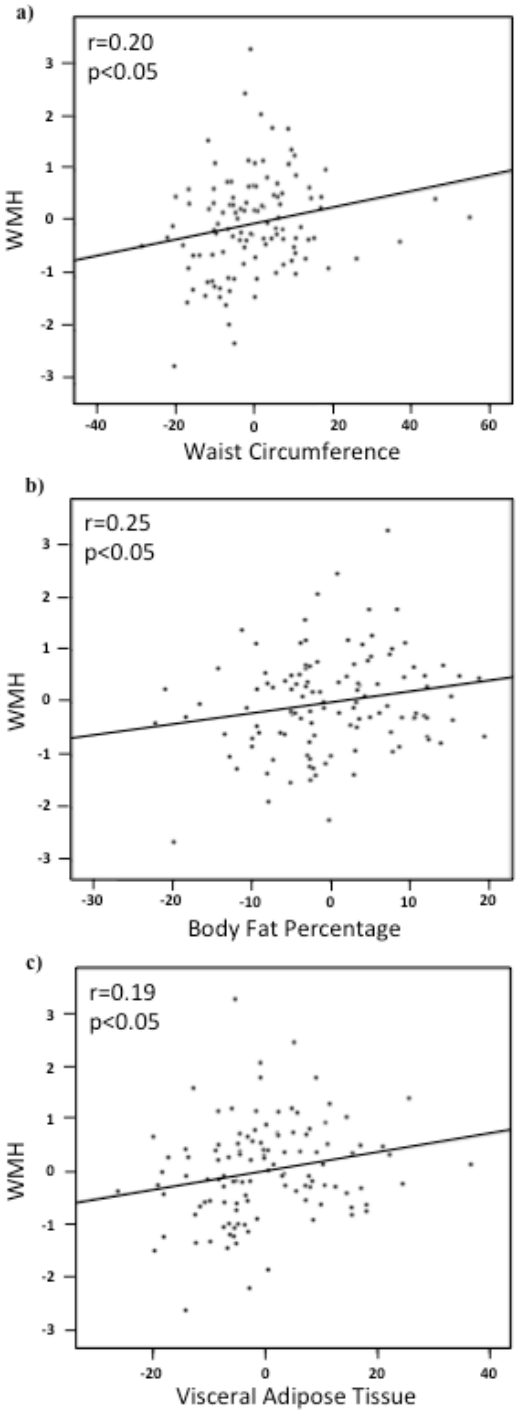
BMI, body mass index; WHR, waist to hip ratio; WC, waist circumference; BF, body fat percent; VAT, square root visceral adipose tissue; SE, standard error
*$p<0.05$
Model 1: Age, sex, years of education controlled
Model 2: Age, sex, years of education, blood pressure, total cholesterol, glucose controlled

Table 2.5. Linear regression models depicting the association between body composition indices and cognitive domain scores

	Domain	Predictor	Model p	β	S.E.	Sig.
Model 1	Executive	BMI	0.119	-0.062	0.009	0.500
	Function	WHR	0.109	-0.087	0.673	0.406
		WC	0.110	-0.078	0.004	0.412
		BF	0.099	-0.099	0.006	0.338
		VAT	0.137	-0.030	0.004	0.754
	Memory	BMI	0.001**	0.013	0.011	0.878
		WHR	0.001**	-0.103	0.850	0.292
		WC	0.001**	-0.054	0.005	0.545
		BF	0.001**	0.025	0.007	0.800
		VAT	0.001**	-0.022	0.006	0.807
Model 2	Executive	BMI	0.016*	0.017	0.010	0.863
	Function	WHR	0.015*	0.024	0.710	0.824
		WC	0.014*	0.050	0.004	0.643
		BF	0.016*	0.000	0.006	0.997
		VAT	0.001**	0.138	0.005	0.211
	Memory	BMI	0.001**	0.013	0.013	0.891
		WHR	0.001**	-0.118	0.926	0.271
		WC	0.001**	-0.056	0.006	0.588
		BF	0.480	0.078	0.008	0.480
		VAT	0.001**	0.013	0.007	0.903

BMI, body mass index; WHR, waist to hip ratio; WC, waist circumference; BF, body fat percent; VAT, square root visceral adipose tissue; SE, standard error
*$p<0.05$
**$p<0.01$
Model 1: Age, sex, years of education controlled
Model 2: Age, sex, years of education, blood pressure, total cholesterol, glucose controlled

Figure 2.1a-c. Linear regression plots depicting the relationship of (a) waist circumference (b) body fat percentage (c) visceral adipose tissue and white matter hyperintensities.



CHAPTER 3: INDIRECT IMPACT OF MIDLIFE ARTERY STIFFENING ON COGNITION THROUGH CERBRAL WHITE MATTER MICROSTRUCTURE INTEGRITY

Abstract

Objective: In addition to being an independent predictor of cardiovascular events, aortic stiffness is related to cognitive dysfunction, white matter disease, and dementia in elderly individuals. Whether stiffening of the central artery is related to white matter integrity and cognitive function at midlife remains unknown. Our aim was to determine if subclinical carotid artery stiffening is associated with lower cerebral white matter integrity (CWMI) at midlife in *a priori* regions of interest (ROIs) susceptible to vascular and cognitive aging. **Methods:** A multi-racial, community dwelling, non-depressed, cohort of middle-aged (40-61 years) adults without clinically evident cognitive impairment was recruited (n=143). Simultaneous ultrasound imaging and arterial tonometry were used to assess carotid arterial compliance, distensibility, and the β-stiffness index. Diffusion tensor imaging (DTI) measured fractional anisotropy (FA), and mean diffusivity (MD) in *a priori* ROIs as indices of CWMI. Executive function, processing speed, and memory domain scores were determined from a cognitive battery. **Results:** Anterior limb of the internal capsule (ALIC) and cingulum CWMI were associated with arterial stiffness metrics ($p<0.05$) independent of age, sex, and waist circumference. Cingulum FA was associated with executive function and processing speed (both $p<0.05$), and carotid artery compliance negatively affected processing speed indirectly through superior corona radiata MD ($\beta=5.6$, 95% CI= 0.58 to 19.14). **Conclusions:** We identified multiple white matter regions vulnerable to the effects of carotid artery stiffening in midlife, including independent associations. Susceptible

regions were associated with executive function and processing speed with arterial stiffness indirectly affecting processing speed. These data suggest that arterial stiffening may negatively affect CWMI prior to clinically overt cognitive decline.

Introduction

Stiffening of the vasculature, known as arteriosclerosis, occurs with aging and chronic exposure to cardiovascular risk factors (174). Arterial stiffness is characterized by remodeling of scaffolding proteins such that stiff collagen fibers are increased, while the number of flexible elastin fibers is diminished (340). Maintenance of vascular elasticity is critical for maintaining Windkessel function, the ability to buffer and cushion pulsatile forces that accompany each heartbeat and convert them into smooth continuous blood flow (31). Loss of this function leaves the microvasculature vulnerable to damaging pulsatile stress, making end organs susceptible to hypoperfusion and hypoxic injury (197, 290).

In addition to being an independent predictor of cardiovascular events, arterial stiffening is associated with increased risk of white matter lesions, cerebral stroke, and dementia in older elderly populations (193, 241, 253). Vascular dysfunction is an early and persistent pathological hallmark in the decline from healthy cognitive functioning to dementia (143). In older adults, central artery stiffening is associated with decreased global cognitive functioning, processing speed, and perceptual speed but not verbal memory (318). Consistent with this notion, individuals with vascular cognitive impairment appear to have weakened cognitive function with the greatest deficits to executive function and processing speed while memory is least affected (309).

Descriptive assessment of cerebral white matter integrity (CWMI) has been popularized since the advent of diffusion tensor imaging (DTI) because of its ability to characterize subtle changes of water diffusion in white matter tracts *in vivo* (12). Fractional anisotropy (FA) determined from DTI represents directional parallelism of

water diffusion in white matter tracts and is reflective of healthy white matter. Conversely, mean diffusivity (MD) represents the magnitude of water diffusion with greater magnitude reflective of poorer CWMI. CWMI tends to peak as early as the third decade of life before beginning a subtle decline in midlife from the fourth to sixth decade of life after which a steep decline ensues (320).

Arterial stiffening of the cardiothoracic arteries is associated with both decreased CWMI and cognitive performance in healthy and cognitively impaired older adults (288). Additionally, arterial stiffening is related to reduced perfusion of frontal white matter responsible for facilitating the performance of executive function tasks (290). Taken together, these findings suggest that arterial stiffening, representing global vascular dysfunction, attenuates cerebral perfusion and compromises CWMI. Whether this potential mechanism operates during midlife prior to stark decline of CWMI or evidence of overt cognitive impairment remains unknown. Most investigations associating arterial stiffness to CWMI have relied upon the abdominal aorta rather than assessing the carotid artery and examined older populations (158, 212, 241). Ostensibly, alterations to carotid elasticity could more directly impact cerebral parenchyma because of its proximity to the cerebral circulation.

With this information as background, the primary aim of this investigation was to determine if midlife stiffening of the carotid artery is associated with lower CWMI in *a priori* regions of interest (ROIs) susceptible to vascular aging. Secondly, we aimed to determine if carotid artery stiffening could directly or indirectly affect cognitive function. To accomplish these aims, robust assessment tools of ultrasound imaging and DTI magnetic resonance imaging sensitive to subtle alterations to white matter were

employed. We hypothesized that increased arterial stiffness would be negatively associated with DTI metrics of healthy CWMI and cognitive performance. We further hypothesized that arterial stiffness would negatively affect executive function and processing speed indirectly through CWMI.

Methods

Participants. A multi-ethnic sample of 143 community-dwelling men and women in midlife (aged 40-61 years) representative of the Austin, Texas area was recruited through local newspaper and online advertisements. To be eligible, participants had to have no pre-existing cardiovascular disease (e.g., coronary artery disease, angina pectoris, myocardial infarction, heart failure, and cardiac surgery), overt neurological disease (e.g., stroke, Parkinson's disease, and clinically significant traumatic brain injury), or contraindications to MRI assessed through self-report on a health history questionnaire. Participants scoring >19 on the Beck Depression Inventory-II, indicating moderate to severe depression were excluded. All subjects provided informed consent, and the local institutional review board approved this study.

Health Assessment. Participants completed a detailed health history questionnaire outlining medication use and current physical activity behavior. Blood samples were collected from the antecubital vein through venous puncture after subjects reported to the laboratory following an overnight fast of at least 8 hours. Plasma glucose and lipid concentrations were determined using standard enzymatic technique. Brachial systolic and diastolic blood pressures were assessed in the supine position after a 15-min period of rest using a blood pressure device (VP-2000; Omron Healthcare, Bannockburn, IL).

Carotid Artery Stiffness Measurement. A B-mode image of the left common carotid artery was captured longitudinally using an iE 33 Ultrasound System (Philips, Bothell, WA) outfitted with a high-resolution linear-array transducer. Images of the near and far wall interfaces were captured perpendicular to the carotid artery 1-2 cm proximal to the carotid bulb. Ultrasound images were digitized and saved in DICOM format for later analysis with computerized image-analysis software (Vascular Research Tool Carotid Analyzer, Medical Imaging Applications, Coralville, IA) by an investigator who was blinded to subject's cardiovascular health. Simultaneously, pulse pressure waveforms from the contralateral common carotid artery were gathered with arterial applanation tonometry (VP-2000; Omron Healthcare, Kyoto, Japan). Because various arterial stiffness indices appear to reflect different aspects of the arterial wall property, a variety of arterial stiffness indices were calculated (180). Arterial elasticity characteristics were described through arterial compliance and distensibility. These measures respectively assess the absolute and relative change in diameter of the carotid artery for a given pressure step at fixed vessel length (209). The β-stiffness index was used to determine carotid artery stiffness calculated as a stiffness measure that was relatively independent of distending pressure.

DTI Acquisition. A 3T Siemens Skyra system (Siemens Medical Solutions, Malvern, PA) with a 32-channel head coil was used to execute MRI. To acquire images in 64 directions at b=700 s/mm, a diffusion-weighted, spin-echo, echo planar imaging pulse sequence was used. A non-diffusion weighted reference image was gathered with b=0. Neighboring 2 mm slices were collected anterior to posterior to cover the cerebrum with the following parameters: FOV = 256 mm, TR = 8,300 ms, TE = 84 ms. To

minimize EPI distortions and optimize the homogeneity of the magnetic field across the brain, advanced shimming was implemented prior to diffusion-weighted imaging.

Using the methods of Hui Zhang et al. (338), diffusion-weighted images were processed with high-dimensional normalization that employed the full tensor, instead of tensor-derived indices in the following processing pipeline. First, using FSL (http://www.fmrib.ox.ac.uk/fsl/), motion and eddy current distortions were corrected with affine transformations. FSL's brain extraction tool was used to remove non-brain signal. FSL's dtifit function (http://cmic.cs.ucl.ac.uk/camino/) performed tensor fitting.

A study-specific template based on 122 participants was created using iterative rigid, affine, and diffeomorphic alignments of the full tensor in DTI-TK (http://www.nitrc.org/projects/dtitk/). Each individual's tensor map was normalized to the study-specific template map using rigid, affine, and diffeomorphic alignments in DTI-TK. The study-specific template was then registered to standard space using the IIT Human Brain Atlas (www.nitrc.org/projects/iit2). Using DTI-TK, standard space FA maps were calculated from each subject's tensor map. ROIs were defined in standard space using the Johns Hopkins International Consortium. ROIs were determined *a priori* based on existing literature as described below. Each participant's FA map was masked by each ROI and the resulting FA ROIs were thresholded at 0.2 to exclude non-white matter signal. The average FA value from each ROI was then extracted. MD maps were calculated in subject space. To define ROIs in subject space, inverse deformation fields were calculated from standard space to subject space and applied to the ROIs.

Region-of-Interest Determination. ROIs were established *a priori* for their pre-existing reported relationships with cognitive aging, arterial stiffness, and aerobic fitness.

ROIs related to aerobic fitness were included because of chronic aerobic fitness has been shown to benefit arterial stiffening (286). The corpus callosum (CC) comprised of the genu, body, and splenium have been investigated as white matter regions vulnerable to aging (158), dementia (127), and arterial stiffening (186, 288). Arterial stiffness has also been related to the corona radiata and internal capsule (186, 288). Lastly, aerobic fitness has been associated with the cingulum, cingulum (hippocampal), and uncinate fasciculus (190, 191).

Cognitive Assessment. A cognitive performance battery was administered containing assessments of global cognitive function, including the Mini Mental State Examination (MMSE), Wechsler Abbreviated Scale of Intelligence-II Full Scale Intelligence Quotient subtest, Beck Depression Inventory-II (BDI-II). The executive function domain was characterized by study specific z-scores on the Trail Making Test A and B, Wechsler Adult Intelligence Scale III (WAIS-III) Digit Span subtest, and Stroop interference subtest. Z-scores were inverted on timed tasks for directional congruity and averaged to construct an executive function domain score. Processing speed was measured by constructing a domain score using the same technique with the Trail Making Test A, Stroop word, and Stroop color tasks included. The memory domain was comprised of the California Verbal Learning Test (CVLT)-II short delay free recall, long delay free recall, and recognition discriminability tasks. Cognitive function testing lasted approximately one hour and was performed with research assistants trained in administration of these tests. The same assistants completed scoring all tests in an effort to maintain the highest standardization.

Statistical analyses. Physiological and cognitive variables were presented as sample means and standard deviations. The statistical analysis pipeline proceeded in three steps as follows. First, the relations of arterial stiffness to CWMI were determined with bivariate correlations. To determine the independent effect of arterial stiffness on CWMI in ROIs with significant bivariate correlations, general linear models adjusted for age, sex, and waist circumference were performed. Second, white matter regions associated with arterial stiffness, determined from significant bivariate correlations, were examined in relation to cognitive function domain z-scores by performing general linear models with age, sex, waist circumference and years of education entered as covariates. Age and sex were included because of their known effects on CWMI (142). In addition, waist circumference was related to CWMI in this sample using whole brain analysis (Birdsill et al., unpublished data). Additional potential cardiovascular covariates (e.g., blood pressure, fasting glucose, triglycerides, and cholesterol) were not included as none was related to CWMI. Third, direct and indirect effects of arterial stiffness on cognitive function through CWMI were determined using non-parametric bootstrapping procedure in Preacher and Hayes' SPSS Process macro (125). Unlike mediation, a significant direct association between the independent and dependent variables is not required for indirect effects to be present. This procedure was performed only if associations existed between arterial stiffness and CWMI, CWMI and cognitive function, and an absence of direct association between arterial stiffness and cognitive function. In short, this procedure takes 1,000 random samples with replacement from the obtained data and calculates the indirect effect for each sample. 95% confidence intervals (CIs) were calculated from the distributions of obtained scores over the samples correcting for bias due to the underlying

distribution. Here, cognitive domain scores were used as dependent variables, arterial stiffness measures as the independent variables, and white matter metrics as the mediator. Age, sex, waist circumference, and years of education were included in all paths of the model as covariates. A 95% bias-corrected CI that excluded 0 was considered significant.

A Bonferroni correction for multiple intercorrelated outcomes was used to determine the level of statistical significance (alpha $p<0.02$). Because the aim of this investigation was to determine the early or subclinical role of arterial stiffness on CWMI and cognitive function small effects were of interest, the uncorrected alpha $p<0.05$ was also noted in tables. SPSS version 24 (SPSS Inc; IBM, Armonk, NY) was used to perform all statistical analyses.

Results

Subject Characteristics. **Table 3.1** displays the basic physiological characteristics of the subject population. Participants were middle-aged, physically active, and well educated. Additionally, subjects were ethnically diverse (37% minority). Metabolic syndrome was prevalent in the sample (25.2%) with the average individual meeting National Heart Lung and Blood Institute and World Health Organization criteria for at least one component (10). Subject's arterial stiffness and CWMI characteristics are delineated in **Table 3.2** and **Table 3.3**.

Arterial Stiffness and Fractional Anisotropy. Bivariate correlations between arterial stiffness indices and DTI metrics of white matters ROIs are outlined in **Table 3.4**. Anterior limb of the internal capsule (ALIC) FA was significantly associated with arterial compliance ($r=0.23$, $p=0.006$) and β-stiffness ($r=-0.20$, $p=0.016$). Corpus callosum (CC) splenium FA was trending to be associated with β-stiffness ($r=-0.17$, $p=0.039$) as was the

association of Cingulum FA with distensibility (r=0.17, p=0.047), while Cingulum FA was significantly associated with arterial compliance (r=0.25, p=0.002). All other relations did not achieve significance (p>0.05).

Age, sex, and waist circumference were added as covariates to general linear models to ascertain the independent associations between stiffness measures and CWMI in regions indicated significant on bivariate analysis. These models are depicted in **Figure 3.1a-b**. In these models, ALIC FA remained significantly associated with arterial compliance (pr=0.22, p=0.008) and trended with β-stiffness index (r=-0.19, p=0.026). FA of the CC splenium lost significance with arterial distensibility (r=0.15, p=0.088). Lastly, cingulum FA remained significantly related to arterial compliance (r=0.22, p=0.008) and was trending with distensibility (r=0.17, p=0.048).

Mean Diffusivity. From bivariate correlations, arterial compliance (r=-0.28, p=0.001), arterial distensibility (r=-0.28, p=0.001), and β-stiffness index (r=0.23, p=0.005) were all significantly associated with MD of the ALIC. Cingulum (hippocampal) MD was trending significance with β-stiffness (r=-0.19, p=0.026). Associations of superior corona radiata (SCR) MD were trending with arterial compliance (r=-0.16, p=0.05) and distensibility (r=-0.18, p=0.028). All other correlations were not significant.

After applying age, sex, and waist circumference as covariates to general linear models in instances of significant bivariate correlations, ALIC MD was significantly and independently associated with arterial compliance (*r*=-0.26, p=0.002), distensibility (*r*=-0.24, p=0.005), and trending with β-stiffness index (r=-0.20, p=0.021). Associations of

cingulum (hippocampal) with β-stiffness index and SCR with arterial compliance and distensibility were abolished ($p>0.05$) with the introduction of covariates.

Cognitive Function. Executive function, processing speed, and memory were investigated for relations to arterial stiffness, and white matter regions demonstrating significant bivariate associations with arterial stiffness. Bivariate correlations of executive function and memory with arterial stiffness indices were not significant ($p>0.05$). Processing speed was significantly related to arterial distensibility ($r=0.20$, $p=0.017$) and trending with β-stiffness index ($r=0.19$, $p=0.023$). Cingulum FA was significantly related to executive function ($r=0.196$, $p=0.020$) while all other regions were not related ($p>0.05$). Cingulum FA trended with ($r=0.20$, $p=0.022$), while cingulum (hippocampal) MD ($r=-0.24$, $p=0.004$), and SCR MD ($r=-0.20$, $p=0.015$) were each related to processing speed. ALIC FA, splenium FA, and ALIC MD were not associated with processing speed ($p>0.05$).

Age, sex, waist circumference, and years of education were added as covariates in general linear models to further scrutinize these relationships. Including these covariates, cingulum (hippocampal) MD ($r=-0.22$, $p=0.010$) remained significant and SCR MD was trending ($r=-0.17$, $p=0.046$) significance with processing speed while all other previously significant bivariate correlations were lost ($p>0.05$).

Indirect Effects. To assess the indirect effects of arterial stiffness on cognitive function through CWMI, non-parametric bootstrapped mediation models were employed. Because significant associations between β-stiffness index, cingulum (hippocampal) MD, and processing speed were present with covariates, the effect of arterial stiffness on processing speed through cingulum (hippocampal) MD was assessed. Including age, sex,

waist circumference, and years of education in the indirect effects model, no significant relation was detected (β=-0.01, 95% CI= -0.04 to 0.00). This analysis was repeated for arterial compliance, SCR MD, and processing speed as well as arterial distensibility, SCR MD, and processing speed. As displayed in **Figure 3.2**, the indirect path of arterial compliance to processing speed through SCR MD was statistically significant (β=5.6, 95% CI= 0.58 to 19.14), although the same path with arterial distensibility was not (β=31.89, 95% CI= -3.65 to 98.26).

Discussion

The present cross-sectional investigation of community-dwelling middle-aged adults aimed to determine the associations of carotid artery stiffening to cerebral CWMI in *a priori* ROIs, as well as their relations with cognitive function. We found stiffening of the carotid artery to be significantly associated with integrity of multiple cerebral white matter regions vulnerable vascular dysfunction independent of age, sex, and waist circumference. These regions were also related to processing speed but to neither executive function nor memory performance after the addition of covariates. Arterial compliance had a significant indirect effect on processing speed through cingulum CWMI. This evidence, to our knowledge, is the first demonstrating midlife carotid artery stiffening to be negatively associated with cerebral CWMI and indirectly related to worse cognitive function.

With accumulating evidence pointing to a common vascular etiology of Alzheimer's disease and vascular dementia, determining early influences of arterial health on the brain prior to overt cognitive symptoms may be informative particularly for intervention purposes (64, 137, 153). To date, most studies examining the relationship of

arterial stiffness, white matter health, and cognitive function have relied on aortic pulse wave velocity (PWV) and white matter hyperintensities showing consistent associations (158, 212, 241). However, the carotid artery may be more anatomically relevant to the cerebral circulation than the aorta, and damage to the white matter may occur prior to manifestation of white matter hyperintensities (47, 210).

By measuring carotid artery stiffness, we were able to identify multiple associations of arterial stiffness with integrity of white matter regions in cognitively healthy community dwelling middle-aged adults. Meanwhile, the aforementioned studies were either reliant on older or clinical populations to demonstrate relations of aortic stiffness to CWMI or cognitive function (158, 212, 241). In older and clinical populations, irreversible vascular-related white matter damage may have already been accumulated. Investigating cognitively intact middle-aged adults allows for the detection of early white mater damage that may be ameliorated with clinical interventions.

More recent investigations are reflective of a shift to using DTI as a marker of early white matter vulnerability in middle-aged populations before incipient cognitive impairment (137, 153, 234). Pulse pressure, a surrogate of arterial stiffness, is significantly associated with reduced CWMI in prefrontal white matter and the ALIC of older adults (age >64 years), as well as the CC Genu (158). An investigation of middle-aged type 1 diabetic men yielded independent associations between aortic PWV and whole brain CWMI (295). A large cross-sectional study of community dwelling middle-aged adults detected a significant association between aortic PWV and reduced FA of the corpus callosum and corona radiata (186). In cognitively normal older adults and those with mild cognitive impairment, carotid-femoral PWV was negatively associated with

DTI indices of CWMI globally and within the corona radiata, internal capsule and superior longitudinal fasciculus (288). In the latter study, global measures of CWMI were significantly associated with the Trail Making Test B-A executive function task.

The most robust relationships identified in the present study were stiffness metrics with the ALIC and cingulum. Damage to the ALIC is consistent with reports of an anterior to posterior vulnerability gradient previously observed in aging individuals and those with metabolic syndrome (261, 334). The ALIC bundle extends to the frontal lobe and white matter lesions in this region have been related to diminished executive function in older adults (268). Individuals with subcortical ischemic vascular disease without dementia exhibited diminished CWMI in the ALIC and cingulum, along with many other tracts (181). The absence of other regions being affected by arterial stiffness indicate that changes to the ALIC and cingulum may be primary to more diffuse white matter damage that occur further along the pathology spectrum (262, 339).

Among the regions we identified as vulnerable to arterial stiffening, integrity of the cingulum and SCR was also related to processing speed, although the relation with SCR MD was lost with the addition of covariates. Still, arterial stiffness had a significant indirect effect on processing speed through SCR CWMI following non-parametric bootstrapping with covariates. Cingulum FA was positively associated with executive function and processing speed in older adults without dementia and elsewhere linked to information processing speed in normal aging (154, 246). Taken together, these findings are suggestive of a temporal relationship behind observations of arterial stiffening and dementia in older adults and those with cognitive complaints (120, 219, 220). It is possible that arterial stiffness preferentially affects regions of cerebral white matter

without disruption of cognitive function until the accumulation of subtle but consistent damages results in reduced processing speed and eventually clinically apparent symptoms. However, this mechanistic relationship needs further investigation and cannot be established from the present study.

How arterial stiffening damages the cerebral white matter remains to be fully elucidated but may likely be multifactorial. As large arteries lose elasticity, their ability to buffer pulsations from the heart is diminished (31). The resulting mechanical stress is transferred to inelastic microvasculature at end organs such as the brain (135, 319). An environment of chronic low-grade hypoperfusion and breakdown of the blood brain barrier initiates inflammation resulting in stifled energy delivery and waste clearance (138, 256, 290). Together, these perturbations could harm oligodendrocytes and induce demyelination (88, 194). With myelin degeneration, oligodendrocyte's production of trophic factors, including insulin-like growth factor-1 and glial-derived neurotrophic factor may be reduced. Loss of these neurotrophic factors causes axonal damage and further demyelination (324). Additionally, oligodendrocyte progenitor cells charged with repairing damaged WM and remyelinating axons are unable to properly mature. Fixed in an immature state, they are powerless to reconstruct myelin due in part to hypoxia (20, 21, 80). Because of myelin's critical role in facilitating action potential potentiation, its degradation impedes cortical communication and disrupts cognitive function. With enough severity, this damage becomes radiologically evident via white matter lesions or altered indices of CWMI as we observed with reduced FA or increased MD, perhaps indicating reduced myelination or membrane density as we observed (28).

The current investigation benefited from a large heterogeneous sample of community dwelling middle-aged individuals who have yet to develop overt cognitive impairments. Using robust imaging techniques to determine carotid artery stiffness and highly sensitive DTI-MRI enabled the identification of multiple cerebral white matter regions demonstrating early susceptibility to arterial stiffening. These relations are made possible by DTI, an imaging modality more sensitive to and descriptive of white matter changes than more traditionally used T2 weighted MRI (283). The assessment of the carotid artery in relation to CWMI and cognitive function is also advantageous compared with the abdominal aorta because it is more anatomically relevant to the cerebral circulation.

The greatest limitation of the current study is its cross-sectional nature. As such, any claims of arterial stiffness directly affecting CWMI or cognitive function are precluded. Nonetheless, associations of arterial stiffness measures to multiple CWMI regions were identified. These relationships were not subjected to strict multiple comparison control. Thus, type 1 error inflation may exist although error control was considered in our results and interpretation. Additionally, the strengths of the relationships detected may be considered small in magnitude. This is likely because we examined a middle-aged cohort without overt cardiovascular diseases that only exhibited mild arterial stiffening. Therefore, we would expect the relationships between arterial stiffness and CWMI to be subtle at this early stage in the pathological process.

In summary, we were able to identify multiple white matter regions vulnerable to stiffening of the carotid artery during midlife. The most robust relation observed was anatomically anterior, suggesting anterior regions may be primarily degraded from

arterial stiffening. Arterial stiffening had an inverse indirect effect on processing speed through CWMI. Since the sample population was without clinically significant cognitive symptoms, these data suggest that arterial stiffening may contribute to early vulnerability of white matter until sufficient damage accumulates to result in disrupted cognitive function. From an intervention perspective, lifestyle behaviors such as chronic aerobic exercise could potentially preserve CWMI and executive function via increased arterial elasticity and reduced cardiovascular risk factors (24). Longitudinal exercise intervention studies observing changes in arterial stiffness, CWMI, and cognition with advancing age may further uncover their mechanistic relationships.

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Table 3.1 Selected subject characteristics

		Mean ± SD
Descriptive	Age, y	48.9 ± 6.2
	Sex, M/F	64/79
	Education, years	16.3 ± 2.3
	BDI-II score	6.0 ± 4.5
	Height, cm	168 ± 9
	Weight, kg	80.1 ± 16.4
	BMI, kg/m^2	28.1 ± 5.6
	Waist Circumference, cm	94 ± 13
	Systolic BP, mmHg	121 ± 13
	Diastolic BP, mmHg	73 ± 10
	Total-C, mg/dL	203 ± 43
	HDL-C, mg/dL	54 ± 17
	LDL-C, mg/dL	130 ± 38
	Triglycerides, mg/dL	121 ± 77
	Glucose, mg/dL	97 ± 26
	Hypertension, n (%)	16 (11.2)
	Hypertriglyceridemia, n (%)	46 (32.2)
	Low HDL, n (%)	43 (30.1)
	Impaired Fasting Glucose, n (%)	40 (28.0)
	MetS Components, n	1.6 ± 1.4
	MetS, n (%)	36 (25.2)
Health Behavior	MV PA, bouts/week	3.9 ± 3.2
	MV Time, hours/week	1.5 ± 1.7
	Sit Time, hours/week	8.0 ± 4.1
	Smoking, n (%)	23 (16.1)
Ethnicity	Caucasian, n (%)	90 (62.9)
	African American, n (%)	11 (7.7)
	Latino, n (%)	29 (20.3)
	Asian, n (%)	5 (3.5)
	Other, n (%)	8 (5.6)
Medication	Anti-hypertensive, n (%)	28 (19.6)
	Anti-cholesterol, n (%)	15 (10.5)
	Anti-diabetic, n (%)	4 (2.8)
	Hormone replacement, n (%)	8 (5.6)

BDI=Beck depression inventory, BMI=body mass index, BP=blood pressure, C=cholesterol, MVPA=moderate to vigorous physical activity, MetS=metabolic syndrome

Table 3.2. Arterial stiffness

	Mean ± SD
Arterial compliance, 100 x cm^2/mm Hg	1.2 ± 0.3
Arterial distensibility, 1000 x mm Hg^{-1}	1.8 ± 0.5
β-stiffness index, AU	6.5 ± 1.9

AU=arbitrary unit

Table 3.3. DTI metrics in *a priori* ROIs

Measure	ROI	Mean ± SD
FA	ALIC	0.53 ± 0.03
	CC Genu	0.59 ± 0.03
	CC Body	0.60 ± 0.04
	CC Splenium	0.65 ± 0.03
	Cingulum	0.49 ± 0.03
	Cingulum (hippocampal)	0.45 ± 0.03
	SCR	0.45 ± 0.03
	Uncinate	0.46 ± 0.03
MD	ALIC	0.76 ± 0.05
	CC Genu	0.90 ± 0.06
	CC Body	1.00 ± 0.09
	CC Splenium	0.99 ± 0.08
	Cingulum	0.79 ± 0.05
	Cingulum (hippocampal)	0.86 ± 0.07
	SCR	0.77 ± 0.04
	Uncinate	0.78 ± 0.04

ALIC, anterior limb of internal capsule; CC, corpus callosum; SCR, superior corona radiata

Table 3.4. Bivariate correlations between white matter ROIs and carotid artery stiffness metrics

			ALIC	CC Genu	CC Body	CC Splenium	Cingulum	Cingulum (hippocampal)	SCR	Uncinate
FA	AC	*r*	**.025****	0.15	0.18*	0.18*	**0.30****	0.12	0.08	0.12
	Dist	*r*	0.18*	0.14	0.16*	0.18*	0.**23****	0.05	0.00	0.09
	β-Stiff	*r*	**-0.20****	-0.11	-0.16*	-0.16*	-0.18*	-0.11	-0.09	-0.03
MD	AC	*r*	**-0.31****	-0.05	-0.08	-0.09	-0.15	-0.14	**-0.19****	-0.15
	Dist	*r*	**-0.31****	-0.08	-0.14	-0.14	-0.13	-0.17*	**-0.22****	0.14
	β-Stiff	*r*	**0.22****	-0.03	0.06	0.05	0.08	0.18*	0.13	-0.13

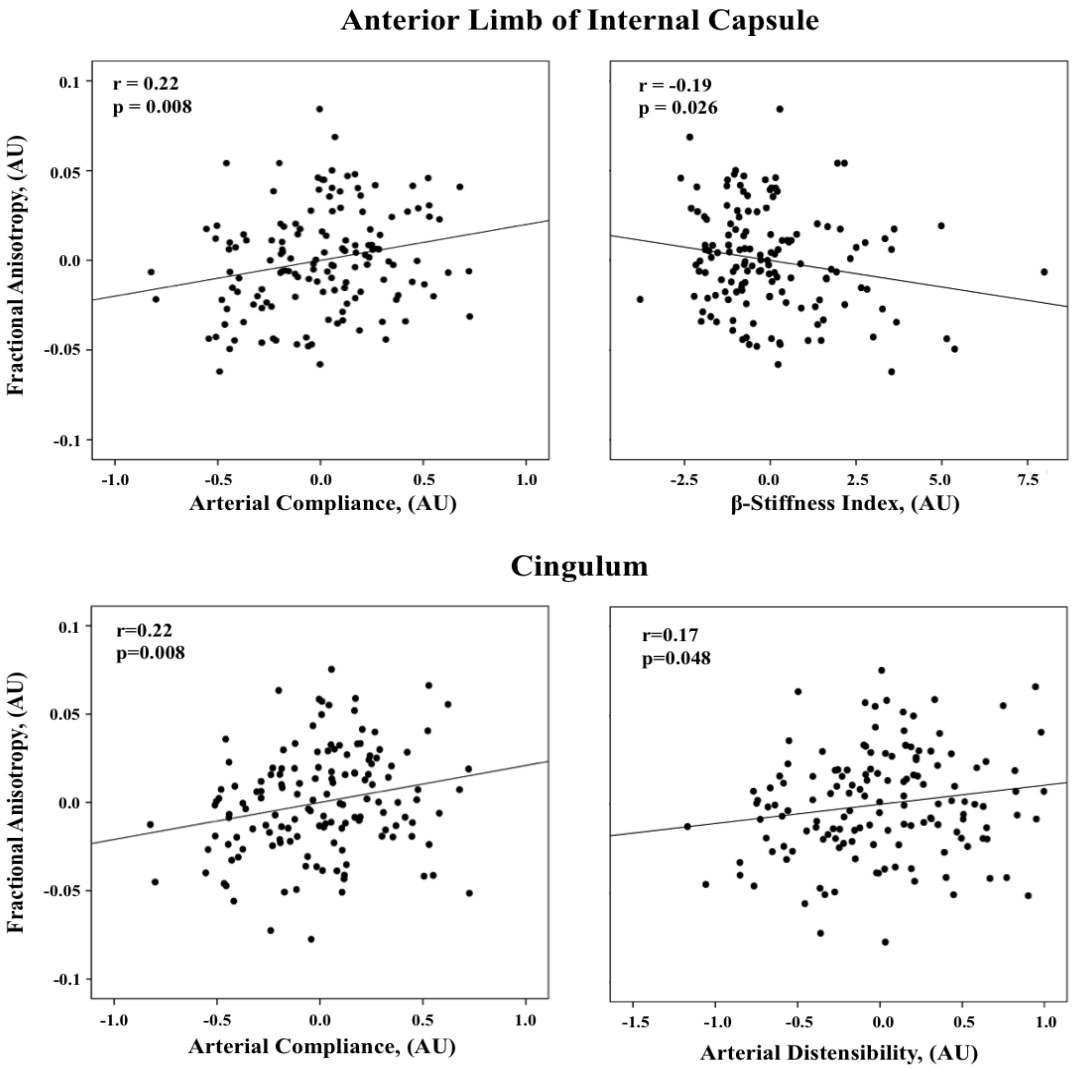
AC=arterial compliance; Dist=arterial distensibility, β-Stiff=β-Stiffness index; ALIC, anterior limb of internal capsule; CC, corpus callosum; SCR, superior corona radiata

*Trending at $p<0.05$

****Significant with adjusted Bonferroni correction at $p<0.02$

Figure 3.1a-b. Partial correlation plots depicting significant independent associations of arterial stiffness with fractional anisotropy (a) and mean diffusivity (b) in *a priori* ROIs controlling for age, sex, and waist circumference.

a)



b)

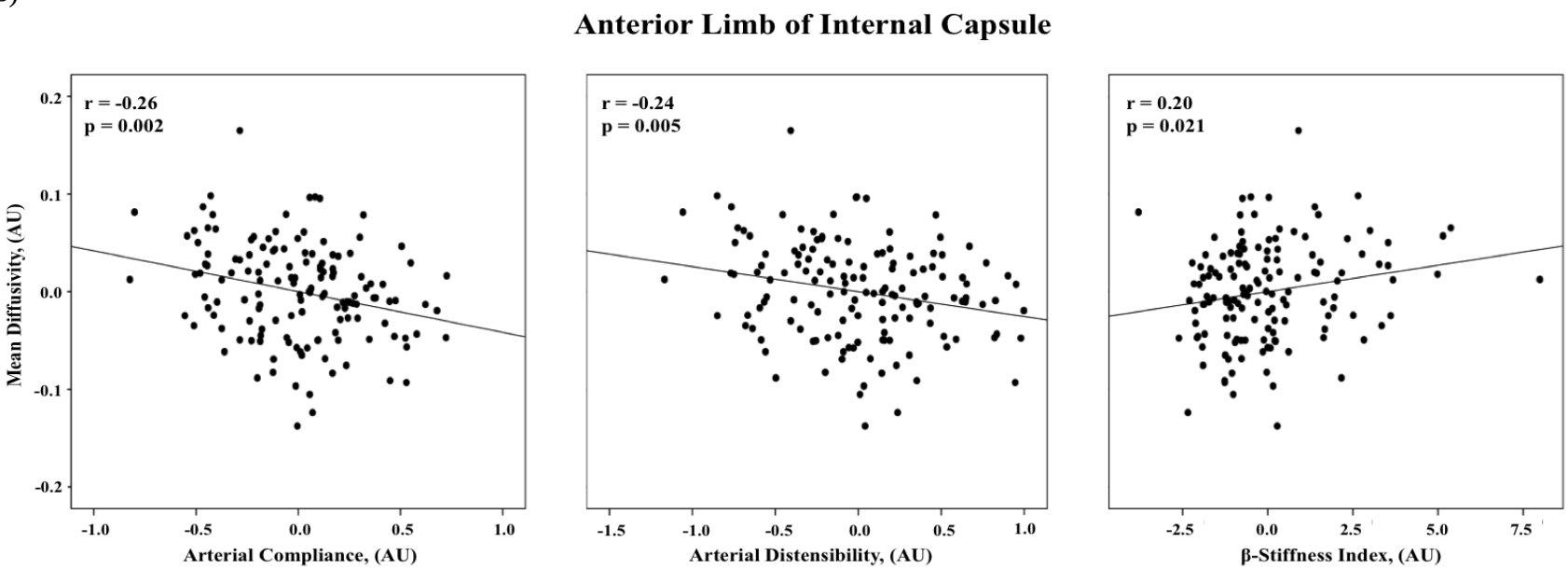
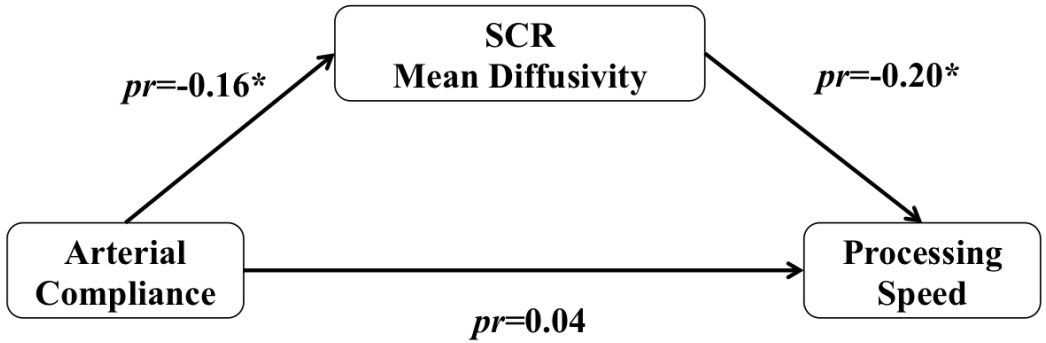

Anterior Limb of Internal Capsule
r = -0.26
p = 0.002
Mean Diffusivity, (AU)
0.2
0.1
0.0
-0.1
-0.2
-1.0
-0.5
0.0
0.5
1.0
Arterial Compliance, (AU)
r = -0.24
p = 0.005
-1.5
-1.0
-0.5
0.0
0.5
1.0
Arterial Distensibility, (AU)
r = 0.20
p = 0.021
-2.5
0.0
2.5
5.0
7.5
β-Stiffness Index, (AU)

Figure 3.2. Path model depicting the indirect effect of arterial stiffness on processing speed through white matter integrity assessed through non-parametric bootstrapping. SCR=superior corona radiata; *p<0.05



Indirect effect of arterial compliance on processing speed

		95% CI	
β	S.E.	Lower Limit	Upper Limit
5.6	4.0	0.58	19.14

CHAPTER 4: PHYSICAL ACTIVITY MITIGATES ADVERSE EFFECT OF METABOLIC SYNDROME ON VASCULATURE AND BRAIN

Abstract

Background: Metabolic syndrome (MetS) adversely affects the vasculature and cerebral white matter (CWM) integrity. Arterial stiffening has been associated with diminished CWM integrity. Physical activity (PA) can ameliorate components of MetS and subsequently affect arterial stiffening and CWM integrity. Our aim was to determine the role of PA on mitigating the adverse influence of MetS on arterial stiffness and CWM integrity. **Design:** In a cross-sectional study design, sixty-six middle-aged adults (40-62 years) composed of 18 sedentary MetS (Sed MetS), 21 physically active MetS (Active MetS), and 27 healthy individuals absent of MetS risk factors were studied. **Methods:** Carotid artery stiffness was assessed via simultaneous ultrasound and tonometry. CWM integrity was measured using diffusion tensor imaging (DTI) through metrics of fractional anisotropy (FA) and mean diffusivity (MD). **Results:** Carotid β-stiffness index in Active MetS was lower than Sed MetS but was not different from Healthy controls (6.6±1.5, 7.7±2.1, and 5.6±1.6 au, $p=0.001$). DTI indicated CWM integrity was significantly greater in Active MetS subjects compared to Sed MetS subjects but statistically equal to Healthy controls in the anterior limb of the internal capsule, body and splenium of the corpus callosum, uncinate fasciculus, cingulum, and superior corona radiata (all $p<0.05$). **Conclusions:** Middle-aged individuals with MetS who habitually perform PA demonstrated lower arterial stiffness and more favorable CWM integrity than their sedentary peers,

indicating that PA may be effective in mitigating the adverse effects of MetS on the vasculature and brain at midlife.

Introduction

Cardiovascular risk factors are frequently accumulated throughout the lifespan and can synergistically lead to a deleterious condition known as metabolic syndrome (MetS) (10). The World Health Organization has declared MetS to be a global epidemic (229) and over a third of U.S. adults are afflicted by MetS (6). This prevalence is troubling, as individuals with MetS not only demonstrate increased risk for cardiovascular disease, but also elevate their probability of acquiring vascular dementia by several fold (187, 235).

Individuals with MetS exhibit markedly elevated arterial stiffening, as virtually all components of MetS have been associated with the pathogenesis of arterial stiffening (178, 248). Arterial stiffness is elevated in elderly individuals with cognitive disease and is predictive of cognitive decline (120, 219). Arterial stiffening has been shown to be associated with regional damage to cerebral white matter (CWM) integrity and reduced executive function (288). CWM plays an integral role in conducting neural information between cortical structures allowing the brain to work in synchrony. Alteration to the CWM is implicated as an early event in the development of dementia (242). Midlife visceral adiposity is associated with arterial stiffening and white matter hyperintensities representative of white matter damage foci (221, 280). Taken together, these findings indicate that arterial stiffening and abdominal obesity, two characteristics of MetS, may leave this population particularly vulnerable to early CWM alterations and subsequent cognitive dysfunction (329).

Regular physical activity (PA) can reduce arterial stiffness and attenuate or even abolish arterial stiffening that occurs with advancing age (37). Aerobic training can also reduce visceral adiposity and various risk factors for coronary heart disease (294, 311). These modifiable cardiovascular risk factors may contribute to carotid artery stiffening and CWM deterioration, making PA an attractive method to mitigate the adverse effects of MetS on arterial stiffening and CWM integrity. However, investigations of PA behavior in relation to CWM integrity are extremely limited. Further, the clinically important question of whether PA can simultaneously mitigate damage to the vasculature and CWM due to MetS has never been addressed.

Accordingly, the primary aim of the present investigation was to determine whether individuals with MetS who are physically active demonstrate lower arterial stiffness and more favorable CWM integrity than their sedentary peers. We measured arterial stiffness using a robust imaging-based technique of the carotid artery because of its anatomical relevance to cerebral circulation. CWM integrity was determined using diffusion tensor imaging (DTI). DTI is a magnetic resonance imaging (MRI) sequence that characterizes the diffusion of water in tissue by producing scalar metrics capable of describing CWM integrity *in vivo* when applied to CWM tracts (12). Increased fractional anisotropy (FA) or reduced mean diffusivity (MD) are reflective of greater CWM integrity (12). In short, arterial stiffness, CWM, and cognitive function were compared in healthy controls and groups of MetS subjects who were either physically active or not. Our working hypothesis was that MetS subjects who are physically active do not demonstrate arterial stiffening and reduced CWM integrity.

Methods

Participants. Community dwelling adults (n=171) aged 40-62 years were recruited for this investigation. For inclusion, individuals were without pre-existing overt cardiovascular, neurological disease, or contraindications to MRI. Of these participants, only individuals who were not significantly depressed as determined by scoring <27 on the Beck Depression Inventory-II (BDI-II) or suffering from cognitive impairment as determined by scoring <23 on the Mini-Mental State Exam were included. The current analysis comprised only of subjects with metabolic syndrome and Healthy controls. These criteria resulted in the admission of 66 participants, who gave their informed consent. The local institutional review board approved this study.

Metabolic Syndrome Characterization. To be categorized as having MetS, participants were required to have 3 or more of the following components: abdominal obesity denoted by waist circumference ≥94 cm for men and ≥80 cm for women; elevated triglycerides (≥150 mg/dL); reduced HDL cholesterol (<40 mg/dL for men and <50 mg/dL for women); increased blood pressure defined as systolic blood pressure ≥130mm Hg and/or diastolic blood pressure ≥85mm Hg; hyperglycemia of elevated fasting glucose (≥100 mg/dL); pharmacological intervention for any condition above (10, 325).

All subjects reported for vascular assessments in the morning after having fasted overnight for at least 8 hours and abstained from physical exercise, alcohol consumption, and caffeine for at least 24 hours. An elastic measuring tape was placed around the trunk at the top of the iliac crest to measure waist circumference. Standard enzymatic techniques were used to quantify blood concentrations of triglycerides, HDL-cholesterol, and glucose. Blood pressure was assessed using the automatic

oscillometric methods (VP-2000; Omron Healthcare, Kyoto, Japan) in the supine position after comfortably resting for 15 minutes in a temperature controlled laboratory setting.

Arterial Stiffness Measurement. A longitudinal B-mode image of the common carotid artery was acquired using an iE 33 Ultrasound System (Philips, Bothell, WA) equipped with a high-resolution linear-array transducer. Images were captured 1-2 cm proximal to the carotid bulb perpendicularly to the blood vessel. Digitized images acquired via ultrasound were analyzed with computerized image-analysis software (Carotid Analyzer, Medical Imaging Applications, Coralville, IA) by a single investigator. Concurrent recordings of pulse pressure waveforms from the contralateral common carotid artery were obtained with arterial applanation tonometry (VP-2000; Omron Healthcare, Kyoto, Japan). Carotid artery compliance and arterial distensibility describe the absolute and relative change in diameter of the vessel for a given pressure step at fixed vessel length(209). β-stiffness was calculated as a measure of carotid stiffness independent of distending pressure.

DTI Acquisition. MRI was performed using a 3T Siemens Skyra system (Siemens Medical Solutions, Malvern, PA) with a 32-channel head coil. A diffusion-weighted, spin-echo, echo planar imaging pulse sequence was used to acquire images in 64 directions at b=700 s/mm. One image with b=0 was collected for a non-diffusion weighted reference image. Diffusion-weighted images underwent high-dimensional normalization (338). Motion and eddy current distortions were corrected with affine transformations in FSL (http://www.fmrib.ox.ac.uk/fsl/). Non-brain signal was removed using FSL's brain extraction tool. Tensor fitting was performed using FSL's dtifit function (http://cmic.cs.ucl.ac.uk/camino/). Participant tensor maps were

normalized to the study-specific template map using rigid, affine, and diffeomorphic alignments in DTI-TK (http://www.nitrc.org/projects/dtitk/). The study-specific template was then registered to standard space using the IIT Human Brain Atlas (www.nitrc.org/projects/iit2) where FA maps were calculated with DTI-TK. Regions-of-interest (ROIs) were determined *a priori* based on existing literature and included corpus callosum (CC) segments, superior corona radiata (SCR), anterior limb of the internal capsule (ALIC), cingulum, cingulum (hippocampal), and uncinate fasciculus for their relations to abnormal cognitive aging (158), dementia (127), arterial stiffening (288), and aerobic fitness (191).

Cognitive Assessment. Encompassed in the battery was the Mini Mental State Examination (MMSE), Wechsler Abbreviated Scale of Intelligence-II Full Scale Intelligence Quotient-2 subtest and Beck Depression Inventory-II (BDI-II). Domain z scores were constructed for executive function, processing speed and memory. The executive function domain was constructed from the Trail Making Test A and B, Wechsler Adult Intelligence Scale III (WAIS-III) Digit Span subtest, and Stroop interference subtest. Included in the processing speed domain were the Trail Making Test A, Stroop word, and Stroop color tasks. The memory domain was comprised of the California Verbal Learning Test (CVLT)-II short delay free recall, long delay free recall, and recognition discriminability tasks. Z scores of each task were inverted where appropriate (e.g., time-based tasks) for directional congruity and averaged to create domain scores. To foster testing standardization, the same assistants performed all scoring.

Physical Activity Behavior. Participants reported days of engaging in low, moderate, and vigorous intensity PA for intervals of at least 15-minute during free time

in a 7-day period using the same classifications as the Godin leisure-time physical activity questionnaire (97). Low PA was defined as "minimal effort" (e.g. yoga, archery, bowling etc.), moderate PA was defined as "not exhausting" (e.g. fast walking, baseball, tennis etc.), and vigorous PA was described as "heart beats rapidly" (e.g. running, hockey, football, soccer etc.). This questionnaire has a high two week retest reliability coefficient of 0.94 (97).

Group stratification. The subject population was first stratified by MetS components. Individuals with ≥3 MetS components created a MetS cohort that was further separated into sedentary (Sed MetS, n=18) and active (Active MetS, n=21) groups based on a median split of self-reported frequency of moderate to vigorous PA. The Sed MetS cohort was described as sedentary because of the paucity of PA this low group displayed following the median split. Individuals without MetS components populated the Healthy control group (n=27).

Statistical Analyses. Differences for categorical variables between groups were determined using Chi Square test while group differences in scalar variables were measured using analysis of variance. Covariates (e.g. age and sex) were considered but did not significantly affect results and were thus not included. Variable homoscedasticity across groups for arterial stiffness and DTI outcomes was assessed with Levene's test with all passing as $p>0.05$ except arterial distensibility ($p=0.039$). Significant *F*-values were further analyzed with least significant difference post-hoc examination to determine group differences. Because small effects were of interest for clinical implications, a Bonferroni correction for multiple intercorrelated outcomes was used to determine the level of significance in DTI metrics, leading to an $\alpha<0.02$

selected for statistical significance. SPSS version 24 (SPSS Inc; IBM, Armonk, NY) was used to perform all statistical analyses.

Results

Group Characteristics. As presented in **Table 4.1**, both MetS groups had greater waist circumference, systolic BP, triglyceride, blood glucose and lower HDL-cholesterol than healthy controls and did not differ from each other except for triglycerides (all $p<0.05$). Frequency of PA was lower in the Sed MetS group compared with Healthy controls and the Active MetS group (all $p<0.05$). Physical activity did not differ between the Healthy control and Active MetS groups and reached the ACSM frequency guidelines for PA.(224) Ethnicity was evenly distributed amongst groups ($p>0.05$).

Arterial Stiffness. As shown in **Figure 4.1**, carotid artery compliance was highest in Healthy controls and lowest in the Sed MetS group (all $p<0.05$). However, no differences in arterial compliance existed between MetS groups. Arterial distensibility was greatest in the Healthy control group compared to either Active MetS or Sed MetS group (all $p<0.05$). The Active and Sed MetS groups did not demonstrate statistically different arterial distensibility. β-stiffness index was significantly lower in the Active MetS group compared with the Sed MetS group and was not different from Healthy controls.

White-Matter Integrity. As shown in **Table 4.2**, CC genu FA was significantly greater in Active MetS compared to Sed MetS but not different than Healthy controls. In the CC body, CC splenium, cingulum, and uncinate, both Active MetS and Healthy controls demonstrated greater FA than Sed MetS and were statistically different from

each other (all $p>0.05$). This trend is demonstrated in **Figure 4.2** using CWM integrity means**.**

No group differences were detected in the CC genu, body, or splenium MD (all $p>0.05$). Alternatively, cingulum (hippocampal) MD was statistically lower in Active MetS compared with Sed MetS group and not different from Healthy. Remaining ROIs including the ALIC, cingulum, SCR, and uncinate all showed the same pattern of significantly lower MD in both Active MetS and Healthy controls compared with Sed MetS (all $p<0.05$). Active MetS and Healthy controls were not significantly different in these ROIs.

Cognitive Function. As shown in **Table 4.1**, cognitive performance was similar across groups on the MMSE and WASI FSIQ - 2 subtests. No differences were observed between groups on executive function or memory performance across groups (all $p>0.05$). Processing speed was greater in Active MetS compared with Sed MetS group (0.1 au ± 0.6 vs. -0.3 au ± 0.5 $p=0.037$) and not different from Healthy controls (0.2 au ± 0.5, $p>0.604$).

Discussion

The principle findings from the present study are as follows. First, sedentary individuals with MetS exhibited increased arterial stiffening and diminished CWM integrity, indicating MetS-associated increases in arterial stiffness and CWM integrity vulnerability. Second, individuals with MetS who performed greater PA had arterial stiffness and CWM integrity comparable with healthy controls. These findings indicate that PA may assuage arterial stiffening while protecting CWM integrity in individuals with MetS.

Investigations relating PA to CWM integrity are few with a greater proportion of existing literature focusing on exercise and cardiorespiratory fitness. A prior investigation reported PA was not related to a reduced rate of white matter lesion progression in a sample of elderly individual with a spectrum of cognitive impairment (227). However, a comparison of physically active individuals demonstrated protection to CWM integrity from carrying the APOE4 gene, a genetic marker of heightened Alzheimer's disease risk (269). In a similar construct, our results are the first to directly relate PA frequency with CWM integrity in individuals with MetS. In the current study, it appears engaging in moderate to vigorous PA was capable of protecting or ameliorating the adverse effects of MetS on arterial stiffening and CWM integrity. Thus, PA represents an attractive method to improve aerobic fitness, arterial health, and brain structure.

A unique aspect of the current investigation is the use of a middle-aged MetS population that is particularly vulnerable to arterial stiffening, diminished CWM health, and cognition. We demonstrated that individuals with MetS even at midlife could perform relatively short bouts of moderate to vigorous PA to protect against arterial stiffening and negative CWM changes. The modesty of the mean frequency and duration of PA performed by the Active MetS group is encouraging in that clinically relevant benefits to the vasculature and CWM can be achieved without overly exhaustive efforts.

The exact mechanisms by which PA enriches CWM integrity remain elusive and are likely complex. PA can improve aerobic fitness, which positively correlates with increased CWM integrity (150, 313). Another probable factor is improving arterial stiffness. Dysregulation of the Windkessel effect results in exposure of small

vessels to pulsatility that enhances arterial stiffening through the loss of elastin and inflict damage to end organs such as the brain (196). If this pulsatility is transferred to cerebral microvessels incapable of accommodating mechanical stress, atherogenic and inflammatory responses that impair microvascular reactivity may result (135). Such changes can reduce cerebral blood flow to white and gray matter in the brain thereby limiting essential nutrients and prompt intermittent ischemic-like conditions (290). This phenomenon of reduced cerebral perfusion has been observed in individuals with MetS (34).

The present study benefited from the distinctive and well-characterized subject population of healthy individuals and those with MetS. Middle-aged adults without cardiovascular risk factors are increasingly sparse. Additionally, the MetS groups were statistically similar in physiological characteristics outside of the independent variable of PA. Methodologically, the assessment of arterial stiffness via ultrasound and CWM integrity via DTI are reliable and robust with DTI particularly suitable for its increased sensitivity to CWM changes compared with other conventional structural MRI techniques (210). This characteristic is critical as changes to the CWM at midlife are likely small but could be indicative of early neuropathology.

There are several study limitations that must be addressed. Inherent to any cross-sectional investigation is the inability to make causal inferences. We cannot specifically assert that PA was solely responsible for these findings, as external factors (e.g. social networks, genetics, etc.) may have influenced the differences of arterial stiffness and CWM integrity (199, 223, 291). Nonetheless, the groups were well characterized and similar across key confounders. Second, characterization of PA from a self-reported questionnaire is vulnerable to reporting bias and retest variability.

Ideally, activity monitors would be given to participants to more accurately distinguish PA behavior. However, dichotomizing moderate to vigorous PA frequency within our sample resulted in largely disparate PA between MetS groups. The Active MetS group seemingly met the ACSM guideline of frequency of PA, while the Sed MetS was nearly entirely inactive. Including a measure of aerobic fitness would have strengthened this investigation. However, we aimed to examine the role of physical activity in the vasculature and brain. Lastly, type-1 error inflation is possible in this study. To combat this, we noted a reduced alpha of $\alpha<0.02$ from the conventional $\alpha<0.05$, and it was deemed clinically valuable to identify potentially vulnerable CWM regions.

Our findings provide novel evidence that PA is associated with more favorable vascular and CWM integrity outcomes in middle-aged adults with MetS. These results reinforce the implication that arterial stiffening could be a mechanistic contributor to reduced cerebral CWM integrity in middle-aged individuals with cardiovascular risk factors and MetS vulnerable for future cognitive decline.

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Table 4.1. Selected group characteristics

		Healthy Controls	Sedentary MetS	Active MetS	P-value
Descriptive	Age, y	50.3 ± 6.5	49.3 ± 6.3	49.5 ± 7.1	0.882
	Sex, M/F	14/13	9-Sep	9-Dec	0.894
	Education, year	17 ± 2	16 ± 3	15 ± 2	0.137
	Height, cm	170 ± 8	170 ± 10	172 ± 8	0.846
	Body Weight, kg	68.0 ± 7.7†	90.7 ± 18.9*	94.9 ± 13.7*	**<0.001**
	BMI, kg/m^2	23.5 ± 2.3†	31.3 ± 6.0*	32.4 ± 5.4*	**<0.001**
	Systolic BP, mmHg	114 ± 7†	124 ± 11*	127 ± 15*	**0.001**
	Diastolic BP, mmHg	70 ± 6	71 ± 8	73 ± 12	0.919
	Total-C, mg/dL	200 ± 34	193 ± 50	217 ± 44	0.206
	HDL-C, mg/dL	62 ± 14†	40 ± 13*	45 ± 19*	**<0.001**
	LDL-C, mg/dL	128 ± 36	121 ± 43	130 ± 40	0.800
	Triglyceride, mg/dL	71 ± 27†	150 ± 62*	212 ± 109*†	**<0.001**
	Glucose, mg/dL	86 ± 7†	115 ± 44*	114 ± 32*	**0.001**
	HbA1c, %	5.3 ± 0.3	6.3 ± 1.7*	6.2 ± 1.9*	**0.034**
	Waist Circumference, cm	83 ± 7†	106 ± 8*	108 ± 10*	**<0.001**
	Post-menopause, n (%)	4 (15)	5 (28)	6 (29)	0.563
Health	MVPA, bouts/week	4.6 ± 3.1†	0.1 ± 0.2*	4.6 ± 2.4†	**<0.001**
Behavior	MVPA, hours/week	1.7 ± 1.7†	0.1 ± 0.3*	1.3 ± 1.1†	**<0.001**
	Sit Time, hours/day	7.5 ± 4.2	9.5 ± 4.7	7.2 ± 4.3	0.222
	Smoking, n (%)	6 (9.1)	2 (3.0)	3 (4.5)	0.568
Ethnicity	Caucasian, n (%)	18 (27.3)	11 (16.7)	13 (19.7)	0.825
	African American, n (%)	1 (1.5)	1 (1.5)	1 (1.5)	0.825
	Latino, n (%)	7 (10.6)	4 (6.1)	7 (10.6)	0.825
	Asian, n (%)	0 (0.0)	1 (1.5)	0 (0.0)	0.825
	Other, n (%)	1 (1.5)	1 (1.5)	0 (0.0)	0.825
Medication	Anti-Hypertensive, n (%)	0 (0.0)†	6 (9.1)*	8 (12.1)*	**0.002**
	Anti-Cholesterol, n (%)	0 (0.0)	6 (9.1)*	7 (10.6)*	**0.004**
	Insulin, n (%)	0 (0.0)	2 (3.0)	2 (3.0)	0.224
Cognitive	MMSE	29 ± 2	29 ± 1	28 ± 2	0.514
Function	BDI-II total	5.7 ± 4.8	8.9 ± 5.5	7.0 ± 5.2	0.118
	WASI FSIQ - 2 subtest	114 ± 13	116 ± 16	111 ± 14	0.518
	Executive function, z score	-0.6 ± 3.3	-0.3 ± 1.1	0.2 ± 5.3	0.744
	Processing speed, z score	0.2 ± 0.5	-0.3 ± 0.5‡	0.1 ± 0.6	**0.027***
	Memory, z score	0.3 ± 0.8	-0.0 ± 0.9	-0.3 ± 0.7	0.063

Data are means ± SD. MetS=metabolic syndrome, BMI=body mass index, BP=blood pressure, C=cholesterol, MVPA=moderate to vigorous physical activity, MMSE=mini mental state exam, BDI=Beck Depression inventory, WASI FSIQ=Wescheler adult scale of intelligence full scale intelligence quotient

*Significantly different from Healthy controls.

†Significantly different from Sedentary MetS.

Table 4.2. Mean DTI white matter integrity coefficients in regions-of-interest

Measure	Region	**Healthy Controls**	**Sedentary MetS**	**Active MetS**	**P-value**
FA	ALIC	0.53 ± 0.03	0.52 ± 0.03	0.54 ± 0.03	0.123
	CC Genu	0.60 ± 0.02	0.58 ± 0.03	0.60 ± 0.03†	**0.039**
	CC Body	0.60 ± 0.03	0.58 ± 0.04‡	0.61 ± 0.04	**0.041**
	CC Splenium	0.66 ± 0.03	0.64 ± 0.02‡	0.67 ± 0.03	**0.010**
	Cingulum	0.50 ± 0.03	0.47 ± 0.03‡	0.50 ± 0.04	**0.022**
	Cingulum (hippocampal)	0.46 ± 0.03	0.44 ± 0.03	0.46 ± 0.04	0.068
	SCR	0.45 ± 0.02	0.45 ± 0.05	0.44 ± 0.03	0.840
	Uncinate	0.46 ± 0.04	0.44 ± 0.03‡	0.47 ± 0.03	**0.012**
MD	ALIC	0.76 ± 0.05	0.80 ± 0.04‡	0.76 ± 0.05	**0.005**
	CC Genu	0.90 ± 0.06	0.92 ± 0.07	0.88 ± 0.06	0.141
	CC Body	1.00 ± 0.08	1.05 ± 0.12	0.99 ± 0.08	0.168
	CC Splenium	1.01 ± 0.09	1.04 ± 0.09	0.98 ± 0.09	0.192
	Cingulum	0.79 ± 0.04	0.82 ± 0.03‡	0.78 ± 0.04	**0.025**
	Cingulum(hippocampal)	0.86 ± 0.06	0.90 ± 0.05	0.85 ± 0.06†	**0.039**
	SCR	0.77 ± 0.03	0.80 ± 0.05‡	0.76 ± 0.04	**0.014**
	Uncinate	0.77 ± 0.04	0.81 ± 0.03‡	0.77 ± 0.04	**0.001**

Data are means ± SD. MetS=metabolic syndrome, FA=Fractional anisotropy, MD=Mean diffusivity, ALIC=Anterior Limb of Internal Capsule, CC=Corpus callosum, SCR=Superior corona radiata

†Significantly different from Sedentary MetS.

‡Significanlty different from Healthy Controls and Active MetS.

Figure Legends

Figure 4.1. Carotid artery stiffness shown in Healthy Controls and Sedentary and Active individuals with MetS. Data are shown as means ± SEM. *Indicates significantly different from Healthy Controls. ‡Indicates significantly different from Healthy Controls and Active MetS.

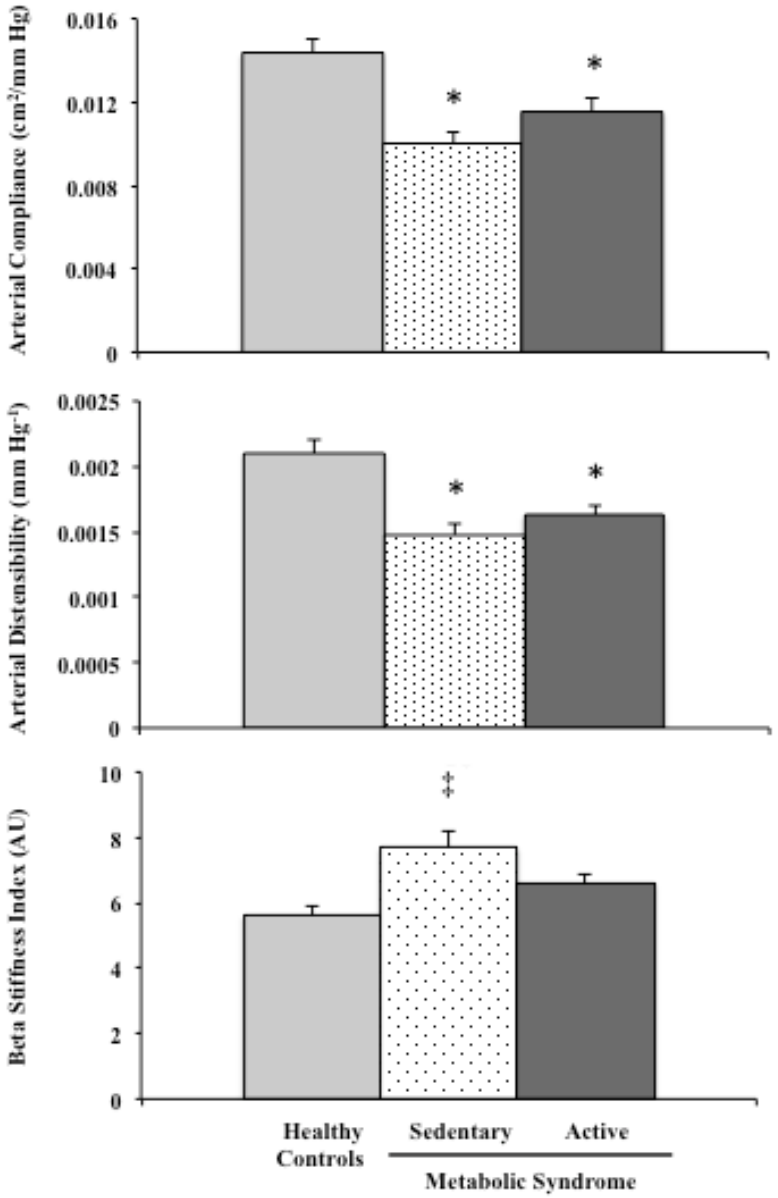
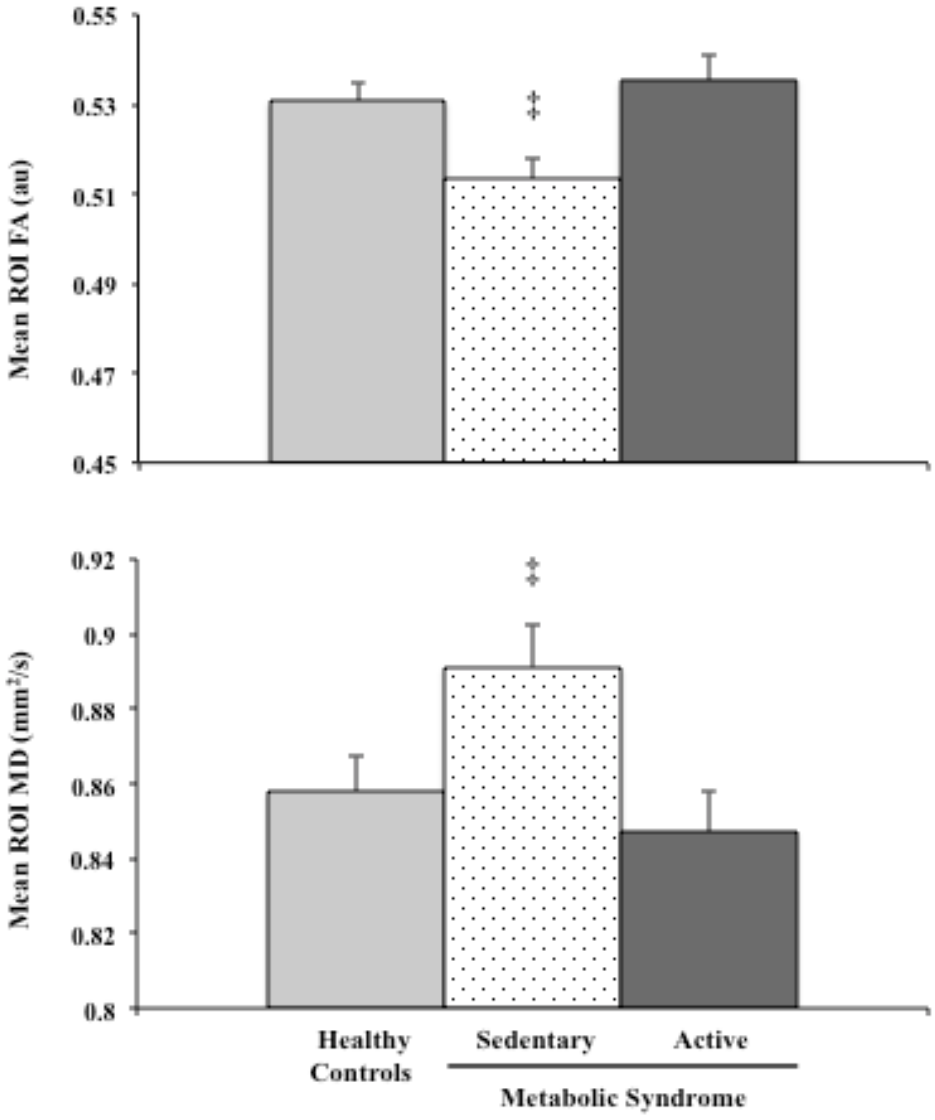


Figure 4.2. Representation of differences in white matter regions-of –interest fractional anisotropy and mean diffusivity displaying preserved microstructural integrity in active individuals with MetS. Data are shown as means ± SEM. ‡Indicates significantly different from Healthy Controls and Active MetS.



CHAPTER 5: REVIEW OF LITERATURE

Dementia: Subtypes and Prevalence

Dementia is an extremely debilitating disease that hinders the ability to perform activities of daily living while robbing their memory of a lifetime of experiences. Of individuals with dementia, 60-80% present with abnormalities characteristic of Alzheimer's disease (AD), such as amyloid-β plaque and neurofibrillary tangles of tau protein. Approximately 50% display some sign of vascular dementia (VaD), as evidenced by cerebral infarcts (18). Representing the most common form of dementia, AD prevalence is projected to increase in the United States nearly three fold from 4.7 million individuals diagnosed in 2010 to 13.8 million in 2050, amounting to one new diagnosis every 33 seconds (128). Against significant efforts to prevent and reduce common causes of deaths, deaths attributed to AD increased 71% from 2000 to 2013, elevating the disease to be the 6th leading cause of death in the U.S. (18) and making dementia a pressing public health problem.

Presently, there is no restorative treatment for dementia. Thus, the development of preventive strategies is imperative to stem the rise of dementia prevalence and attenuate symptom severity (64). To adapt the best preventive strategies, understanding temporal relationships of dementia biomarkers to disease pathogenesis is crucial. The complexity of dementia etiology is daunting in that tracing its source is difficult, yet presents multiple opportunities for targeted treatment. Currently there are two major competing hypotheses surrounding the development of dementia: vascular and amyloid. While they possess seemingly separate

pathophysiology, they may work synergistically to lead to the common end result of dementia.

Mechanisms of Dementia

Although there are multiple factors associated with causing dementia, the leading candidates are amyloid-β, tau protein misfolding, and vascular dysregulation (145, 153). While these mechanisms have been viewed as distinct causes of dementia subtypes (63), it is evident that they are interrelated as hallmark features of AD and VaD are evident 50% of all dementia cases, representing mixed dementia (18). More recently, a multifactorial data-driven analysis spatiotemporally assessed alterations of amyloid-β levels, metabolism, vascular regulation, functional activity at rest, structural tissue properties, and protein levels in relation to late onset Alzheimer's disease progression. Findings revealed vascular dysregulation to be a key early and persistent event in disease progression (143). Because of its early and continued dysregulation, vascular function represents a crucial target for the primary prevention of cognitive dysfunction at midlife.

VASCULAR MECHANISMS

The role of the vascular system in dementia progression has long been hypothesized, dating back to the early 1900s (138). Considering cerebral perfusion must match oxygen and energy demands of the brain, a vascular etiology of dementia seems logical. Because of the brain's reliance on cerebral perfusion, blood delivery is normally a highly regulated system where the neurovascular unit, comprised of vascular cells such as endothelium and pericytes, glial cells, and neurons that maintain the blood brain barrier (BBB), is tightly synchronized (341). Cardiovascular risk

factors, including obesity, hypertension, diabetes, dyslipidemia, and smoking, insult this unit over time, beginning a negative series of events, including vascular dysfunction, atherosclerosis, and arteriosclerosis (342). When these cardioavascular risk factors cluster in a single individual at defined subclinical cuttoffs, it is termed metabolic syndrome (MetS) (10), which is associated with damage to the brain (332).

Cardiovascular risk factors impair endothelial function, cerebral autoregulation, and neurovascular function. Endothelial cells are vital in maintaining vascular tone and reacting to changes in arterial pressure to ensure continuous cerebral blood flow (51). Cerebral endothelial cells are joined by tight junctions that help ensure BBB integrity (76). As insults to the vasculature stemming from cardiovascular risk factors accumulate, oligemia and breakdown of the BBB begins (65, 300). Leakiness of the BBB allows for extroversion of plasma proteins such as fibrinogen, albumin, and immunoglobulins (8, 9). Glial cells detect these proteins and become activated leading to the production of reactive oxygen species that further degrade endothelial cells (263). Vascular damage from reactive oxygen species is additive to the oxidative stress already produced by cardiovascular risk factors and cerebral hypoperfusion (53, 139, 141). Tissue hypoxia and oxidative stress induced by cerebral hypoperfusion signal the production of inflammatory cytokines, including tumor necrosis factor and interleukins among others (35).

Arteriosclerosis of larger, central vessels may also produce effects similar to cerebral hypoperfusion (290). Larger central vessels, such as the carotid artery, eventually feed cerebral microvessels, which perfuse the deep white matter of the brain. A fundamental function of large vessels is to buffer hemodynamic pulsatility and transfer smooth continuous blood flow from the heart to the systemic vasculature

(205). This cushioning effect of the large vessels is known as the Windkessel model. Dysregulation of Windkessel function results in exposure of small vessels to pulsatility and inflicts damage to distal-end organs, such as the brain (196). Chronic exposure to this pulsatility may invite atherogenic and inflammatory responses that impair microvascular reactivity. Such changes can reduce cerebral blood flow to white and grey matter in the brain thereby limiting essential nutrients and prompting intermittent ischemic-like conditions (247, 290).

These mechanisms converge to reduce cerebral blood flow, beginning insidiously as oligemia and eventually progressing to ischemia causing slow neurodegeneration of cerebral white and grey matter (43, 69, 342). In addition to providing the brain with nutrients, the cerebrovascular system is also responsible for cleansing superfluous amyloid-β (137). Over accumulation of amyloid-β is neurodegenerative, impairs cerebrovascular function, and limits cerebral blood flow (4, 207, 293). Cardiovascular risk factors, cerebral hypoperfusion, and amyloid-β, and other mechanistic contributors are all associated with disruptions of cognitive function (29, 101, 134, 276).

Typically, AD presents with accumulation of amyloid-β, degeneration in the medial temporal lope, and memory loss while VaD is characterized by ischemia, frontal grey matter atrophy, and reduced executive function (165). Although memory is the most clinically noticeable change with medial temporal lobe atrophy, language comprehension, behavior, and attention are also affected. Detriments to frontal grey matter can affect decision-making, judgment, attention, and problem solving, all of which fall under the umbrella of executive function. In spite of distinct differences in their clinical presentations, the causal mechanisms of AD and VaD appear intertwined.

With either disease, identification of biomarkers, early in dementia progression when damage is still reversible, can lead to prevention/treatment targets. An important correlate of cognitive function and emerging early biomarker of AD and VaD is the health of the cerebral white matter (19, 33, 175, 242).

CEREBRAL CIRCULATION

The brain is a notoriously metabolically demanding organ, weighing only 2% of the body weight, yet receiving 15% of the cardiac output and 20% of the oxygen used by the body at rest. A complex circulatory network exists to accommodate this demand. The cerebral circulation originates from the left and right internal carotid arteries as well as the vertebral arteries. Building from the internal carotid arteries is the Circle of Willis, an anastomosis consisting of the bilateral anterior and posterior communicating and cerebral arteries as well as the basilar artery. Branching from the Circle of Willis are multiple vessels that lead to both hemispheres bilaterally including the left and right middle cerebral arteries that flow into smaller arteries, extrinsically innervated pial arteries that run across the surface of the brain before penetrating to deliver blood to the cortex and subcortical structures. For example, the middle cerebral artery is a principal contributor to cortex and white matter blood supply, including the frontal, parietal, and occipital lobes along with the insula. To supply interred white matter and diencephalic structures, extraparenchymal pial arteries further branch perpendicularly to the cerebral surface into intrinsically innervated pial arterioles that are separated from the brain tissue by the Virchow-Robin space that diminishes with depth (225). As pial arterioles dive deeper, they contact neural tissue and astrocytes. The triad of vascular cells, neurons, and astrocytes interacting together comprise a

functional neurovascular unit capable of directing blood flow in response to neural activation and to meet metabolic demands (137). At each step of reduced vessel lumen diameter, vascular resistance and susceptibility to pulsatile flow increases. Although the cortex has almost four fold greater demand for cerebral blood flow, the white matter is also metabolically demanding.

Cerebral White Matter

ANATOMY

Cerebral white matter (WM) is interred beneath the cortical exterior forming ~50% of the total volume of a healthy human brain (117). The principle duty of the cerebral WM is to conduct neural information between grey matter regions allowing the cortices to work synchronously. To accomplish this function, the WM is organized into axon bundles wrapped with myelin that accelerates action potential propagation by 100 fold (202, 203). Although there are many classifications for WM bundles, they are predominantly organized into three major fiber groups. Commissural fibers bridge the cerebral hemispheres and include the corpus callosum. Projection fibers link the spinal cord, diencephalic, and mesencephalic structures with the cortex in long ascending and descending pathways and include such fibers as the corona radiate and anterior internal capsule (188). Association fibers are divided into short fibers that connect neighboring cortices and long fibers that unite remote grey matter. Other anatomical terms are often encountered when describing WM. Periventricular WM refers to WM near the lateral ventricles while deep WM refers to the other fibers. Subcortical WM refers to both. WM is particularly vulnerable to vascular damage that leads to cognitive dysfunction

and dementia. Lesions to the WM are associated with hypoperfusion and ischemia (33).

PATHOLOGY

Damage to the white matter is conferred in a multitude of ways including through cardiovascular risk factors and vascular dysfunction. Vascular perturbations disrupt cerebral perfusion, prompt BBB breakdown, initiate inflammation, and promote reactive oxygen species formation. Together, they harm oligodendrocytes and induce demyelination (88, 194). With myelin degeneration, oligodendrocyte's production of trophic factors, including insulin-like growth factor-1 and glial-derived neurotrophic factor is attenuated. Loss of these neurotrophic factors causes axonal damage and further demyelination (324). Additionally, oligodendrocyte progenitor cells charged with repairing damaged WM and remyelinating axons are unable to properly mature. Stuck in an immature state, they are powerless to reconstruct myelin due to hypoxia (20, 21, 80). Because of myelin's critical role in facilitating action potential potentiation, its degradation impedes cortical communication and disrupts cognitive function. Estimates of WM damage can be obtained through structural magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI).

WHITE MATTER HYPERINTENSITIES

White matter hyperintensities (WMH) are the most common radiological evidence of white matter lesions. These lesions appear on T2-weighted MR images as bright spots that begin as punctate and become more confluent with advancing pathology (188). These lesions can be the result of multiple diseases but are the most common feature of vascular cognitive impairment in relation to alterations of

microvasculature (148, 299). These lesions are reflective of rarefication of white matter and are associated with axonal loss, demyelination, microvascular arteriosclerosis, and endothelial dysfunction (42, 82, 250). The best predictor of WMH is age (66) and other predictors include hypertension, obesity, dyslipidemia, and dysglycemia (3, 39, 314). These cardiovascular risk factors can be targeted and altered through behavior modification and pharmacological interventions throughout the lifespan making them attractive treatment targets. WMH are thought to be foci of underlying small vessel disease, leaving the possibility that WM impairments may manifest even prior to the emergence of WMH. Therefore, assessment of both WMH and WM integrity is integral to understanding the early changes of vascular-related WM dysfunction.

Quantification of White Matter Hyperintensities

The most prominent imaging modality to monitor white matter status is structural MRI. T1-weighted MRI, in combination with fluid attenuated inverse recovery (FLAIR) sequences, produce excellent anatomic resolution allowing for identification of WMH. Quantifying WMH volume can be accomplished in a number of ways. Simple visual ratings of WMH severity can be performed but is limited by converting a scalar variable into one that is categorical, thereby reducing data variance and sensitivity (188). Various visual rating scales have been constructed to increase sensitivity, yet the aforementioned limitations remain along with the problem of interrater reliability. Alternatively, computerized, automated methods to estimate WMH volume have been developed. Thresholding evaluates pixel intensity values and can sum the number of pixels that achieve a predetermined threshold (244). A seed-

growing technique, in which investigators interactively select regions of interest, run an algorithm growing the seed, and identify the total number pixels of similar intensity can be used (266). Lastly, lesions can be manually traced. Regardless of the method used, expression of WMH volume should be reported in relation to total intracranial volume to account for differences between individuals.

WHITE MATTER VULNERABILITY

White matter hyperintensities can be visually obvious radiologically, yet white matter integrity may be compromised prior to their manifestation (47, 210). To capture an earlier glimpse into WM vulnerability, diffusion tensor imaging (DTI) is used. DTI describes the underlying microstructure of WM by measuring the magnitude and direction of water molecules (26). In healthy intact WM, water encounters cellular barriers, including myelin, that restrict its movement (12). Conversely, in the event of tissue breakdown, water does not encounter such barriers and diffuses unimpeded. Scalar metrics are intensively computed to characterize this water diffusion. Mean diffusivity (MD) represents the apparent diffusion coefficient irrespective of direction such that high values exemplify freely diffusing water and reduced microstructural integrity. For example, MD is elevated in WMH (189). Counter to MD, fractional anisotropy (FA) is indicative of the degree of anisotropic water diffusion ranging on a scale of 0-1 with 0 representing random diffusion and 1 representing completely directional diffusion (173, 188). Healthy WM FA values typically fall above 0.35, while in damaged WM values dip below 0.3. More descriptive still, are the radial diffusivity (D_r), and axial diffusivity (D_a) measures that can ascribe specificity to WM

damage. Animal models have revealed demyelination is related to increased D_r whereas axonal damage or loss may occur with increased D_a (121, 274, 275, 282, 298).

CLINICAL IMPORTANCE

As foci of damage to WM, the clinical implications of WMH will be discussed rather than DTI metrics. The clinical importance of WMH has long been debated, but there is mounting evidence that WMH is related to cognitive dysfunction and rate of cognitive decline (19, 40, 307). It is possible that WMH mediates the relation of cardiovascular risk factors and vascular dysfunction to cognitive dysfunction. The role of modifiable cardiovascular risk factors in relation to WMH and cognitive function will be discussed in greater detail in subsequent sections. Regardless of the cause, many studies have outlined associations between WMH and cognitive function. In particular, WMH appears to retard executive functioning tasks as well as memory in older adults (213). Some memory tasks appear more related to WMH than others. For example, the Digit Span is consistently unrelated to either deep or periventricular WMH, yet other working memory tasks are significantly related to WMH (214). The relation of cognitive function to WMH may have best been summarized in a quantitative review that found global functioning, speed tasks, immediate memory, delayed memory, and executive function were all significantly associated with WMH scores (108).

Given the relationship between WMH and cognitive dysfunction, it is not surprising that WMH is related to cognitive disease. A large longitudinal study with an average follow-up of 7.3 years showed an accelerated decline of global cognition on the Mini-Mental State Exam with increasing severity of WMH after controlling for

numerous covariates (61). This increased rate of cognitive decline appears to carry into the development of dementia. One study demonstrated a 1.6 fold increased risk of developing dementia for every standard deviation increase of WMH severity independent of other possible disease contributors including age, sex, education, hypertension, diabetes, smoking, and apolipoprotein E (APOE) 4 genotype (233). Both of these findings are supported by a systemic review and meta-analysis suggesting that WMH are associated with a 1.9 fold increased risk of dementia and hastened decreases in global cognition, executive function, and processing speed (69). The inclusion of confounding influences in the statistical analyses of these studies suggests the independence of WMH in its relation to negative outcomes and may indicate the WM damage may be irreversible.

Dementia Risk Factors

NON-MODIFIABLE RISK FACTORS

Some risk factors for cognitive decline and dementia are non-modifiable while others can be manipulated through behavioral or pharmacological interventions. Age is an unwavering, non-modifiable risk factor for cognitive decline, WMH, and dementia (67, 333). While family history does not definitively predetermine the development of dementia, it is another formidable, non-modifiable risk factor that varies across race (104). Having a first-degree relative with dementia increases AD risk by about 39% and having more than one first-degree relative increases risk even further (171). Heritability of dementia risk factors is another non-modifiable phenomenon. Inheritance of one APOE4 allele increases the risk of AD by about three times, while inheriting two copies increases the risk 8-12 fold (133, 182). APOE4

carriers tend to exhibit increased WM vulnerability compared with non-carriers (129). In young adults (20-35 years), older adults (50-78 years), or when pooled, APOE4 carriers showed decreased FA compared with non-carriers. In older adults, MD was significantly elevated in APOE4 carriers compared with non-carriers. This finding suggests that APOE4 exerts a negative effect on cerebral WM irrespective of age. Other genetic risk factors include the passing of duplications or mutations of amyloid precursor protein, presenelin 1, and presenelin 2 genes (182). Nonetheless, APOE4 is the most commonly recognized genetic risk factor for AD. Little can be done to assuage the neurocognitive damages conferred from these non-modifiable risk factors. However, modifiable cardiovascular risk factors are significant contributors to vascular dysfunction, deterioration of WM, and ultimately dementia can be positively influenced.

MODIFIABLE RISK FACTORS

Adiposity

Adipocytokines. Excess adipose tissue is not a benign, inert, harmless byproduct of weight gain and obesity. On the contrary, excess adipose tissue is hormonally active and constitutes the largest endocrine organ in the body (322). Adipocytes are larger in size in obese individuals and produce proinflammatory proteins known as adipocytokines (232). Visceral adiposity, adipose tissue surrounding internal organs, may secrete more adipocytokines than subcutaneous fat (13). These cytokines include, but are not limited to, interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), leptin, and adiponectin (44). Pro-inflammatory cytokines including C-reactive protein (CRP) and TNF- α are elevated in

the obese phenotype (105, 152). Such inflammatory factors are associated with vascular dysfunction and promote blood brain barrier disturbances, thus contributing to dementia. These associations were demonstrated in a 25-year follow-up study of middle-aged adults, participants above the first quartile of CRP exhibited a 3-fold increased risk of acquiring vascular dementia or AD (251).

Hormones such as leptin and adiponectin can also advance dementia pathology. Leptin usually combats adiposity by increasing metabolism and appetite. However, individuals with obesity may lose sensitivity to leptin thereby stimulating overproduction and elevated levels of the metabolic hormone (123). Leptin has been associated with accumulation of amyloid-β related to AD, and elevated levels of leptin are correlated to poor cognitive function in elderly women (85, 336). Adiponectin is the most secreted adipocytokine and serves multiple roles including fatty acid metabolism, anti-inflammation, and, importantly, aiding in the maintenance of glucose homeostasis through enhancing insulin sensitivity and reducing liver gluconeogenesis (183, 273). Withdrawn control of these functions from reduced adiponectin production or sensitivity has detrimental effects on the brain. Impaired cognitive functioning has been associated with lower adiponectin, but not with further cognitive decline or advancement to Alzheimer's disease (292). Despite this evidence, investigations of leptin and adiponectin in relation to dementia are sparse. Since these damaging proteins largely originate from visceral adipose tissue accurate anthropometric measurement of visceral adiposity for large studies is of critical importance. Honing the most reliable anthropometric assessments reflective of visceral adipose tissue will strengthen our ability to accurately evaluate the relations of adiposity and the brain.

Adiposity Measurement. As of 2015, 69% of adults in the U.S. were classified as overweight and 34% classified as obese (200). This alarming prevalence is a significant public health concern as adiposity is negatively related to WM health and cognitive function and positively to dementia at midlife (74, 115, 278). Adding to the difficulties in this area of research are the many ways in which adiposity is assessed. While anthropometric measures were developed for their ability to represent underlying adiposity, each vary in their specificity. Body mass index (BMI) is calculated by mass in kilograms divided by height in meters squared (kg/m^2). BMI is epidemiologically valuable because of its ease of use. However, this blunt metric is not necessarily indicative of adiposity (57). Waist-to-hip ratio (WHR) divides waist girth by hip girth and has solid predictive power for cardiovascular disease events (238). Using this ratio may be less viable for cross-sectional studies due to sex differences in adipose deposition despite sex specific cutoffs implemented to reduce such concern. Waist circumference (WC) is strongly related to visceral adiposity. Neither WHR nor WC effectively characterizes subcutaneous fat (230). Other methods to estimate body fat include simple anthropometry of hip circumference and waist to thigh ratio, as well as more complex procedures of skinfolds, air plethysmography, and underwater weighing. Dual energy x-ray absorptiometry (DXA) can sensitively quantify whole body, subcutaneous, and visceral adipose tissue mass and volume. While DXA is a valuable tool in clinical settings, anthropometric measures of adiposity are more useful for large-scale population based studies.

Ascertaining adiposity indices most indicative of WM health and cognition in a controlled setting is a necessity. Despite the multitude of methods for assessment, those most indicative of underlying adiposity and sensitive to composition are best

suited as indicators of cerebral health. While studies investigating the relation of anthropometric measurements of adiposity and brain healthy are common, their comparative value as indicators of white matter health at midlife is missing. This omission in the literature is undoubtedly in need of addressing. Nonetheless, previous studies have used a variety of methods to determine the relationship between adiposity, brain structure, and cognitive function.

***White Matter Integrity*.** In relation to WM integrity, BMI is negatively associated with FA of multiple WM tracts, including the corpus callosum, fornix, cingulum, and corona radiata (166). These tracts aide in the integration of temporal and frontal regions typically associated with facilitating executive functioning and memory. WMH are also associated with increased BMI in older adults and elderly cohorts in some, but not all, studies (116, 119, 146). The relationship of BMI and WMH has also been observed at midlife (216). With prevalent reports of relations of WM with cognitive function, and obesity, increased risk of dementia with greater BMI is logical. Indeed, individuals with obesity at midlife were found to be twice as likely to acquire dementia 18 years later (160). Therefore, it stands to reason that obesity can negatively affect executive function and memory with advancing age.

Cognitive Function. The relationship of adiposity and cognition across the lifespan remains a controversial topic. Obesity appears to impair cognitive function from an early age through adolescence (4-19 years), with evidence indicating poorer cognitive function in obese individuals compared to those of normal weight (110, 179, 277). At midlife, the same relationship exists, with most cross-sectional studies finding a negative association between BMI and cognitive function (109, 110, 206). This linear relationship may veer off course in the elderly as obesity has shown to be

positively associated with cognitive function in septuagenarians (167). It has been hypothesized that individuals who are obese throughout the lifespan experience a steeper decline in weight during old age (113). This trajectory is contrasted with individuals of normal weight whose weight decline is more gradual. Taken together, this theory explains the divergent, non-linear relationship between adiposity and cognitive function. Individuals with a higher BMI at midlife, but underweight in old age exhibited poorer survival from dementia after seven years of follow-up (86). Regardless of age demographic, in instances of lower cognitive functioning, executive function is the domain most frequently affected (267). Despite the non-linear relationship of adiposity and cognition across the lifespan that may be moderated by obesity, midlife obesity is associated with increased risk of dementia, as evidenced with prospective studies (86, 236, 323). Compounding this increased risk are other cardiovascular comorbidities at midlife including metabolic syndrome (MetS) components that are independently associated with heightened risk of dementia (160).

Metabolic Syndrome

Components and Prevalence. Modifiable cardiovascular risk factors are often accumulated comorbidly throughout the lifespan. When a cluster of three risk factors of abdominal obesity, dyslipidemia, elevated blood pressure, and hyperglycemia occurs in a single individual, it is ascribed as metabolic syndrome (MetS) (10). These risk factors are highly prevalent in the U.S. Currently, 69% of adults in the U.S. are overweight, while 43% have hypercholesterolemia, 33% have hypertension, and 9% have diabetes (200). The prevalence of MetS in the U.S. was estimated to be 34.7% in 2011-2012 (6).

Specific cutoffs for MetS components are largely agreed upon, though there is some variability for impaired fasting glucose and abdominal obesity due to population differences between ethnicities. Nonetheless, in the U.S., the abdominal obesity criteria for MetS is denoted by waist circumference (≥94 cm for men and ≥80 cm for women); elevated triglycerides (≥150 mg/dL); reduced HDL cholesterol (<40 mg/dL for men and <50 mg/dL for women); increased blood pressure (systolic blood pressure ≥130mmHg and/or diastolic blood pressure ≥85mmHg); elevated fasting glucose (≥100 mg/dL); pharmacological intervention for any condition above. The National Heart, Lung, and Blood Institute and World Health Organization established these criteria (2, 10). Whether they exist in isolation or together in an individual, MetS components can contribute to maligned WM and cognition.

White Matter Integrity. Investigations of MetS and WM are limited with few assessing cerebral microstructure. Nonetheless, individuals with increasing vascular risk factors showed incrementally reduced FA (185). Separately, a sample of older adults with MetS displayed significantly reduced WM integrity in the frontal lobe bilaterally compared with healthy controls (261). These MetS subjects who had lower FA in anterior regions further displayed poorer performance on executive function speed tasks (260). The anterior to posterior gradient of damaged WM is a recognized pattern in normal aging (158). Because WM damage acquired by individuals with MetS presents in a similar pattern, it may reflect an accelerated aging phenotype.

Cognitive Function. Anterior brain regions are tasked with the performance of executive function. Within the executive function domain are duties essential to the performance of everyday tasks including decision-making, judgment, attention, and problem solving. This functional relationship may explain previous observations of

reduced executive function in older individuals with MetS, as frontal regions may be more vulnerable to vascular insults (36, 46, 252). WM integrity in individuals with MetS has also been associated with hindered performance on recall and memory tests (124, 163, 201). However, these findings are not all in agreement. MetS has been shown to affect different domains of cognitive function. Although results are sometimes inconsistent across gender, some cross-sectional studies showed MetS having no associations with any domain of cognitive function (118, 332). These differential findings may be explained through sampling differences between studies in relation to age, neurocognitive assessment differences, or risk factor exposure duration. Despite these differences, MetS has been associated with impaired verbal memory, fluid intelligence, and psychomotor speed as well as executive function in large and case control cross-sectional studies (46, 59, 259, 303). Longitudinal investigations support these results showing that MetS is related to impaired global cognition, verbal fluency, and psychomotor speed independent of age, sex, and education (161, 328).

Dementia. Decrements of cognition in relation to MetS seem to result in increased risk of dementia. Cross-sectional and prospective studies have found deleterious effects of MetS on cognitive function and increased risk of dementia (59). Investigators have reported increased risk of cognitive impairment, vascular dementia, and Alzheimer's disease in both cross-sectional and longitudinal studies (235, 237, 271, 306). However, one prospective study was unable to find a link between MetS and risk of dementia in the elderly 65 years and older, while another showed a decelerated cognitive decline in elderly adults 85 years and older in relation to MetS (201, 302).

Damage mechanisms. The mechanisms by which MetS components cause damage to the brain have yet to be fully described, but undoubtedly, MetS increases risk for cardiovascular disease and dementia several fold (187, 235). Whether MetS components confer WM damage individually or synergistically remains to be elucidated. Furthermore, individuals with MetS have impaired endothelial function that could limit cerebrovascular reactivity and cerebral activation in relation to memory tasks (87, 100, 172). The pro-inflammatory state that exists with MetS may also exacerbate vascular dysfunction while damaging the BBB (77, 308). What has been shown is MetS contributes to arterial stiffening that leads to cerebral WM damage (248, 255).

Arterial Stiffness

Characteristics and Mechanisms. Arterial stiffness is a hallmark of vascular aging that develops from structural and function changes. Vascular stiffening is non-uniform in the arterial tree affecting central and conduit arteries more than peripheral and muscular arteries (32). Continuously heightened intravascular pressure as seen in hypertension can result in structural remodeling of the blood vessel. This remodeling is characterized by loss of flexible elastin protein and over-production of collagen (327). The mechanical stress of elevated pressure combined with increased inflammatory substances promotes excessive collagen production (149, 327). In addition to these histological changes, the surrounding smooth muscle layer hypertrophies, further contributing to arterial stiffening (310).

Separate from structural alterations, functional changes influence arterial stiffness. Hormones, salt, and glucose regulation among other vasoactive factors can

influence the degree of arterial stiffness (340). Vascular smooth muscle tone can be modified by mechanical influences and endothelial cell signaling via vasoactive substances. In the stiffened artery, endothelial dysfunction is characterized by mismatched reactivity to acetylcholine conferred through disparate nitric oxide (NO), endothelial-derived hyperpolarizing factor, and constrictor hormones (195). The presence of vasoconstrictors angiotensin and endothelin as well as oxidant stress increases fibrosis and vascular smooth muscle cell hypertrophy (340). In contrast, production of NO can reduce macrophage infiltration and help preserve vascular function and arterial elasticity. However, endogenous nitric oxide synthase inhibitor asymmetrical dimethylarginine, reactive oxygen species such as peroxynitrite, and advanced glycosylated end products collectively diminish vascular NO bioavailability (198, 284). Excessive dietary salt intake is also harmful to the vasculature. Vascular smooth muscle tone is heightened in response to salt. Furthermore, salt prompts vascular smooth muscle cell hypertrophy and proliferation of collagen and elastin (107, 218, 243). Lastly, sodium increases asymmetrical dimethylarginine thereby impeding NO production and impairing endothelial function (22).

The causal directionality between arterial stiffening and endothelial dysfunction has not been established, as both often coexist. Rather, the two may negatively influence each other cyclically. Major conduit arteries such as the aorta and carotid arteries are most subjected to stiffening, resulting in impaired ability to buffer pulsatile flow from the heart (95, 340). Loss of this function results in the transfer of pulsatility to resistance vessels less capable of accommodating pulsatile stress. Arterial stiffening is observed in many disease states, including aging, hypertension, diabetes, and MetS (89, 107, 248, 337).

Influence of Sympathetic Nerve Activity. Sympathetic nerve activity (SNA) is associated with total peripheral resistance and is an indicator of vasoconstrictor tone (50). SNA serves an integrative role in the regulation of blood pressure, heart function, and arterial stiffness through direct and indirect mechanisms. Arterial baroreceptors are charged with detecting acute changes in blood pressure. In the event of hypotension or unloading of these receptors, the arterial baroreceptors signal the nucleus tractus solitarius that communicates with the rostral ventrolateral medulla (RVLM) to increase SNA and restore adequate pressure. This is accomplished through the release of acetylcholine that prompts secretion of neurotransmitters norepinephrine, epinephrine and isoprenaline from neurons and the adrenal medulla, that have a number of actions dependent on receptor type and location. At the heart, β_1 receptors increase heart rate and left ventricular contractility that results in increased stroke volume and together increase cardiac output (343). At the vasculature, binding of norepinephrine and epinephrine at α_1 receptors leads to increased intracellular calcium that promotes vasoconstriction from contraction of smooth muscle cells and increased vascular tone (226). Altogether, activation of this sympathetic network can cause acute increases in arterial stiffness (217). If chronically activated, the arterial baroreflex can become reset to a greater set point that is linked to greater SNA leading to hypertension and arterial stiffening (49). Although, the causal direction of these events has not been fully elucidated.

SNA and arterial stiffness can be further induced via the renin angiotensin aldosterone system (RAAS). Principally, the RAAS is designed to ensure appropriate perfusion pressure to the kidneys so that blood can be adequately filtered of toxins. When flow decreases to the glomerulus, juxtaglomerular cells release renin that

converts angiotensinogen to angiotensin 1 which is then converted to angiotensin 2 by angiotensin converting enzyme. Angiotensin 2 has numerous effects on the vasculature. Specifically, angiotensin 2 increases SNA, absorption of sodium that allows for water retention, and signals aldosterone secretion from the adrenal glands that furthers sodium reabsorption (222). Additionally, angiotensin 2 prompts secretion of antidiuretic hormone form the pituitary gland to aid in water retention. Each of these angiotensin 2 actions aid in the restoration of necessary perfusion pressure to the kidneys. However, dysregulation of this system could result in chronically elevated SNA, hypertension, and corresponding vascular stiffening.

Cardiovascular risk factors have also been associated with overactive SNA. In individuals with essential hypertension, muscle SNA is elevated to a degree corresponding with severity (331). While this elevation may come about through chronic excess sodium intake or resetting of the arterial baroreflex, individuals with hypertension tend to exhibit a heightened sensitivity to hypoxia and carbon dioxide resulting in an overactive chemoreflex (272). Overactive SNA can be further exacerbated by excessive adipose tissue that can secondarily perpetuate hypertension. Obese individuals with excess adipose tissue exhibit SNA over activation that is directly associated with visceral adipose tissue (14). Mechanistically, this may exist because neurotransmitters associated with SNA such as isoprenaline, norepinephrine and epinephrine can act on β_3 receptors located on brown adipose tissue that increase lipolysis and thermogenesis via increases in cyclic adenosine monophosphate (215). Although this mechanism aims to reduce excess fat, the corresponding increase in SNA likely also increases the tone of the vascular smooth muscle making obese individuals more susceptible to the development of hypertension. Chronically elevated

blood pressure in turn can prompt remodeling of the vascular scaffolding proteins characterized by greater collagen and reduced elastin expression that is commonly observed in the pathogenesis of arterial stiffening. On top of obesity and hypertension, hyperinsulinemia potentially leads to elevated SNA. Indeed, individuals who are insulin resistant demonstrate elevated resting heart rate and SNA when compared with healthy controls (16, 84).

Sex Differences. Sympathetic control of blood pressure appears to diverge between men and women. In healthy young men and women, SNA was unrelated to mean arterial pressure (122). The absence of this relationship highlights the high level of interindividual variability of SNA as well as the fact that there are myriad inputs governing blood pressure control. Young men and women display differences in the relationship of SNA and cardiac output in that the relationship was absent in young women, while SNA was significantly inversely associated with stroke volume in young men (122). Women also have shown greater increases in heart rate with a lesser change in total peripheral resistance compared with men when taxed with an orthostatic challenge (71, 91). This finding suggests sex differences in baroreflex sensitivity. This divergence in physiological response to blood pressure challenges may be explained by differences in catecholamine production between sexes. In rats, estrogen may have an attenuating effect on catecholamine production, however, sex differences in catecholamine production and responses in humans remain equivocal (83, 343).

Estrogen in premenopausal women has significant effects on the vasculature and consequently SNA control of blood pressure. Estrogen stimulates the release of vasoactive molecules such as nitric oxide that potentiate vasorelaxation as evidenced by increased endothelium-dependent vasodilation (204). Estrogen likely also

influences vascular tone through effecting calcium channels either through attenuated release, influx or increased efflux of calcium (321). Interactions with high-density lipoprotein that lead to reduced oxidation of low-density lipoprotein demonstrate estrogen's potential anti-oxidant and anti-inflammatory properties (321). This combination of effects on the vasculature can mitigate atherosclerosis and consequently arteriosclerosis with aging.

With age, both men and women experience increased SNA. When compared with young men, premenopausal women tend to have reduced SNA until after menopause, when estrogen is significantly attenuated, SNA sharply increases (192). Differences in SNA are important to investigations of arterial stiffening as it has recently been associated with carotid arterial compliance in young and old men (287). It is possible that this relationship is absent in young women due to the presence of estrogen and may begin post menopause, however, this has never been investigated.

Assessment. Assessing the stiffness of arteries can be accomplished in many ways depending on the blood vessel being measured. In relation to cardiovascular disease, arterial stiffness of major central blood vessels is indicative of coronary heart disease and stroke (193). This relationship is demonstrated in the assessment of aortic stiffness with carotid to femoral pulse wave velocity (cfPWV). With this method, applanation tonometery of the carotid and femoral arteries can track the transit time of the forward traveling pulse wave between the two sites. The straight distance between the two sites when divided by the transit time from foot to foot of the wave form calculates the rate of the pulse wave, which is indicative of the stiffness of the blood vessel (239).

Because of the high cost of arterial tonometers necessary to measure cfPWV, a more simple measure involving only the inflation and deflation of blood pressure cuffs at the four extremities was developed. With this method, brachial-ankle pulse wave velocity (baPWV) can be determined; yielding qualitatively similar information as cfPWV that also includes the periphery in its determination of arterial stiffness (281). Although neither cfPWV nor baPWV has been identified as a significant predictor of dementia, they are both significantly associated with cognitive impairment, WMH, cerebral microbleeds, and cerebral infarcts in middle-aged and older cohorts (305). Additionally, pulse wave velocity is related to increased amyloid-beta deposition in the brain in the very elderly, suggesting that the two may be related in the development of dementia (136).

Compared with the central aorta, the carotid artery is closer to the cerebral circulation, providing blood flow to the middle cerebral arteries. Measurement of the stiffening of the carotid artery is accomplished with the coupling of B-mode ultrasound and arterial tonometry. When paired together, indices of arterial elasticity and stiffness can be calculated. Carotid artery compliance (CAC) is calculated as the absolute change in vessel diameter for a given pressure step. Distensibility is the relative change in vessel diameter for a given pressure step. Because these indices are heavily related to blood pressure, beta-stiffness index is often calculated to correct for distending pressure (209). Together, these previously discussed methods serve as comprehensive markers of arterial stiffness for major blood vessels.

Metabolic Syndrome. MetS components each insidiously affect arterial stiffness. As mentioned above, excessive adiposity is highly associated with increased inflammation that is damaging to the endothelium and NO production. Individuals

with heightened adiposity could also have elevated circulating triglycerides or reduced presence of anti-atherogenic molecule high-density lipoprotein (HDL). Reduced HDL is independently associated with increased aortic PWV (240). MetS is correlated with stiffening of the vasculature, and it is likely that central adiposity and elevated blood pressure are key contributors to this relation (70). Specifically, abdominal obesity measured through waist circumference or visceral adiposity as measured through DEXA is significantly related to cfPWV and baPWV (280). General adiposity, often characterized by BMI, is not related to aortic stiffness at midlife (248). It appears that MetS accelerates the age-associated increase in arterial stiffening throughout the lifespan (254). This finding is concerning considering dementia is an age-related disease exacerbated by arterial stiffening. Taken together, these notions suggest that MetS could raise the risk of dementia through an arterial stiffening mechanism.

Neural Consequences. Arterial stiffening regardless of etiology has marked effects on brain structure and cognitive function. Further, transmission of pulsatile forces from stiffened proximal central blood vessels elicits damage to cerebral microvessels ill equipped to handle pulsatile stress (197). Additionally, loss of Windkessel function, the ability of vessels to cushion pulsatility from the heart, as a result of arterial stiffening can disrupt consistent perfusion to end organs, including the heart and brain (31). The chronic mechanical stress of elevated pulsatile flow prompts structural changes in cerebral arterioles in an attempt to protect vulnerable cerebral capillaries.

From a structural perspective, smooth muscle hypertrophy often observed with arterial stiffening occurs at the expense of the vessel lumen diameter (144). Consequently, greater vascular resistance and reduced cerebral blood flow can occur (38). Compounding the detrimental effects of increased resistance, these structural

adaptations impair cerebral arteriole endothelial function, thus partially impairing functional hyperemia (27). The protrusion of pulse pressure into cerebral arterioles can damage the blood brain barrier, leading to a cyclic inflammatory cascade (196, 208). The cumulative effects of arterial stiffening damage the grey and white matter parenchyma through attenuated perfusion. Demonstrating this oligemic effect are associations of arterial stiffness with reduced deep subcortical grey and WM perfusion (289, 290).

White Matter. Reduced cerebral perfusion suggests a possible mechanistic explanation for the 13 cross-sectional investigations highlighted in a review observing the associations between arterial stiffness measures and WMH or lacunar infarctions (264). All but four of these investigations were in older populations. Only two longitudinal studies assessed the relationship between arterial stiffness and WMH tracking individuals at midlife for 7 years and older adults for 10 years (159, 241). Both studies identified arterial stiffness as an independent predictor of WMH volume. Pulsatility corresponding with arterial stiffness is further associated with lower whole brain, grey matter, and WM volumes (197).

Despite these results, probes of the relationship between arterial stiffening and WM integrity, particularly at midlife, are remarkably few. In healthy older adults and those with mild cognitive impairment, arterial stiffness is associated with reduced global FA (288). An epidemiological study supporting this finding observed reduced FA in the corpus callosum and increased arterial stiffness in a middle-aged community sample (186). The paucity of research in middle-aged cohorts needs correction as DTI indices of WM integrity can reveal early damage to the cerebral WM in relation to cardiovascular targets.

In relation to cognition, arterial stiffening exerts a consistently negative effect on executive function. In a prospective study of older adults, arterial stiffness was significantly associated with poorer performance on an executive function task (228). Cross-sectional investigations of middle-aged and older adults support this finding (78, 289). Memory, global cognition, and other cognitive tasks are also negatively affected by arterial stiffening in older adult and elderly cohorts (257, 258, 297, 318). Despite these associations, the link of arterial stiffness to cognitive decline and dementia has yet to be examined prospectively (228). Nonetheless, cross-sectional and longitudinal evidence asserts a robust relationship between arterial stiffening with brain structure and cognitive function. Less precisely defined, is this relationship at midlife. Observing more sensitive measures of early changes to the WM and an intensive cognitive battery in relation to stiffening of the carotid artery may bring to light the early deleterious nature of arterial stiffness. The carotid artery is of particular interest because it is closer to the cerebral circulation than the aorta and is often the subject of arterial stiffening.

Physical Activity

VASCULAR RISK FACTORS

The effects of physical activity, in particular aerobic exercise, on cardiovascular risk factors and arterial stiffness are well documented. Chronic aerobic exercise is a valuable strategy to attenuate vascular risk factors. Aside from reducing caloric intake to achieve caloric deficit, physical activity is an efficacious intervention to lose adipose weight (73). In a large cross-sectional study of middle-aged men, physical activity performed commuting to employment and practicing high-intensity

recreational activities was negatively associated with BMI, waist circumference, and body weight (315). Reduced adiposity through physical activity may reduce corresponding low chronic inflammation in parallel. Indeed, men and women aged 40 and older who frequently perform physical activity have significantly lower markers of c-reactive protein, white blood cell count, and fibrinogen (5). In older Chinese adults, total physical activity was associated with reduced C-reactive protein levels and odds of acquiring MetS (335). In this same study, quartiles of inflammatory profile and adipocytokine z-scores are also related to increased odds of MetS regardless of physical activity tertile. Taken together, these data suggest that physical activity can improve adiposity, inflammation.

Aerobic exercise, defined as physical activity intentionally performed for health benefits through elevated heart rate and oxygen consumption, positively affects components of MetS beyond adiposity. In a cohort of 30-40 year old men and women with reduced HDL and high triglycerides, an aerobic exercise intervention for 20-weeks with increasing duration and/or intensity caused a significant increase in HDL, reduction in triglycerides, and an overall decrease in total cholesterol (58). Systolic and diastolic blood pressure also reduced following dynamic exercise training of at least 4-weeks. A meta-analysis of 14 studies showed a 3 and 2 mmHg reduction of systolic and diastolic pressure, respectively, in normotensive adults; whereas individuals with hypertension exhibited greater reductions of 7 and 6 mmHg (79). Lastly, physical activity is related to insulin sensitivity. This relation was demonstrated in a cross-sectional study of men and women aged 30-60 years that found total physical activity time was significantly associated with insulin sensitivity (23). Simply performing 2.5 hours of walking per week was related to a 60-70% reduced risk of acquiring diabetes

after an average four years of follow-up in middle-aged adults (168). The cumulative effects of physical activity on MetS components appear largely positive. Chronic physical activity and aerobic exercise can also ameliorate arterial stiffening associated with metabolic components.

ARTERIAL STIFFNESS

In general, performance of physical activity for health purposes is affordable, easily accessible, and safe for middle-aged and older adults who need to ameliorate arterial stiffening. Physical activity and chronic aerobic exercise are well-documented robust lifestyle interventions capable of improving arterial stiffness irrespective of age or sex (151, 285, 286). This relationship has been demonstrated across a number of indices of arterial stiffening. These same interventions can ameliorate components of MetS related to the stiffening of arteries (58, 79, 176, 177, 280). Beneficial vascular adaptations to chronic aerobic exercise, and ostensibly moderate to vigorous physical activity, are accomplished through a combination of structural and functional changes. In stiffened vessels, where collagen is overexpressed and elastin is diminished, the cross-linking of stiff collagen fibers may be stretched leading to greater overall vessel flexibility. Functionally, chronic shear stress caused by physical activity and exercise can stimulate the production of vasoactive factors such as nitric oxide. Using different macro- and microvascular function assessments, including flow-mediated dilation, acetylcholine infusion, and others, endothelial dependent vasodilation tends to be improved following exercise interventions (103). Increased NO bioavailability in the central blood vessels could lead to reduced arterial stiffening. Reductions in inflammation and reactive oxygen species from up-regulated superoxide dismutase

occur with chronic physical activity (92). These changes lead to decreased scavenging of NO. These vascular adaptions to physical activity are valuable from a clinical perspective as physical activity and aerobic exercise may be used to combat neurocognitive disease of vascular etiology. To date, an insufficient number of studies have examined the role of physical activity behavior in improving both arterial stiffness and brain structure, specifically the WM.

WHITE MATTER INTEGRITY

Current research supports the view that physical activity positively affects the cerebral white matter. The observed white matter benefits of physical activity could be crucial in the avoidance of unhealthy cognitive aging. While physical activity may not impact global WMI, positive associations between regional white matter regions have been observed cross-sectionally. In young and old adults, estimations of aerobic fitness showed significant associations with the cingulum and uncinate fasciculus independent of age or sex (191). The same investigators observed peak oxygen consumption to be moderately related to increasing FA in the left middle cingulum (190). Additionally, two separate large cross-sectional cohorts of older adults demonstrated self-reported physical activity to be related to WMI in a multitude of white matter regions (98, 102). Intervention studies support these findings. A progressive 6-month aerobic exercise intervention was compared with a stretching control group investigating white and grey matter volumes in cognitively normal older men and women. After the intervention, white and grey matter volumes increased in frontal and temporal cortices (55). Separately, a one-year walking intervention was capable of improving both aerobic fitness and WMI. Here, changes in aerobic fitness were significantly

associated with changes in frontal, parietal, temporal, and occipital white matter FA (313). Changes in aerobic fitness were also related to improved short-term memory in the walking group. Using fitness to support WMI is a valuable strategy to preserve cognitive function, as age-related decrements in decision related task performance are mediated by changes in WMI (184). Considering deterioration of cerebral white matter exists with aging and is accelerated in dementias, its preservation through physical activity could be an integral strategy to prolonging healthy cognitive function.

COGNITIVE FUNCTION

Consistent with structural improvements in the brain stemming from physical activity, similar benefits are observed in cognitive function. Impairments in executive function are most often related to aging and vascular dementia. Aerobic exercise interventions and the chronic performance of moderate-vigorous physical activity can impact multiple domains of cognition, but executive function appears most affected. Cross-sectional evidence from 24-76 year olds, showed that aerobic fitness was significantly associated with executive function tasks after accounting for age, sex, and intelligence (301). Prospectively, baseline cardiorespiratory fitness is significantly associated with protection of global cognitive function, attention, and executive function, as well as memory and verbal fluency (25). Exercise intervention studies support this observation. In older adults aged 55-70 years, four-months of aerobic exercise training resulted in improved performance on a number of neuropsychological tests, including significantly improved executive function and reaction time among others (75). Additionally, sedentary older adults exposed to a one-year aerobic exercise-training program were more resistant to decreases in cognitive performance

on a logical memory subtest than those who remained sedentary (132). This evidence demonstrates the importance of maintaining or developing aerobic fitness for cognitive benefits.

In relation to risk of dementia, physical activity seems to offer a strong protective effect. Time and again, prospective evidence of elderly individuals (>65 years) yields significant associations between physical activity and reduced risk of cognitive decline. These findings are consistent with performance of either moderate or vigorous physical activity (270). With respect to frequency, three exercise sessions or more every week resulted in a significantly lower hazard ratio of developing incident dementia compared with inactive participants during follow-up after controlling for age and sex (169). Finally, a 5-year longitudinal study showed a dose-response relationship with levels of physical activity and protection from developing Alzheimer's disease among women (170). These intervention and observational evidences demonstrate that performing physical activity and improving aerobic fitness are viable strategies to prevent cognitive decline and prevent dementia.

While these studies encourage the use of physical activity and aerobic exercise to prevent further cognitive decline and development of dementia, the efficacy of PA to improve cognition in individuals already exhibiting signs of cognitive impairment must be considered. An excellent synthesis of this work was performed and analyzed the effects of different exercise modes on physical and cognitive function in subjects 65 years or older with baseline Mini-Mental Status Examination scores of less than 26 (130). This meta-analysis revealed that exercise interventions of aerobic training, resistance training, or stretching had significant medium-large effect sizes on physical fitness outcomes, as well as cognitive outcomes. This study asserts that

despite already being cognitively impaired, older adults can participate in regular physical activity and improve diminished cognitive function.

MECHANISMS

How physical activity benefits successful cognitive aging remains to be fully understood. However, there are a number of potential mechanisms explaining the therapeutic and disease preventing properties of physical activity. With exercise, a number of neurobiological adaptations in the brain occur. Animal studies suggest that aerobic exercise in aged rats leads to proliferation of neurons in the dentate gyrus, increased mRNA expression for excitatory neurotransmitter receptor *N*-methyl-D-aspartate in the dentate, and up-regulated brain derived neurotropic factor mRNA levels in the hippocampus (81, 93, 304). Insulin-like growth factor-1 (IGF-1), a molecule critical for neurogenesis and mediating neuronal activity, levels is amplified with chronic exercise (45, 296). The neural effects of IGF-1 may also explain why greater effect sizes were observed in studies examining combined strength and aerobic exercise interventions in relation cognitive function (54). Increased vascular endothelial growth factor (VEGF) has also been seen with exercise in old rats (72). VEGF is a critical molecule involved in angiogenesis. In this context, aerobic exercise may up-regulate VEGF concentration to form new vessels and increase blood flow to meet the added metabolic demands associated with the formation of new parenchyma. However, in humans, the response of VEGF to exercise following acute and chronic training in older adults (>60 years) is still controversial (312).

The aforementioned physiological changes in response to exercise of elevated neurotrophins, synaptogenesis, and angiogenesis to support neural proliferation result

in functional improvements related to cognitive function. Evidence from cross-sectional and randomized controlled studies shows support for the argument that chronic exercise leads to greater functional cerebral activation during cognitive tasks with fMRI (54, 164). Specifically, older adults with greater aerobic fitness showed significantly greater activation in the right middle frontal gyrus, superior frontal gyrus, superior parietal lobule and less activation in the anterior cingulate cortex while performing an executive function task (56). These results were essentially replicated with a 6-month aerobic intervention study in older adults where participants significantly increased activation in the right middle frontal gyrus, superior frontal gyrus, superior parietal lobule and less activation in the anterior cingulate cortex while performing a flanker task (56). The mechanisms assisting functional hyperemia are many and compensatory (140). However, greater activation could be the result of increased blood flow or flow velocity as a byproduct of exercise. Cross-sectional evidence has shown that individuals with greater aerobic fitness have greater cerebral blood flow velocity at any age (7). Alternatively, improved vascular function and reduced arterial stiffening could improve delivery of blood to the brain to better meet the metabolic demands of the cognitive task. With either explanation, a larger hemodynamic response could result.

SUMMARY

Dementia is a significant and costly public health problem that is projected to worsen over the coming decades.Cognitive function is a critical factor for quality of life and functional ability with aging, but it begins to decline as early as the second decade of life (245). Therefore, exhaustive research must be performed to curb its rise

(94, 245). Without effective pharmaceutical interventions to halt dementia progression, restore lost parenchyma function, or rebuild atrophied cortex, developing evidence based primary prevention strategies is a critical task for the scientific community.

The two most common forms of dementia, Alzheimer's disease and vascular dementia, appear to have a common vascular mechanism characterized by chronically reduced cerebral perfusion. Vessels that are normally distensible become increasingly stiff with aging and exposure to metabolic syndrome components and cardiovascular disease risk factors lead to the loss of Windkessel function and transference of dangerous pulsatile forces to vulnerable cerebral microvasculature. Interruptions of critical nutrients to metabolically demanding parenchyma may lead to oligemia and eventual loss of function in cortices and the white matter circuitry that connects them. Alterations of the cerebral white matter are considered to be early events in AD pathogenesis and a discrete characteristic of AD (175, 242). Although considerable work regarding exercise, cerebral white matter, and cognitive function has been performed, their integration with arterial stiffness in midlife as an incipient event remains unclear.

Physical activity, in many ways, is the closest intervention to a panacea that exists in the prevention and treatment of cardiovascular diseases and dementia. Known agitators to vascular health, adiposity, hypertension, dyslipidemia, and dysglycemia can all be assuaged by moving from a sedentary to a more active lifestyle. Arterial stiffening can also be improved with physical activity. Perhaps most importantly, individuals with greater aerobic fitness have greater cerebral blood flow velocity at any age (7). Together, these attributes identify physical activity and improvements to arterial stiffness as critical intervention tools for individuals in

midlife afflicted with cerebrovascular risk factors who are more likely to acquire dementia.

APPENDIX A: DEFINITION OF TERMS

Adipose tissue: fat cells that primarily store energy and have endocrine like properties

Alzheimer's disease: a dementia subtype characterized functionally by impaired communication, poor judgment, memory loss, and pathophysiologically by medial temoral lobe degeneration, accumulated beta-amyloid plaques, and tau tangles in neurons.

Arterial compliance: the absolute change in arterial volume for a given increment in pressure.

Arterial distensibility: the relative change in arterial volume for a given increment in pressure.

Arterial stiffness: hardening of artery walls that reduces the capability of vessels to buffer pulsatile blood flow ejected from the heart to deliver smooth continuous blood flow to end organs as the result of structural and functional changes.

β-stiffness: an arterial stiffness measure independent of the effect of distending blood pressure.

Blood brain barrier: a physiological mechanism that functionally preserves a selective permeable neurovascular unit, comprised of vascular cells such as endothelium and pericytes, glial cells, and neurons.

Cognitive function: mental processes that construct our thinking often deconstructed into domains consisting of attention, memory, language, problem solving, decision making and others that are evaluated with paper-based tests or tasks designed to challenge specific domains.

Dementia: a major neurocognitive disorder that interferes with cognitive function and activities of daily living.

Fractional anisotropy: *in vivo* measurement of water diffusion through diffusion tensor imaging representing directional parallelism of water diffusion in parenchyma with greater values representing greater tissue integrity.

Mean diffusivity: *in vivo* measurement of water diffusion through diffusion tensor imaging representing the magnitude of water diffusion in parenchyma reflective tissue with greater values representing poorer tissue integrity.

Metabolic syndrome: a cluster of three risk factors that include abdominal obesity, dyslipidemia, elevated blood pressure, and hyperglycemia occurring in a single individual.

Middle-age: chronological age of 40-60 years.

Physical activity: a behavior defined by skeletal muscle movement resulting in energy expenditure.

Sedentary: activities that result in a metabolic expenditure below 1.5 metabolic equivalent or negligible energy expenditure often involving non-upright activities.

Vascular dementia: a dementia subtype characterized by impaired judgment or executive function often with co-occurrence of gait instability. Vascular dementia is characterized by cerebral infarcts of ischemic or vascular etiology.

White matter hyperintensities: lesions appearing on T2-weighted MR images as bright spots often the result of multiple diseases but are a common feature of vascular cognitive impairment. These lesions are reflective of rarefication of white matter and are associated with axonal loss, demyelination, microvascular arteriosclerosis, and endothelial dysfunction.

White matter integrity: the structural status of white matter tracts described by diffusion tensor imaging metrics characterizing the diffusion of water molecules *in vivo*.

Windkessel: the ability of the vasculature to buffer and cushion pulsatile forces that accompany each heartbeat and convert them into smooth continuous blood flow.

APPENDIX B: QUESTIONNAIRES, NEUROPSYCHOLOGICAL ASSESSMENTS, AND SUPPLEMENTARY INFORMATION

(See supplemental documentation)

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