AORTIC STIFFNESS, WHITE MATTER INTEGRITY AND DEPRESSIVE SYMPTOMS AMONG OLDER ADULTS

Jingkai Wei

A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology in the Gillings School of Global Public Health.

Chapel Hill
2019

Approved by:

Allison E. Aiello

Gerardo Heiss

Anna Kucharska-Newton

Michelle L. Meyer

Priya Palta

Brian W. Pence

ABSTRACT

Jingkai Wei: Aortic Stiffness, White Matter Integrity and Depressive Symptoms among Older Adults
(Under the direction of Gerardo Heiss)

Background: Aortic stiffness is a hallmark of aging and is associated with neurocognitive outcomes among older adults. Late-life depression, often associated with structural damage in cerebral white matter integrity, is an important public health burden. This doctoral research examined the associations of aortic stiffness with white matter microstructural integrity and depressive symptoms among older adults.

Methods: Data from the 5th and 6th examinations of the Atherosclerosis Risk in Communities cohort (2011-2013, 2016-2018) were analyzed. A total of 1,484 participants (aged 67 to 90 years) were included in the analysis of aortic stiffness and white matter microstructural integrity, and 4,511 participants (aged 66 to 90 years) were included in the analysis on aortic stiffness and depressive symptoms. Aortic stiffness was measured as carotid-femoral pulse wave velocity (cfPWV). Cerebral white matter microstructural integrity was measured as fractional anisotropy (FA) and mean diffusivity (MD) using diffusion tensor imaging. Depressive symptoms were assessed using the 11-item Centers for Epidemiologic Studies-Depression (CES-D) Scale. A CES-D score ≥9 was considered indicative of clinically significant depressive symptoms (CSDS).

Results: Relating aortic stiffness and white matter microstructural integrity, each 1 m/s increment in cfPWV was associated with lower overall FA (β=-0.03, 95% confidence interval

(CI): -0.05, -0.02) and higher overall MD (β=0.03, 95% CI: 0.02, 0.04). Elevated cfPWV (upper 25thpercentile) was associated with lower FA (β=-0.26, 95% CI: -0.39, -0.14) and higher overall MD (β=0.21, 95% CI: 0.11, 0.32). Similar associations were observed at individual cerebral regions of interest. In cross-sectional analyses of aortic stiffness and depressive symptoms we observed a positive association of elevated cfPWV with the greater CES-D score (standardized beta (β)=0.07, 95% CI: 0.004, 0.15) and greater odds of CSDS (odds ratio (OR)=1.37, 95% CI: 1.01, 1.85). No association was observed between baseline cfPWV and temporal change in depressive symptoms or incident CSDS.

Conclusions: These results add to the evidence suggesting that aortic stiffness may serve as a modifiable target for the prevention of poor cerebral white matter microstructural integrity. Given the limited evidence, the longitudinal association between aortic stiffness and depressive symptoms among older adults warrants further investigation.

ACKNOWLEDGEMENTS

It has been my great honor to have had tremendous help, support, and love during my time in the PhD program at UNC. This helped me overcome the difficulties along my journey.

I am thankful for my PhD advisor, Dr. Gerardo Heiss, whose support and dedication is unparalleled. During these four years I have been inspired by his rigor in research and his personality, that strengthen my determination to be an epidemiologist dedicated to improving population health.

Dr. Priya Palta skillfully guided me through different research projects and helped me accumulate valuable experience since the start of my PhD life at UNC. I have greatly benefitted from her timely response and feedback on my research.

Drs. Anna Kucharska-Newton and Michelle Meyer have provided me with outstanding support and help in all my research projects, and I learned a lot from them.

I am very grateful to Drs. Brian Pence and Allison Aiello for being part of my dissertation committee and for providing valuable feedback throughout the process of completing my dissertation work.

My thanks also to the staff in the EPID department of UNC Chapel Hill, particularly Valerie Hudock, and Jennifer Moore, for their great help throughout these years. Thanks also to the colleagues and friends that I met during these four years, whose encouragement have spiritually supported me.

Finally, special thanks to my family who helped me throughout my life and during my PhD studies. They sacrificed a lot for me. Thank you for being so understanding.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ARIC	Atherosclerosis Risk in Communities
CES-D	Center for Epidemiologic Studies Depression Scale
cfPWV	carotid-femoral pulse wave velocity
CI	confidence interval
CSDS	clinically significant depressive symptoms
CSVD	cerebral small vessel disease
DTI	diffusion tensor imaging
FA	fractional anisotropy
MD	mean diffusivity
MRI	Magnetic resonance imaging
OR	odds ratio
ROI	regions of interest
WMH	white matter hyperintensities

CHAPTER I. INTRODUCTION

Late-life depression, defined as a major depressive episode taking place in older adulthood (65 year or older) is a significant public health issue. The existing literature suggests that cardiovascular risk factors play an important role in the development of late-life depression, and the “vascular depression”, which claims that cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes.[1] The hypothesis is supported by the evidence that white matter hyperintensities (WMHs), manifestation of CSVD are shown on magnetic resonance imaging (MRI) tool older adults with depression. While WMHs have been used as a biomarker to detect pathology of white matter, it may only reflect the tip of the iceberg, since previously reported correlations between clinical features of CSVD and WMHs are not consistent. The diffusion tensor imaging (DTI) is considered a more sensitive tool to detect microstructural pathological changes of white matter, since it detects disruption of white matter integrity both within WMHs and in normal-appearing white matter.

Arterial stiffness increases pulsatility, which damages microvascular circulation, resulting in poor vasoreactivity and cerebral hypoperfusion that leads to cerebral small vessel disease manifested as WMHs. Carotid-femoral pulse wave velocity (cfPWV) is considered the gold standard measure of aortic stiffness. Previous studies have shown that higher levels of arterial stiffness are associated with cerebral small vessel disease, while only a few studies have examined associations of white matter outcomes measured with DTI. Among the latter, the results have been inconsistent, and moststudies were based on small study samples with

comorbidities. Although studies suggest that cfPWV is associated with lower fractional anisotropy, an index of white matter microstructural integrity, the associations between cfPWV and mean diffusivity (MD), another important index of white matter microstructural integrity, remains unknown. Additionally, the degree to which WMHs account for the associations between cfPWV and DTI measures needs to be further examined.

Only a few studies have examined the association between arterial stiffness and depressive symptoms among older adults. Conflicting results have been reported on the association between aortic stiffness and late-life depression, and all the extant studies used a cross-sectional design, which is subject to the possibility of reverse causality, since depression may lead to unhealthy lifestyle and finally cause aortic stiffening among older adults. It is therefore desirable that the associations between aortic stiffness and late-life depression be examined in a longitudinal study.

The proposed dissertation research will be based on the Atherosclerosis Risk in Communities Neurocognitive (ARIC) Study, which started in 1987 with 15,792 men and women aged 45 to 66 years at baseline in four U.S. communities. Information will be mainly derived from the 5th (2011-2013) and 6th visit (2016-2018) of the ARIC study. Taking the advantage of the measurement of aortic stiffness (cfPWV), white matter microstructural integrity (using DTI), as well as repeated assessment of depressive symptoms, the study will examine the cross-sectional association of aortic stiffness with DTI measures, as well as both cross-sectional and longitudinal associations of aortic stiffness with depressive symptoms.

CHAPTER II. SPECIFIC AIMS

The goals of the dissertation were to: 1) determine the cross-sectional relationship of aortic stiffness with white matter integrity among in older adults; 2) determine the relationship of aortic stiffness with depressive symptoms in older adults.

Specific Aim 1

Aim 1: Determine the cross-sectional relationship of aortic stiffness with white matter microstructural integrity in older adults.

- **Aim 1.1:** Determine the cross-sectional association of aortic stiffness (i.e. carotid-femoral pulse wave velocity [cfPWV]) with white matter integrity (i.e. fractional anisotropy [FA]], mean diffusivity [MD]) among older adults.

Specific Aim 2

Aim 2: Determine the relationship of aortic stiffness with depressive symptoms among older adults.

- **Aim 2.1:** Determine the cross-sectional association of aortic stiffness (i.e. cfPWV) with depressive symptoms and odds of clinically significant depressive symptoms among older adults.
- **Aim 2.2:** Determine the association of baseline aortic stiffness (i.e. cfPWV) with the 5-year risk of clinically significant depressive symptoms among older adults.
- **Aim 2.3**: Determine the association of baseline aortic stiffness (i.e. cfPWV) with 5-year change in depressive symptoms among older adults.

CHAPTER III. BACKGROUND AND RATIONALE

3.1. Aortic stiffness

3.1.1. Structure and function of normal arterial system

In general, there are two major functions of the arterial system, which are correlated. One of these is the delivery of blood from the heart to peripheral tissues, in a way that is responsive to metabolic needs. This is known as the conduit function. The second function of the normal arterial system is to dampen blood flow and pressure oscillations, providing a steady perfusion of the peripheral tissues and organs.[2]

The arterial wall is made up of three layers from inside to outside of the arterial lumen: the intima (endothelial cells), the media (smooth muscle cells and extracellular matrix) and adventitia.[3] The extracellular matrix is mainly composed of collagen and elastin, which jointly maintain the structural integrity and elasticity of the vessel.[4] The structure of artery walls varies by the location of arteries---from aorta to peripheral arteries, the amount of elastic fibers declines and that of muscular components increases as the lumen dimension is reducing.[5] The muscle cell layers make up of a greater proportion in the heart-distal arteries.[6] Therefore, the arterial system can be divided into two parts, based on the structures---the large elastic arteries (e.g., aorta and carotid vessels) and muscular arteries (e.g., peripheral and femoral vessels).[7]

The extracellular matrix of vessels serves for a variety of functions.[6] The resilience and compliance of the vascular wall are often indicated by collagen and elastin,[8] which are the major components of extracellular matrix. Elastin contributes to elasticity and resilience allowing the pulsatile mechanic stretching of the vessels. Collagen, in contrast, provides the tensile

strength of the vessel wall. The normal function of the vessels relies on a balance between the production and degradation of collagen and elastin. As arterial walls are stretched, compliance and distensibility decrease and the incremental elastic modulus shifts from muscle and elastin loading to elastin and collagen loading.[9]

The cellular components of the arterial wall are also important to the regulation of hemodynamics. The balance between structural and cellular components of the arterial wall can be affected by pathologic conditions (e.g., hypertension, diabetes, etc.) and progress to arterial stiffness.[10]

3.1.2. Arterial stiffness

Arterial stiffness indicates "the relationship between change in pressure and change in volume".[11] The functional effects of arterial stiffness include both changes in mechanical behaviors and effects due to geometric changes and tension of arterial properties, defined as fractional deformation (referred to as "strain") due to an applied force per unit area (referred to as "stress").[12] The stiffness of an artery is described as elasticity, defined as the ratio of uniaxial stress to uniaxial strain.[12] Arterial stiffness of the aorta, known as aortic or central stiffness, is of major interest, since the aorta contributes the most to arterial buffering function, and aortic stiffness has been found to be associated with health outcomes.[13]

Arterial stiffness typically involves degenerative processes that affect the extracellular matrix of elastic arteries associated with aging.[14] Arterial stiffness is developed due to the loss of balance between synthesis and degradation of collagen and elastin.[7] The extracellular matrix of arterial walls, which consists of collagen, elastin, glycoproteins and proteoglycans is degraded by catabolic metalloproteases producing damaged collagen and elastin.[7] Advanced glycation end-products (AGEs), formed by nonenzymatic protein glycation, also plays a role as it forms

irreversible cross-links.[8] Endothelial mechanisms may contribute to arterial stiffness, as endothelial dysfunction leads to the reduced bioavailability of vaso-relaxing factors.[15]

While arterial stiffness is characterized by the physical properties of vessels, non-invasive methods are therefore applied to measure arterial stiffness in vivo. Among the various arterial stiffness measurement methods, pulse wave velocity (PWV) is considered the most simple, robust and reproducible measure of stiffness along an arterial section.[13] The concept of PWV is based on the property that the speed of a pressure wave depends on the geometric and elastic properties of arterial wall when generated by ventricular ejection and propagated along the arterial tree.[11] PWV is calculated as the velocity (m/s) of the pulse wave, i.e., the distance between two sites divided by the time elapsed. A higher PWV indicates greater arterial stiffness. Considerable heterogeneity exists among segment-specific PWV measured along the arterial tree, since the architecture and composition of the arterial wall differs by location. Among PWVs at different segments, carotid-femoral pulse wave velocity (cfPWV) has been accepted as the referent standard measurement of aortic stiffness in epidemiological studies (**Appendix 1**).[16]

3.1.3. Age and aortic stiffness

The values of aortic stiffness measurements change with age. Aortic stiffness increases from young adulthood throughout the whole lifespan, particularly with risk factors of cardiovascular disease.[17]

3.1.4. Aortic stiffness as a predictor of subsequent health outcomes

Cardiovascular disease

A number of population-based prospective cohort studies have found that aortic PWV is independently associated with subsequent cardiovascular events, including cardiovascular mortality,[18-21] risk of coronary artery disease [22,23] and stroke,[24] in both high-risk and

general populations. An updated meta-analysis by Zhong et al. shows that elevated cfPWV was associated with about 80% higher pooled risk of cardiovascular events (hazards ratio [HR]: 1.80, 95% confidence interval [CI]: 1.45-2.14) in 14 studies, and 85% higher pooled risk of cardiovascular mortality (HR: 1.85, 95% CI: 1.46-2.24) in 11 studies. These associations are consistent whether using one standard deviation or one unit increase are used as predictors.[25] The evidence from the pooled results suggests that cfPWV is a useful marker to predict subsequent adverse cardiovascular events.

Cognitive decline and dementia

Aortic stiffness has been found associated with cognitive decline and dementia. In a meta-analysis of six longitudinal studies including 3947 subjects over an average course of more than 5 years, higher aortic stiffness marginally predicted lower Mini-Mental State Examination scores (β=-0.03, 95% CI: -0.06 to 0.01). This association turned statistically significant after removing one study with a younger cohort and lower median aortic stiffness (β=-0.04, 95% CI: -0.07 to -0.01).[26] These associations may be explained by neurological conditions including stroke, white matter hyperintensities and lacunar infarction as potential mediators between aortic stiffness and cognitive decline.[26]

There are fewer studies that examine the association between aortic stiffness and risk of dementia, and results are not consistent. Pase et al. found that higher aortic stiffness independently predicted higher risk of mild cognitive impairment (HR: 1.40, 95% CI: 1.13-1.73) and all-cause dementia (HR: 1.45, 95% CI, 1.13-1.87) in the Framingham Offspring study.[27] In a cross-sectional examination of the Atherosclerosis Risk in Communities Study-Neurocognitive Study (ARIC-NCS) by Meyer et al., individuals with higher cfPWV had a greater prevalence of mild cognitive impairment (OR: 1.27, 95% CI: 1.02-1.56), while no

association was found between cfPWV and dementia.[28] In the Malmö Diet and Cancer study 2007-2012, Nilsson et al. found that cfPWV was not cross-sectionally associated with all-cause dementia (OR: 0.95, 95% confidence interval 0.83-1.08), or incident all-cause dementia (OR: 1.00, 95% confidence interval 0.91-1.09).[29]

3.1.5. Risk factors of aortic stiffness

In addition to age, other risk factors of cardiovascular disease associated with high aortic stiffness include hypertension, diabetes or elevated fasting glucose, obesity, high heart rate, and dyslipidemia.[30]

Blood pressure

Elevated blood pressure increases pulsatile aortic wall stress, and that accelerates the process of elastin degradation.[31] Hypertension is considered accelerating vascular aging and leading to aortic stiffening,[31] although temporal relationship between aortic stiffening and blood pressure has not been unequivocally described in the literature, as several prospective cohort studies showed that higher cfPWV was associated with increasing blood pressure.[32-35] The results of studies on the association of high blood pressure and aortic stiffness are therefore mixed. Kaess et al. found that initial blood pressure level was not independently associated with progressive aortic stiffening in the Framingham Heart Study.[35] In contrast, El Khoudary et al. reported that higher levels of systolic blood pressure were associated with increasing cfPWV in a sample of 240 men aged 40 to 49 years free of cardiovascular disease in the US.[36] The Baltimore Longitudinal Study of Aging showed that systolic blood pressure (SBP) ≥120 mm Hg was associated with faster rates of increase in cfPWV compared to SBP<120 mm Hg in both men and women free of cardiovascular disease.[37] The Study of Women's Health Across the Nation (SWAN) Heart Study showed that SBP was among the strongest predictors of increasing

cfPWV among a sample of 303 African-American and European-American female participants.[38] Although these results are not fully consistent, evidence in general supports the conclusion that high blood pressure independently predicts aortic stiffness. From the information reported in the literature a bidirectional association between systolic blood pressure and aortic stiffness can also be posited.

Diabetes and glucose

Diabetes or high fasting glucose from middle age may increase the level of aortic stiffness. Population-based studies have observed associations between aortic stiffness and diabetes and hyperglycemia. Strain et al. found that cfPWV was greater in subjects with type 2 diabetes compared to controls among Europeans and Afro-Caribbeans.[39] In a prospective cohort study, McEniery et al. found in the Whitehall II Study that HbA1c was associated with accelerated progression of cfPWV in 4,386 participants without diabetes.[40]

Obesity

In a systematic review and meta-analysis that included 10 studies comparing the levels of aortic stiffness between obese and non-obese individuals, a pooled analysis of three studies showed that obese individual had higher level of cfPWV than non-obese individuals (β=0.54, 95% CI: 0.32-0.76).[41] In another systematic review and meta-analysis, based on 16 intervention trials on weight loss and change of PWV, showed that weight loss was associated with lower cfPWV (β=-0.35, 95% CI: -0.44, -0.26).[42] Obesity may thus be associated with higher levels of cfPWV.

Heart rate

Heart rate has been identified as a risk factor of aortic stiffness in a few observational studies. In the Multi-Ethnic Study of Atherosclerosis (MESA) study, an increase in resting heart

rate was associated with decreasing aortic distensibility.[43] Albaladejo et al. showed that 24-hour ambulatory heart rate was correlated to cfPWV in patients with essential hypertension, and is stronger among patients over 50 years of age.[44]

Lipids

There are different potential mechanisms for the association between aortic stiffness and plasma lipids, such as atherosclerosis, elements change of the arterial wall, endothelial dysfunction and inflammation.[45] High-density lipoprotein cholesterol (HDL-C) is inversely related to cfPWV,[46,47] while total cholesterol and low-density lipoprotein cholesterol (LDL-C) are positively related to cfPWV.[46] High triglyceride levels are associated with greater cfPWV.[48]

3.1.6. Therapy for aortic stiffness

A number of studies have reported interventions, including pharmacological and non-pharmacological means to reduce aortic stiffness. The non-pharmacological interventions are mainly focused on improving risk factors related to cardiovascular diseases, mostly by increasing physical activity and a healthy diet. In other intervention studies, higher n-3 fatty acid consumption improves arterial compliance among individuals with obesity or diabetes.[49,50] A meta-analysis indicated that aerobic exercise significantly improved arterial stiffness and that the effect was larger with higher aerobic exercise intensity and those with greater baseline arterial stiffness.[51] Combination of a healthy diet and exercise may have better effects in reducing aortic stiffness. In a 7-week nonrandomized clinical trial involving a low-calorie diet and an intensive lifestyle intervention among morbidly obese patients, low-calorie diet combined with aerobic exercise was associated with a sharper decline of arterial stiffness than taking a low-

calorie diet alone.[52] In addition, smoking cessation has been shown effective in reducing aortic stiffness.[53]

The pharmacological interventions tested include antihypertensive agents, lipid-lowering drugs and antidiabetic agents.[54] A meta-analysis of randomized controlled trials of antihypertensive agents showed that angiotensin receptor blockers (ARB) may work better than other antihypertensive agents in improving arterial stiffness.[55] Another recent meta-analysis of randomized controlled trials showed that statin therapy was beneficial for improving aortic stiffness.[56]

3.2. White matter integrity

3.2.1. Structure and function of the brain

The brain is made up of brainstem, cerebellum, and cerebrum. The cerebrum is the largest part of the brain and is composed of right and left hemispheres, which performs higher functions like “interpreting touch, vision and hearing, as well as speech, reasoning, emotions, learning, and fine control of movement”. The surface of the cerebrum has a folded appearance known as the cortex. The axons beneath the cortex make up the white matter. [57]

The cerebrum is divided into four lobes: frontal (controls personality, behavior, emotions, judgment, planning, problem solving, speech, body movement, intelligence, concentration and self-awareness), parietal (hosts the interpretation of language, words, sense of touch, pain, temperature, interpretation of signals from vision, hearing, motor, sensory and memory, spatial and visual perception), temporal (controls understanding language, memory, hearing, sequencing and organization), and occipital lobe (controls interpretation of vision). [57]

3.2.2. Structure of cerebral small vessels

The blood flow in the brain is supplied by intracranial arteries, which derive from the circle of Willis.[58] The pial vessels are intracranial vessels on the surface of the brain and branch into smaller arterioles that eventually penetrate into the brain. “Penetrating arterioles lie within the Virchow-Robin space and are between pial and parenchymal arterioles; the penetrating arteries become parenchymal arterioles after penetrating into the brain tissue”.[59,58] All vessels in the brain have endothelium with barrier properties that regulate exchange of nutrients, solutes, and water between the brain and the blood, known as blood-brain barrier (BBB).[60]

3.2.3. Application of neuroimaging to assess pathological changes of cerebral small vessels

The study of pathology of the white matter used to be based on post mortem studies. In general, the pathological changes of white matter are demyelination and axonal degeneration, as sampled from selected brain regions and reflective of late-stage disease.[61] Neuroimaging enables detecting pathological changes of white matter at an earlier stage when it is less severe.[61]

Magnetic resonance imaging (MRI) has been a useful tool used in the diagnosis of stroke and cerebrovascular disease. Diffusion-weighted imaging (DWI), T1, T2, Fluid Attenuated Inversion Recovery (FLAIR) and gradient echo imaging (GRE) are most informative.[62] T2 and FLAIR sequences are sensitive for detecting white matter disease.[62]

Traditional MRI is able to capture penetrating arteries and small draining veins, enlarged perivascular spaces, microbleeds, and microinfarcts. An MR image showing a high cerebral small vessel disease (CSVD) burden is reflective of a significant chance that cognitive impairment may be related to components of CSVD.[63]

3.2.4. Cerebral small vessel disease (CSVD)

The term CSVD refers to a range of neuroimaging, pathological and associated clinical features with different etiologies that "affect the small arteries, arterioles, venules and capillaries of the brain".[64,65] CSVD affects the vessels of the basal ganglia, peripheral white matter, leptomeningeal arteries, thalamic and cerebellar white matter vessels, and vessels of the brainstem.[66] It results from damage to the cerebral microcirculation, affecting the blood supply, as well as tissue of deep white and grey matter.[65,67] The phenotypes of CSVD include deep brain infarcts, white matter lesions and cerebral microbleeds (**Appendix 2**).

Deep brain infarcts

Deep brain infarcts can be detected on FLAIR and T1-weighted MRI.[68] The term deep brain infarcts often refers to subcortical infarcts, defined as small subcortical infarcts of 3 to 20 mm in diameter identified on either CT or MRI.[69,66] These lesions are consistent with previous acute small subcortical infarcts or hemorrhages in the territory of one perforating arteriole.[66] Deep brain infarcts account for 20% to 30% of all strokes; the incidence of deep brain infarcts is about 33 per 100,000 persons-years.[70]

The prevalence of deep brain infarcts increases with age. A systematic review indicated that the prevalence of silent brain infarcts is between 8% to 28%, according to results from individual studies.[71] In the Cardiovascular Health Study, the prevalence of deep brain infarcts was 22.1% in the 65-to-69-year age group, and 42.9% among those aged over 85 years.[72]

Endothelial dysfunction plays an important role in deep brain infarcts, since it causes "leakage of plasma fluid components and migration of cells into the vessel wall with disruption of the normal architecture of vessels", which may lead to "dilation, narrowing of vessel lumen, and loss of normal autoregulation".[65] Endothelial dysfunction may also damage the BBB as

endothelium is an essential part of BBB.[73] Hypertension also contributes to the development of deep brain infarcts, since they also impair the integrity of BBB.[74]

White matter hyperintensities

White matter lesions, or white matter hyperintensities, are areas of "decreased attenuation on CT, increased signal on T2-weighted and FLAIR in the periventricular and white matter of the cerebral hemispheres, basal ganglia (deep gray matter), pons, and brainstem and cerebellum".[66] White matter hyperintensities are more prevalent and more extensive among patients with lacunar strokes, and often coexist with deep brain infarcts, enlarged perivascular spaces, microbleeds and brain atrophy.[65]

The prevalence of white matter hyperintensities is high even among healthy older adults. In a population-based sample of 123 subjects aged 64 to 74 years, the prevalence of subcortical and periventricular hyperintensities detected by MRI are 90% and 67%, respectively.[75] The Rotterdam Scan Study investigated 1077 subjects aged 60 to 90 years from general population, and only 5% were free of white matter lesions. The report also indicated that the prevalence and the extent of cerebral white matter hyperintensities increases with age. Women have a higher degree of white matter hyperintensities than men.[76]

Ischemia plays a critical role in white matter hyperintensities, according to results of pathological studies.[77] Loss of integrity of endothelium and the BBB may also play a role in the development of white matter hyperintensities.[78]

Cerebral microbleeds

Cerebral microbleeds are small deep or superficial hemorrhages with of diameters of 2 to 10 mm shown on MRI.[66] "These lesions correspond to small collections of hemosiderin-laden macrophages around small perforating vessels".[66] Cerebral microbleeds are associated with

lacunar stroke and white matter hyperintensities.[65] According to the Rotterdam Scan Study, cerebral microbleeds can be categorized into deep and lobar cerebral microbleeds.[79] The former are likely to be associated with cardiovascular risk factors, as well as deep brain infarcts and WMHs. The latter may be associated with genotypes of *APOE4*.[79]

It has been reported that the prevalence of cerebral microbleeds is 5% in healthy adults, 34% in people with ischemic stroke, and 60% in people with non-traumatic intracerebral hemorrhage.[80] The prevalence of cerebral microbleeds is 24% among people with Alzheimer's disease.[81] The Rotterdam Scan Study, which investigated 3979 community-dwelling people (mean age, 60.3 years), reported that 15.3% have at least 1 cerebral microbleed, and that the prevalence increases with age, from 6.5% among persons aged 45-50 years to 35.7% among persons aged 80 years and older.[82]

Because of the observed strong associations, cerebral microbleeds may share common mechanisms with white matter hyperintensities.[83] In addition, amyloid angiopathy may play a role in the pathogenesis of cerebral microbleeds.[84]

3.2.5. Risk factors associated with CSVD

A series of risk factors have been examined in epidemiological studies for their association with cerebral small vessel disease, including age, sex, race, hypertension, diabetes, dyslipidemia and smoking. Older age and hypertension are generally accepted risk factors for CSVD.

Age has been recognized as among the most important risk factors for CSVD, as documented in population-based epidemiological studies, including the Rotterdam scan study and the Northern Manhattan Study.[85,71] However, the development of CSVD over the course of aging has not been well characterized. [86]

High blood pressure is considered the most influential modifiable risk factor for CSVD but no threshold for a rise in the prevalence of CSVD over the range of blood pressure has been identified.

3.2.6. White matter in the brain

The central nervous system consists of neurons and glial cells.[87] Myelinated axons and glial cells are major components of the normal white matter.[88] Myelin has a water content of about 40%, and its dry part (60%) is mainly composed of lipids (70%–85%), with a smaller component of proteins (15%– 30%).[89] Spinal cord myelin has an even higher lipid-to-protein ratio than the brain.[89] The main lipid components of myelin include cerebrosides and lecithin, and the main protein elements of myelin include proteolipid protein and myelin basic protein.[89]

3.2.7. Diffusion tensor imaging (DTI) for white matter integrity

Diffusion tensor imaging (DTI) is a neuroimaging tool that assesses both the orientation and diffusion of white matter tracts in vivo.[90] It has proved evaluate white matter integrity in both research and clinical settings.[91]

DTI allows a quantification of the characteristics of water diffusion in tissues. The diffusion of water molecules measured in tissues differs by direction, which is different from that in pure water.[92] If movements encounter barriers and obstacles, then molecules of water will follow Brownian motion, in all directions, known as “anisotropic”. The direction of greatest diffusivity is identified by DTI, characterizing the paths and integrity of white matter tracts.[93] The level of anisotropy is thought of as caused by bundled parallel axons. Diffusion is reduced by the axonal cell membrane and myelin sheath, which is perpendicular to the long axis of the axons, while these barriers are less pronounced along the long axis of the axons. Decreases in

anisotropy and increase in diffusion can thus measure whether axonal microstructure and myelination are compromised.[91]

The most commonly used DTI measure is fractional anisotropy (FA), whose direction is made up of diffusion tensor eigenvectors (ϵ_1, ϵ_2, ϵ_3) and its shape is characterized by three eigenvalues (λ_1, λ_2, λ_3). λ_1 represents the water movement parallel to the axonal fibers, known as axial diffusivity (AD). The average of λ_2 and λ_3 represents the water movement perpendicular to the axonal fibers, known as radial diffusivity (RD).[94] The FA is calculated as $FA = \sqrt{\frac{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_1-\lambda_3)^2}{2(\lambda_1^2+\lambda_2^2+\lambda_3^2)}}$. The value of FA ranges from 0 to 1. An FA of 0 indicates there is no anisotropy in water movement, with diffusivity equal in all directions, and an FA of 1 indicates that water movement is purely unidirectional. The magnitude of FA may vary by microstructure within the same individual. In general, lower FA is reflective of lower directionality of water molecule diffusion along fiber pathways and considered to reflect lower microstructural connectivity.[95]

Mean diffusivity (MD) is another important measure for DTI. MD is the average rate of diffusion in the noncollinear directions, with an increase value showing an increase in water diffusion. MD is calculated as MD= $(\lambda_1+\lambda_2+\lambda_3)/3$. In general, higher MD is reflective of less constrained water molecule diffusion and considered to reflect lower microstructural connectivity (**Appendix 3**).[96,95] DTI demonstrates the variability in the extent of white matter disruption both within lesions and in normal-appearing white matter.[97]

3.2.8. Correlation between DTI and MRI parameters

Positive correlations between white matter integrity measured with DTI and white matter hyperintensities measured with conventional MRI have been identified in several studies. In a sample of 57 older adults (mean age: 78±7 years), WMH pathology was associated with lower

FA in projection (including internal capsule and corona radiate) and association (including superior longitudinal, superior and inferior fronto-occipital fasciculi) fiber tracts.[98] In 27 patients with Alzheimer's disease, severe WMHs increased MD values in the bilateral parietal lobes, anterior internal capsule, posterior internal capsule, and in the right occipital region. Lower FA values were found in right occipital and right parietal areas, as well as right anterior internal capsule and right posterior internal capsule.[99] In the Lothian Birth Cohort 1936 which is composed of 676 subjects (mean age: 73 years), compared to normal-appearing white matter, FA values were significantly lower, and MD significantly higher in WMH.[100] In a study of 65 HIV seropositive and 29 HIV seronegative adults over 60, total WMH volume predicted FA in corpus callosum and sagittal stratum, and are marginally associated with FA in the external capsule.[101] In 266 participants of the Radboud University Nijmegen Diffusion Tensor and MRI Cohort (RUN DMC) Study (mean age: 62.5±7.8 years), higher baseline MD values in normal appearing white matter were associated with increased WMH progression during 9 years.

3.2.9. Major clinical consequences associated with loss of white matter integrity among older adults

Cognitive impairment

Cognitive function has been studied for its relation to the microstructural integrity of white matter in a few studies of older adults, although the results were not consistent. Zhong et al. studied 75 subjects aged from 43 to 85 years with leukoaraiosis, observing that FA of normal appearing white matter and FA of white matter hyperintensities were independently associated with global cognitive function.[102] In the RUN DMC study, among 499 patients with CSVD (aged 50-85 years), mean MD and FA of the normal appearing white matter, white matter lesions, and total white matter did not substantially contribute to the variance of cognitive

function explained, and only showed limited additional information value compared to conventional MRI parameters.[103]

Late-life depression

The prefrontal cortex and limbic areas are important for emotion and mood regulation, and loss of white matter integrity of frontal-limbic tracts has been posited to clinical features in major depressive disorder.[90] A number of studies examined the relationship between microstructural integrity and late-life depression. Shimony et al. studied white matter integrity measured using DTI in multiple regions (deep white matter, corpus callosum, prefrontal, temporal, parietal, occipital, motor) in 73 depressed elderly subjects and 23 non-depressed control subjects, and found that all regions combined showed significantly higher MD among depressed older adults, and the prefrontal regions alone demonstrated significantly lower FA among depressed older adults.[104] Yang et al. evaluated microstructural changes in different regions (frontal, temporal, corpus callosum) among 31 late-life depression patients and 15 healthy controls using DTI; their results showed that FA values were significantly lower in superior and middle frontal gyrus, and right parahippocampal gyrus among elderly patients with depression compared to healthy controls.[105] Nobuhara et al.[106] examined frontal white matter anisotropy 13 late-life depression patients and 13 healthy controls, observing that significantly lower FA values of widespread regions of the frontal and temporal lobes were found among depressed patients, and FA values of the inferior frontal area of the brain were inversely correlated to severity of depression.

Taken together, damage to the microstructure of white matter, particularly that of prefrontal regions is seen in patients with late-life depression.

3.2.10. Risk factors associated with white matter integrity

Only a few studies have examined the risk factors of white matter integrity.

Vascular risk factors were explored in the ARIC study, including plasma total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), serum glucose, SBP and diastolic blood pressure (DBP).[107] The results showed an adverse association between high lipids at midlife and high total cholesterol, LDL-C, and HDL-C in late life were associated with better overall FA among those who are cognitively normal, independent of WMH volume. High triglycerides in late life showed a positive association with higher MD. High serum glucose in midlife was associated with higher MD, and high glucose at baseline was marginally associated with lower overall FA. High SBP and DBP at both midlife and late life were strongly associated with lower FA and higher MD.[107]

Reports from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) indicated that age, sex, education, *APOE4*, and all targeted vascular factors and heavy alcohol consumption were associated with lower FA. Heavy alcohol drinking, hypertension, and diabetes are associated with higher MD, and the associations of hypertension and diabetes with MD remained statistically significant after controlling WMH volume. The study also indicated that among *APOE4* carriers, having any of 4 vascular risk factors (current smoking, heavy alcohol consumption, hypertension and diabetes) was associated with lower FA and higher MD even with full covariates adjustment.[108]

The RUN DMC showed that an increase of 10mm Hg in SBP was significantly associated with a decrease of FA in both normal appearing white matter and white matter lesions. Similarly, every 10-mm Hg increase in DBP was associated with a decrease of FA in normal appearing white matter and white matter lesions. A 10-mm Hg increase in both systolic and diastolic blood

pressures was significantly related to an increase in MD in white matter lesions. In normal appearing white matter, this association was only found for SBP. In addition, subjects with hypertension had a significantly lower mean FA in normal appearing white matter and white matter lesions than those without.[109] The RUN DMC study also showed that cigarette smoking was associated with reduced white matter integrity, while physical activity was associated with better white matter integrity.[110,111]

Taken together, cardiovascular risk factors are reported to affect white matter integrity among older adults.

3.3. Aortic stiffness, cerebral small vessel disease and white matter integrity

3.3.1. Aortic stiffness and cerebral small vessel disease

Several studies have examined the association between aortic stiffness using cfPWV or aortic PWV and manifestations of CSVD, including WMH, cerebral microbleeds and cerebral infarcts.

Aortic stiffness and white matter hyperintensities

Henskens et al. reported that a higher cfPWV was significantly associated with a greater volume of WMH (unstandardized regression coefficient: 0.041; 95% CI: 0.005, 0.078) among 167 hypertensive patients with no history of cardiovascular or cerebrovascular disease (mean age: 51.8±13.1 years) after adjusting for age, sex, brain volume, mean arterial pressure, and heart rate.[112] King et al. found that aortic arch PWV predicts WMH volume independently of the other demographic and cardiovascular risk factors, including age, systolic blood pressure, hypertension treatment, and congestive heart failure (β=0.29; 95% CI: 0.17, 0.42).[113] Poels et al. studied 1,460 participants (mean age: 58.2 years) in the Rotterdam Scan Study and found higher cfPWV to be associated with larger volume of WMH (the difference in volume per SD

increase in cfPWV was 0.07; 95% CI: 0.02, 0.12), and higher cfPWV was significantly associated with larger volume of WMH (the difference in volume per SD increase in cfPWV was 0.09; 95% CI: 0.00, 0.18) in persons with uncontrolled hypertension.[114] van Sloten et al. studied 2,058 participants (mean age: 79.6 years) in the AGES-Reykjavik study and found that higher cfPWV was associated with greater WMH volume (β=0.05, 95% CI: 0.002, 0.097).[115] The Framingham Offspring Study also showed that cfPWV was associated with greater WMH volume ($p<0.05$).[116]

Laugesen et al. examined the associations between cfPWV and volume of WMH among 89 patients recently diagnosed with type 2 diabetes and 89 sex- and age-matched controls. Every 1 m/s increase in cfPWV was associated with high greater WMH volume (OR:1.32, 95% CI: 1.16, 1.51).[117] Gustavsson et al. studied 208 individuals without any symptoms of cognitive impairment (mean age: 72 years) in Swedish BioFinder study, and found a positive association between cfPWV and WMH independent of age or sex (OR: 1.58; 95% CI: 1.04, 2.40), although the effect was attenuated after adjustments for several cardiovascular risk factors.[118] van Elderen et al. found that aortic PWV was independently associated with the presence of periventricular WMH (OR: 1.43, p=0.048) and subcortical WMH (OR: 1.48, p=0.02) among 86 consecutive type 1 diabetic patients (mean age: 46.9±11.7 years).[119] In a biracial cohort (n=303, mean age: 82.9 years, 41% black), Rosano et al.[120] found that higher aortic PWV was associated with greater WMH volume in the left superior longitudinal fasciculus (p=0.023), and that the associations were stronger in African Americans than in European Americans.

Taken together, higher aortic stiffness measured by cfPWV or aortic PWV is associated with the presence of WMH and higher volume of WMH.

Aortic stiffness and cerebral microbleeds

Henskens et al. showed that a higher cfPWV was not associated with microbleeds among 167 hypertensive patients with no history of cardiovascular or cerebrovascular disease (mean age: 51.8±13.1 years).[112] Similarly, Poels et al. detected a significant association between aortic PWV and deep or infratentorial microbleeds (OR: 2.13; 95% CI: 1.16, 3.91) only among persons with uncontrolled hypertension.[114] Gustavsson et al. reported that cfPWV was not associated with the presence of cerebral microbleeds among 208 cognitively healthy older adults.[118] van Elderen et al. reported no independent associations between aortic PWV and cerebral microbleeds among 86 consecutive type 1 diabetic patients.[119] No association was found between cfPWV and microbleeds in the AGES-Reykjavik study.[115]

Taken together, extant studies do not indicate that higher aortic stiffness measured by cfPWV or aortic PWV is associated with the presence of cerebral microbleeds.

Aortic stiffness and cerebral infarcts

The reports on associations between aortic stiffness and cerebral infarcts are mixed. Henskens et al. showed that aortic PWV was associated with the presence of lacunar infarcts (OR [per SD increase in PWV]: 1.78; 95% CI: 1.06, 2.99) in 167 hypertensive patients with no history of cardiovascular or cerebrovascular disease.[112] The AGES-Reykjavik study showed that cfPWV was associated with the presence of subcortical infarcts (OR: 1.78, 95% CI: 1.06, 2.99) among 2,058 participants (mean age: 79.6 years).[115] Poels et al. did not detect a significant association between aortic PWV and lacunar infarcts, while a marginal association between aortic PWV and lacunar infarcts (OR: 1.63, 95% CI: 0.98, 2.70) was seen among persons with uncontrolled hypertension in the Rotterdam Scan Study.[114] van Elderen et al.

reported no independent associations between aortic PWV and lacunar infarcts among 86 consecutive type 1 diabetic patients.[119]

3.3.2. Aortic stiffness and white matter integrity

Several studies have examined the putative association of aortic stiffness with white matter outcomes measured with DTI. The Framingham Heart Study Third-Generation cohort showed that higher carotid-femoral pulse wave velocity was associated with lower FAs.[121,122] Tarumi et al. reported that higher cfPWV was independently associated with lower FA.[123] Sala et al. indicated that increased aortic arch PWV was associated with lower white matter FA among patients with hypertension.[124] Tjeerdema et al. showed that aortic stiffness was independently associated with lower white matter integrity in patients with type 1 diabetes.[125]

3.4. Depression

3.4.1. Definition of depression

Depression is one of the most commonly diagnosed mental disorders among adults. People with depression may experience “a lack of interest and pleasure in daily activities, significant weight loss or gain, insomnia or excessive sleeping, lack of energy, inability to concentrate, feelings of worthlessness or excessive guilt and recurrent thoughts of death or suicide”.[126] During the last few decades the understanding of depression has developed from that of an acute and self-limiting illness to a chronic, lifelong illness.[127]

3.4.2. Diagnosis and classification of depression

The Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV-TR) categorizes depression into major depressive disorder (MDD) and dysthymic disorder.[127] MDD is defined as depressed mood or loss of interest or pleasure present for at least 2 weeks, representing a change from previous functioning. This includes depressive mood and loss of

interest in most activities, appetite and sleep disturbance, feelings of worthlessness and guilt, suicidal thoughts and ideation.[127] The World Health Organizations'(WHO) International Classification for Diseases and Related Disorders (ICD-10) describes the criteria for a depressive episode, where at least four items, such as loss of interest in activities, lack of emotional reactions, sleep disturbance, loss of appetite, motor retardation, weight loss, loss of libido, and decreased energy are present for 2 weeks.[128] Compared to DSM-IV-TR, the threshold of symptom requirements for ICD-10 is lower, while both classifications systems for depressive episode have shown high concordance.[129]

3.4.3. Measurement of depressive symptoms

In addition to standardized clinical diagnoses of depression, self-reported depressive symptoms assessed through standardized scales are common in clinical and research settings. Frequently used standardized scales for depressive symptoms include the Beck Depression Inventory (BDI), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), and Hospital Anxiety and Depression Scale (HADS).

Beck Depression Inventory (BDI)

The Beck Depression Inventory (BDI) is a 21-item self-reporting questionnaire that evaluates the severity of depression in both normal and psychiatric populations. The symptoms include mood, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal, indecisiveness, body image change, work difficulty, insomnia, fatigability, loss of appetite, weight loss, somatic preoccupation, and loss of libido.[130] The score of each item is a 4-point scale ranging from 0 (symptom absent) to 3 (severe symptoms). The minimum score is therefore 0 and maximum

score is 63. In those diagnosed with depression, scores of 0-13 indicate minimal depression, 14-19 (mild depression), 20-28 (moderate depression) and 29-63 (severe depression).[131]
In addition to the original version of BDI, revised versions of the BDI, including BDI-IA and BDI-II have been created. The BDI-IA is similar to the original, with the exception of the time frame that extends "over the past week, including today" as that some rephrased items. The BDI-II assessment of symptoms corresponds to the DSM-IV criteria.[132] Moreover, the BDI FastScreen for Medical Patients contains 7 cognitive and affective items from the BDI-II to assess depression in individuals with biomedical or substance abuse problems, while the somatic items from BDI-II were excluded.[133]

The mean correlation coefficients of BDI-IA scales and clinical ratings of depression are 0.72 and 0.60 for psychiatric and non-psychiatric populations, respectively.[134] The BDI-IA was significantly correlated to the depression subscale of the Symptom Checklist-90-Revised (r=0.76). BDI-II is positively correlated to Hamilton Rating Scale for Depression (HRSD) (r=0.71).[135] The internal consistency has been improving. The Cronbach's coefficient alphas for the revised BDI's are between 0.79 and 0.90.[132]

Center for Epidemiologic Studies Depression Scale (CES-D)

The CES-D scale is a self-report developed to assess depressive symptoms among the general population and identify persons at risk of clinical depression.[136] The CES-D scale contains four factors, including depressed affect, positive affect, somatic problems and retarded activity, and interpersonal relationship problems, with a focus on the affective component of depression. The original CES-D scale has 20 items, with each item on a 4-point scale, where 0 indicates rarely or none of the time (<1 day), 1 indicates some or a little of the time (1-2 days), 2 indicates occasionally or a moderate amount of time (3-4 days), and 3 indicates most or all of the

time (5-7 days).[136] Therefore, the total score ranges from 0 to 60. CES-D score ≥16 is often used as a cutoff for clinical depression and warrants a referral for a more thorough diagnostic evaluation.[132]

CES-D has high internal consistency, with coefficients ranging from 0.85 in the general population to 0.90 in psychiatric populations.[137] CES-D correlates with depression measures (coefficients ranged from 0.51-0.61), and the CES-D is moderately correlated to clinical interview ratings of depression (r=0.49).[132] The CES-D is able to discriminate between psychiatric inpatients and general population samples using a cutoff of 16.[138] There is however, a high false-positive rate for clinical depression with a standard cutoff score of 16.[132] In general, based on results of a large number of studies, the CES-D has been considered a reliable and valid instrument in research settings in different populations. However, it is worth noting that CES-D scores correlate with anxiety, so that the CES-D may just be a measure of general distress.[132]

Multiple brief versions of CES-D have been developed based on the original CES-D scale, including 8-item,[139] 10-item,[140] 11-item,[141] and 12-item CES-D (**Appendix 4**).[142,143] These forms have been validated and applied across varied population groups.

Geriatric Depression Scale (GDS)

The GDS was developed as a screening tool to measure depressive symptoms in older adults and identify late-life depression by distinguishing symptoms of depression and dementia.[132] The original version of GDS contains 30 items, representing characteristics of depression in the elderly in the affective (e.g., sadness) and cognitive domains (e.g., hopelessness), while somatic symptoms (e.g., disturbances in energy level) are not included in the GDS. The range of GDS score is from 0 to 30, with a higher score showing more severe

depressive symptoms. GDS score≥11 is considered possible depression.[144] A short form of GDS containing 15 items have also been developed.[145]

Compared to other measurement of depression, the GDS more consistently distinguishes depressed from non-depressed older adults.[146] The range of correlation between GDS and CES-D is between 0.58 and 0.89.[146]

Hospital Anxiety and Depression Scale (HADS)

The HADS was developed to assess anxiety and depressive symptoms in a general medical population ages 16 to 65 years. The HADS contains 14 items, with 7 for cognitive and emotional aspects of depression (HADS-D subscale), as well as 7 for emotional aspects of anxiety (HADS-A subscale). Each item is a 4-point question, ranging from 0 to 3, and the total score ranges from 0 to 42, with 0 to 21 for depression and anxiety, respectively. HADS of 0 to 7 is considered non-case, 8 to 10 is considered possible case, 11 to 21 is considered probable case.[147]

Compared to commonly used depression and anxiety measures, correlations with the HADS-D and HADS-A vary between 0.60 and 0.80.[132] For internal consistency, the correlation coefficient ranges from 0.78-0.93 for the HADS-A and from 0.82-0.90 for the HADS-D.[148]

3.4.4. Depression among older adults

The prevalence of clinically significant depressive symptoms is between 8% to 16% among community-dwelling older adults,[149] which is lower than that in midlife. Late-life depression is categorized into early-onset depression (with first episode of depression observed in childhood, adolescence or young adulthood) and late-onset depression (with a first episode of depression observed around 60 years of age or older).[150]

The prevalence of late-life depression is higher among Mexican Americans compared to European Americans and African Americans.[149] The prevalence of late-life depression among European Americans and African Americans is similar,[151] though African Americans are less likely to receive antidepressant treatment.[152]

Late-life depression is associated with severe outcomes, including higher risk of mortality,[153] suicide,[154] physical disability[155] and poor quality of life.[156] Late-onset depression accounts for the majority of individuals suffering from major depression or dysthymia, with no history of previous psychiatric treatment.[157] Compared to early-onset depression, the etiology of late-onset depression is more complex and heterogeneous, "with more cognitive and neuroradiological abnormalities, greater disability, medical morbidity and mortality, and lower familial prevalence of mood disorders than elderly early-onset depression".[158] Vascular factors may contribute a possible explanation for the distinction between late-onset and early-onset depression.

Alexopoulos et al. hypothesized that "cerebrovascular disease may predispose, precipitate, or perpetuate a depressive syndrome in many elderly patients", which is known as "vascular depression".[1] Vascular depression is regarded as a subtype of late-life depression characterized by a distinct clinical presentation and an association with cerebrovascular damage, featured with a variety of cerebrovascular lesions shown in the MRI image.[159] Vascular depression is therefore known as "MRI-defined vascular depression". Although widely accepted diagnostic criteria of vascular depression are lacking, some clinical features of vascular depression have been summarized, including late onset (at age of 65 years or later), absence of family history, cognitive impairment (particularly in executive function and processing speed), higher cardiac illness burden and vascular risk factors, white matter hyperintensities on neuroimaging, and

greater treatment resistance and poorer outcome.[159] Therefore, the vascular depression hypothesis provides a background for studies of mechanisms of late-life depression, particularly late-onset depression.

Structural imaging studies have been conducted to characterize the clinical features of late-life depression. A number of studies has shown that late-onset depression in late life were characterized by more frequent and intense white matter abnormalities shown on MRI.[160,161] DTI-based studies consistently showed that reduced anisotropy in the dorsolateral prefrontal cortex and uncinate fasciculus of patients with late-life depression, which may suggest that the pathogenesis of late-life depression may be partially attributed disruption of frontal and frontal-to-limbic white matter tracts.[162]

3.4.5. Risk factors of late-life depression

Consistent with the vascular depression hypothesis, cardiovascular and cerebrovascular diseases are important risk factors of late-life depression. Depression also shares risk factors of cardiovascular disease, such as hypertension, diabetes, obesity and smoking.

Cardiovascular disease

Cardiovascular disease has a bidirectional association with depression: patients with depression are at significantly higher risk for cardiovascular disease and mortality, and depression is more prevalent among patients with cardiovascular disease and contributes to a worse prognosis of cardiovascular disease.[163] A meta-analysis of cohort and case-control studies showed that depression was associated with higher risk of cardiovascular disease among older adults (OR=1.39, 95% CI: 1.26, 1.54), although heterogeneity exists among studies.[164] A few studies examined existing cardiovascular disease as a risk factor of depression. Kendler et

al. studied 30,374 twins (mean age: 57 years) and found that coronary artery disease was a predictor of increase in major depression (HR: 2.83, 95% CI: 1.90, 4.21).[165]

Hypertension

Hypertension may be particularly relevant to the etiology of late-life depression due to the chronic effects of this condition on the cerebral small vessels disease, which may increase the risk of depression among older adults.[166] However, results of studies on the association between hypertension and depression are mixed. Long et al. pooled 5 cohort studies with 9647 participants in a meta-analysis showing that the hypothesis that hypertension being a risk factor of depression among older adults was not supported.[167]

Diabetes

Diabetes has been proposed as a potential risk factor of depression, while studies have shown inconsistent results. Kim et al. did not find a significant association between diabetes and risk of late-life depression in 661 community participants aged ≥65 years in Korea.[168] In the Longitudinal Aging Study Amsterdam, diabetes was not found associated with depression.[169] However, in the Health ABC study, diabetes mellitus was marginally associated with a higher risk of incident depressed mood (OR: 1.20, CI: 0.97, 1.48), and associated with recurrent depressed mood (OR: 1.91, CI: 1.32, 2.76) among older adults aged 70 to 79 years.[170] In a community-based study in Spanish elderly subjects (age≥55 years), diabetes was associated with an increased risk of prevalent (OR: 1.47, 95% CI: 1.16, 1.83) and incident (OR: 1.40, 95% CI: 1.03, 1.90) depression.[171] Luijendijk et al. found in the Zaragoza Dementia and Depression (ZARADEMP) study that diabetes was associated with incident depressive disorder (OR: 2.07, 95% CI: 1.11, 3.85) among 2931 older adults≥61 years.[172]

Obesity

An association between obesity and risk of depression has been found in multiple studies. In a meta-analysis of 15 longitudinal studies with 58,745 subjects, obesity at baseline increased the risk of depression (unadjusted OR: 1.55, 95% CI: 1.22, 1.98). Overweight increased the risk of depression (unadjusted OR: 1.27, 95% CI: 1.07, 1.51). This association was statistically significant among older adults (≥60 years).[173]

Smoking

Associations between smoking and depression have been explored, and smoking is consistently found associated with depression among older adults. In a cross-sectional study of older adults attending general practice (aged 60 to 101 years) that current or past heavy smoking was associated with greater odds of clinically significant depression when compared to never or past light smoking (OR: 1.58, 95%CI: 1.01, 2.48).[174] Lam et al. found that current smokers (For male: OR: 1.62, 95% CI: 1.34,1.96; for female: OR: 1.43, 95% CI: 1.20,1.70) and former smokers (For male: OR: 1.18, 95% CI: 0.99,1.40; for female: OR: 1.29, 95% CI: 1.12,1.47) were more likely to have depressive symptoms than never smokers among 56,167 Chinese elderly aged 65 or older in Hong Kong.[175] In the Longitudinal Aging Study Amsterdam of 1,280 community-dwelling older adults, van Gool et al. found that depressed people (n=176 at baseline) were more likely to be smokers (OR: 1.71; 95% CI: 1.17, 2.52).[176]

3.4.6. Subsequent health outcomes associated with late-life depression

Mortality

Late-life depression is an important risk factor of all-cause mortality among both community-dwelling and institutionalized elderly. Among all causes of death, cardiovascular disease is over-represented.

A number of population-based studies have examined the associations between late-life depression and mortality, according to a newly published systematic review and meta-analysis.[177] Late-life depression was associated with increased risk of all-cause (risk ratio 1.34; 95% CI 1.27, 1.42) and cardiovascular mortality (risk ratio 1.31; 95% CI 1.20, 1.43).[177] Studies of inpatients have also shown that depression in late life is associated with mortality among hospitalized older adults, or those with comorbidities. Cullum et al. studied 617 medical inpatients (≥65 years) and found that depressive symptoms were associated with higher likelihood of inpatient death. [178] In the large cohort of Women's Health Initiative with female participants aged 50 to 79 years, depression diagnosed 3 years before diagnosis of breast cancer was associated with higher risk of all-cause mortality.[179]

Cognitive impairment

Several studies have found that patients with late-life depression have poorer performance on cognitive testing. Dias et al. examined the association between depression (assessed with the Mini International Neuropsychiatric Interview and GDS-15) and cognitive function (Mini-Mental State Examination, brief cognitive battery, clock-drawing test, category fluency test and Pfeffer's Functional Activities Questionnaire) among community-dwelling older adults aged 75 years or above. The results indicated that depressed individuals scored lower than subjects without dementia/depression on the Mini-Mental State Examination overall and on several of the Mini-Mental State Examination subscales, including time and spatial orientation, attention/calculation, and language. Individuals with late-life depression had worse performance on the incidental and immediate memory and learning tasks, category fluency test, clock-drawing test, and the Functional Activities Questionnaire. In addition, depression severity was inversely correlated with incidental memory, and positively correlated with the Functional Activities

Questionnaire score.[180] O'Shea et al. found that higher depressive symptoms measured with the CES-D were associated with worse executive function among individuals with high level of education. Increases in CES-D scores were associated with decreases in language ability and executive function but not memory or visual-spatial ability.[181] Hamilton et al. found that African American older adults who had more depressive symptoms (measured with the GDS-15) show significantly lower scores on measures of memory, language, processing speed, and executive functioning.[182]

Studies have also shown that late-life depression increases the risk of dementia. A meta-analysis of 23 community-based cohort studies indicated that Late-life depression was associated with a significantly higher risk of all-cause dementia (RR: 1.85, 95% CI: 1.67, 2.04), including Alzheimer's disease (RR: 1.65, 95% CI: 1.42, 1.92) and vascular dementia (RR: 2.52, 95% CI: 1.77, 3.59).[183]

3.4.7. Aortic stiffness and late-life depression

Aortic stiffness increases pulsatility, which damages microvascular circulation, resulting in poor vasoreactivity and cerebral hypoperfusion that is reflected in CSVD.[184] CSVD has been shown to impair frontal and subcortical structures, which are related to mood regulation, a key feature of depression.[1,185] It is also possible that there are other pathways apart from CSVD, through which aortic stiffness is associated with depressive symptoms. For example, studies have shown that high cfPWV increases the amount of β-amyloid, [186-188] whose accumulation and deposition may cause Alzheimer’s disease, [189] and that β-amyloid is associated with depressive symptoms among older adults. [190,191] The latter suggests that aortic stiffness may be linked to depression through a mechanism of neurodegeneration. Only a few studies have examined the association between aortic stiffness and late-life depression in cross-sectional

studies, and results are mixed. van Sloten et al. studied 2,058 participants (mean age: 79.6 years, 59.0% women) and found that higher cfPWV was associated with a higher GDS-15 score (β=0.096, 95% CI: 0.005, 0.187).[115] Among 3,704 participants aged 60 years or above in the Rotterdam Study, individuals with increased cfPWV were more likely to have depressive symptoms, with ORs for depressive symptoms of 1.17 (95% CI: 1.00, 1.38) per standard deviation increase in cfPWV.[192] Paranthaman et al. studied 25 elderly subjects with depressive disorder compared with 21 nondepressed control subjects and found that cfPWV was 1.6 m/sec higher in depressed subjects than those undepressed subjects (p=0.08).[193] Onete et al. found that cfPWV is not associated with either major depressive disorder (using the Mini-International Neuropsychiatric Interview) or depressive symptoms (dichotomized, defined as the Patient Health Questionnaire-9) in 1,399 men and women aged 60 years or older. [194] Thus, the associations between cfPWV and late-life depression should be examined in more studies, longitudinal studies are needed to examine the prospective association of aortic stiffness with risk of late-life depression and change of depressive symptoms.

3.5. Summary

3.5.1. Public health significance of understanding the relationship between aortic stiffness, white matter integrity and late-life depression

Depression among elderly populations, or late-life depression has become an important public health problem associated with severe consequences.[195,149] Compared to depression in young adults, the prevalence of late-life depression is lower but with higher prevalence of somatic depressive symptoms (e.g., fatigue, sleep),[195] which may contribute to a poor prognosis of late-life depression, such as multiple morbidities and mortality. Different from

depressive disorders among young adults, late-life depression is considered a geriatric syndrome involving multiple etiologies.[196]

Vascular depression is categorized as a subtype of depression, which originates from the recently proposed hypothesis of vascular depression.[197] According to the vascular depression hypothesis, cerebrovascular disease is likely to contribute to the development of late-life depression.[1] Typically, vascular depression occurs in the presence of WMH, a manifestation of CSVD. CSVD impairs frontal and subcortical structures, which are related to mood regulation, a key feature of depression.[1,185]

Aortic stiffness increases pressure pulsatility, which damages microvascular circulation, resulting in poor vasoreactivity and cerebral hypoperfusion that manifests as CSVD.[184] Population-based studies have shown that higher levels of aortic stiffness are associated with cerebral small vessel disease. Given the associations between aortic stiffness with CSVD, as well as the association between CSVD and late-life depression, one may hypothesize that aortic stiffness be associated with late-life depression.

WMH has been considered a manifestation of CSVD and found to be associated with decreased cognitive performance, particularly executive function.[198] However, reported correlations between WMH and cognition measurements have not been consistent, perhaps reflecting the inability to characterize the microstructural properties related to WMH.[199] DTI uses a tensor model to measure both the rate and directionality of the diffusion distributions of water molecules in tissue.[200] The DTI has high sensitivity in detecting cerebral damage.[201] Higher mean diffusivity (MD) and lower fractional anisotropy (FA) are thought to be independently related to poor white matter tract integrity. Studies have suggested that white matter microstructural integrity measured by DTI and white matter hyperintensities measured

with conventional MRI are correlated and indicate common pathophysiologic processes.[202-206]

With a better characterization of white matter integrity, DTI may provide insights into the associations between white matter integrity and its associated health conditions and on the relationship between aortic stiffness and white matter integrity.

Given the health and quality of life consequences of late-life depression, a better understanding of the relationship between aortic stiffness, white matter integrity and late-life depression is warranted. The potential for aortic stiffness to serve as a modifiable target for intervention through pharmacologic agents and/or lifestyle changes adds significance to this line of research.

3.5.2. Gaps in understanding of the relationship between aortic stiffness and late-life depression

Only a few studies have examined the association between cfPWV and depressive symptoms among older adults, with conflicting results. All reports to date are based on cross-sectional designs, and thus susceptible to bias and conceivably also reverse causality. A prospective study on aortic stiffness and incident depression based repeat measures of depressive symptoms will help to elucidate these associations.

3.5.3. Summary

Based on these gaps in the knowledge base, the goals of this dissertation proposal were to: 1) determine the cross-sectional relationship of aortic stiffness with white matter integrity among in older adults; 2) determine the cross-sectional and longitudinal relationship of aortic stiffness with depressive symptoms in older adults.

CHAPTER IV. METHODS

4.1. Source population

The Atherosclerosis Risk in Communities Study Neurocognitive Study (ARIC-NCS)

The Atherosclerosis Risk in Communities Study (ARIC) is an ongoing bi-ethnic, population-based prospective cohort study conducted in four communities in the U.S., including Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland. ARIC is designed to investigate the etiology and natural history of atherosclerosis, etiology of clinical atherosclerotic diseases, and variation in cardiovascular risk factors, medical care and disease by race, gender, location, and date. The study was initiated in 1987, with a total of 15,792 men and women aged 45 to 66 years who at enrollment participated in an extensive examination, which included detailed assessments of their current medical, social, and demographic status.[207]

The Atherosclerosis Risk in Communities Study Neurocognitive Study (ARIC-NCS) started as the visit 5 of the ARIC study. The study aims to elucidate factors underlying ethnic disparities in dementia burden and provide the scientific basis for prevention strategies by identifying vascular therapeutic targets, optimal timing for interventions and useful intermediate outcomes. In 2011-2013 all surviving ARIC participants were invited to take part in the ARIC Neurocognitive Study, and the second visit of ARIC-NCS, which is the 6th visit of the ARIC study was conducted from 2016 to 2017.

4.2. Measurement

4.2.1. Measurement of aortic stiffness (Visit 5)

cfPWV was measured using the VP-1000 plus system (Omron Co., Ltd., Kyoto, Japan). Carotid-femoral pulse wave velocity (cfPWV) is the gold standard measure of central arterial stiffness.[208] cfPWV was calculated using the following formula: path length (cm) = carotid-femoral distance (cm) – (suprasternal notch – carotid distance (cm))/transit time. A minimum of two measurements were taken per participant and the last two usable measurements (i.e., non-zero values) were averaged.

Quality control procedures for PWV measurements included central training and recertification, quarterly equipment calibration, and quality control reviews by Dr. Hirofumi Tanaka on a random sample of 40 records per month stratified by center with feedback provided to technicians.[209,210] The intraclass correlation coefficient for cfPWV (95% CI) is 0.70 (0.59, 0.81),[210] which suggest acceptable repeatability of cfPWV measurements.

4.2.2. Measurement of white matter integrity (visit 5)

A subset of ARIC V5 participants without contraindications was selected for a brain MRI: 1) all persons who had previous scans in 2004-2006, 2) those with low cognitive test scores/declines on longitudinally-administered tests, and 3) an age-stratified random sample of the remaining individuals. Sampling fractions for the random sample were set for participants <80 and ≥80 years of age to approximate the age distribution of those selected from the cognitively suspect group and were modified slightly over the course of the study to achieve a goal of approximately 2000 total MRI scans.[211] All scans included sagittal T1-weighted MPRAGE (magnetization-prepared rapid gradient-echo imaging), axial T2 FLAIR (fluid

attenuation inversion recovery), and axial DTI pulse sequences. Data were processed by the ARIC MRI Reading Center at the Mayo Clinic (Rochester, MN).[107]

DTI data was acquired using 2.7 mm slices for Skyra and Verio scanners and 3 mm slices for Trio scanners. FA and MD were extracted for regions of interest (ROIs) using the Lobar-22 Atlas.[212] ROIs include the following ones: frontal lobe, temporal lobe, occipital lobe, parietal lobe, anterior corpus callosum, posterior corpus callosum and a whole-brain composite measure. White matter hyperintensities measured by brain MRIs were obtained from a 3D-1.5T MRI scan at visit 5/ARIC-NCS (2011-2013).

4.2.3. Measurement of depressive symptoms (visit 5 and visit 6)

Depressive symptoms were measured by the 11-item Centers for Epidemiologic Studies-Depression (CES-D) Scale, with a higher score indicating for more severe depressive symptoms. Specifically, the CES-D has 11 items, including questions on appetite, effort, sleep, fatigue, feeling depressed, happiness, loneliness, unfriendliness, enjoyment, sadness, and dislike. Responses to questions are scored on a range from 0 to 2 points, with 0 points indicating 'hardly ever or never', 1 point as 'some of the time', and 2 points as 'much or most of the time'. The CES-D score was analyzed both continuously and categorically. The conventionally accepted score cut point for the CES-D-11 for depressive symptoms is 9 points or greater.[213]

4.3. Methods for specific aim 1

Aim 1: Determine the cross-sectional relationship of aortic stiffness with white matter integrity in older adults.

- **Aim 1.1:** Determine the cross-sectional association of aortic stiffness (i.e. carotid-femoral pulse wave velocity [cfPWV]) with white matter integrity (i.e. fractional anisotropy [FA]], mean diffusivity [MD]) among older adults.

4.3.1. Study population

Our study population includes participants of the ARIC-NCS study at visit 5, with measurements of cfPWV and DTI. We excluded prior history of stroke, missing DTI or aortic stiffness data. Due to small numbers, race other than black or white, and black participants examined at MD or MN were excluded. For optimal PWV data quality, the analyses also excluded participants with evidence of a major arrhythmia on the 12-lead ECG (MN code 8-1-3, 8-3-1, 8-3-2), and participants with aortic aneurysm, aortic stenosis or aortic regurgitation.

4.3.2. Variables

The exposure of interest is cfPWV of participants at visit 5 of the ARIC-NCS study. The two outcomes of interest include FA and MD measured with DTI at visit 5 of the ARIC-NCS study. In addition, age, sex, race-center, education, smoking, alcohol use, BMI, heart rate, *APOE* genotype, mean arterial pressure, diabetes, WMH volume were included as covariates in the analysis.

4.3.3. Statistical Analysis

For quantification of aortic stiffness, cfPWV was dichotomized at the upper 25^{th} percentile to indicate 'high' aortic stiffness. Z-scores were created for DTI measures for all regions of interest based on means and standard deviations. Analysis of participant characteristics at visit 5 were conducted using T-test or chi-square test according to categories of cfPWV, respectively.

We incorporated the ARIC-NCS MRI sampling fractions as weights in the analysis. Thus, weighted linear regression models were used to assess the relationship between each measure of aortic stiffness (cfPWV) with overall and region-specific DTI measure of white matter integrity (FA and MD). Due to their associations with both aortic stiffness and cerebral small vessel disease, potential confounders include age, sex, race-center, education, smoking, heart rate,

APOE4 allele genotype, mean arterial pressure, diabetes, LDL-C, physical activity. We further adjusted for white matter hyperintensities (as measured by structural MRI), due to the strong correlation between WMH and FA and MD.

4.3.4. Limitations

Cross-sectional design

The study was designed in a cross-sectional manner, since the exposure (cfPWV) and outcome (DTI measures) are only at visit 5. The cross-sectional design of this study precludes causal inferences about aortic stiffness and white matter integrity, and the possibility that the lack of white matter integrity may cause high aortic stiffness may not be completely excluded.

4.4. Methods for specific aim 2

Aim 2: Determine the cross-sectional and longitudinal relationship of aortic stiffness with depression in older adults.

- **Aim 2.1:** Determine the cross-sectional association of aortic stiffness (i.e. cfPWV) with depressive symptoms and odds of clinically significant depressive symptoms among older adults.
- **Aim 2.2:** Determine the association of baseline aortic stiffness (i.e. cfPWV) with the 5-year incidence of depressive symptoms among older adults.
- **Aim 2.3**: Determine the association of baseline aortic stiffness (i.e. cfPWV) with 5-year change in depressive symptoms among older adults.

4.4.1. Study population

The study included cohort members who participated in visits 5 and 6 of the ARIC study, with cfPWV measured at visit 5, and CES-D scores available at visit 5 and/or visit 6.

The following were exclusions for the primary analyses: Prior history of stroke, missing aortic stiffness at visit 5, or missing CES-D score at visit 5. Due to small numbers, race other than black or white, and black participants examined at MD or MN were excluded. For optimal PWV data quality, the analyses also excluded participants with evidence of a major arrhythmia, and participants with aortic aneurysm, aortic stenosis and aortic regurgitation.

4.4.2. Variables

The exposure of interest is the cfPWV of participants at visit 5 of the ARIC-NCS study. The outcomes of interest include incident depression at visit 6 (defined as CES-D score≥9 at visit 6) and change of depressive symptoms from visit 5 to visit 6 (measured with difference of CES-D scores between visit 5 and visit 6). In addition, age, sex, race-center, education, smoking, BMI, hypertension, diabetes, physical activity were included as covariates in the analysis.

4.4.3. Statistical analysis

Descriptive analysis

For quantification of aortic stiffness, cfPWV was analyzed in a continuous manner and categorized into quartiles based on distribution. High cfPWV was defined as upper 25^{th} percentile of cfPWV. Analysis of participant characteristics at visit 5 was conducted using T-test or chi-square test according to categories of cfPWV, respectively. Differences in CES-D score between visit 5 and visit 6 were calculated. Z-scores of cfPWV and CES-D score were created.

Analysis for Aim 2.1

Multivariable linear regression models were applied to assess the associations of z-score of cfPWV and high cfPWV with z-score of CES-D score at visit 5; Multivariable logistic regression models were used to assess the associations of z-score of cfPWV and high cfPWV with odds of clinically significant depressive symptoms at visit 5.

Analysis for Aim 2.2

Multivariable logistic regression models were used to assess the associations of z-score of cfPWV and high cfPWV with 5-year incident clinically significant depressive symptoms.

Analysis for Aim 2.3

Multivariable linear regression models were used to assess the associations of z-score of cfPWV and high cfPWV with 5-year change in z-score of CES-D scores.

4.4.4. Limitations

Selection bias

Participants of this study only included male or female ARIC cohort members able and willing to attend an examination visit, which may introduce selection bias. Also, high rate of attrition (about 40%) occurred from visit 5 to visit 6 of the ARIC study. Multivariate Imputation by Chained Equations (MICE) for CES-D score was used to address this.

Misclassification bias

The definition of clinically significant depressive symptoms using a cutoff of CES-D score ≥9 may correspond to major depressive disorders, which opens the opportunity for potential information bias.

CHAPTER V. MANUSCRIPT I: AORTIC STIFFNESS AND WHITE MATTER MICROSTRUCTURAL INTEGRITY ASSESSED BY DIFFUSION TENSOR IMAGING: THE ATHEROSCLEROSIS RISK IN COMMUNITIES NEUROCOGNITIVE STUDY

5.1. Introduction

Neurodegenerative conditions have become an increasingly greater burden among older adults. Cerebral small vessel disease (CSVD), a set of pathological processes of various etiologies that affect cerebral small arteries, arterioles, and capillaries, is associated with the risk of dementia.[65,214] White matter, as well as subcortical nuclei are supplied by deep penetrating arterioles that are susceptible to arteriolosclerosis.[201] Structural and functional neuroimaging techniques, including magnetic resonance imaging (MRI), can quantify morphologic changes in the cerebral small vessels.[201] As detected by MRI, white matter hyperintensities (WMHs) are associated with decreased cognitive performance, particularly executive function.[198]

Microstructural damage to white matter may be found prior to the detection of WMHs.[215] While the microstructural pathology to white matter cannot be captured by conventional MRI,[199] diffusion tensor imaging (DTI) is a MRI tool that quantifies the microstructural integrity of white matter. DTI uses a tensor model to measure both the rate and directionality of the diffusion distributions of water molecules in tissue, which is believed to be an indicator of white matter microstructural integrity, particularly within the axons of neuronal cells.[200] DTI is considered to be sensitive to loss of microstructural integrity in white matter before volumetric MRI is, since demyelination and cell death (as in white matter

hyperintensities) affect diffusion before the cells completely disappear (atrophy).[204,206] White matter hyperintensities may statistically account for some aspects of white matter microstructural integrity,[205,202] suggesting that DTI measures and WMHs are on a continuum of the same pathological processes.

The elasticity of the aorta facilitates delivery of blood supply to peripheral tissues, dampening sudden oscillations in blood pressure associated with systolic ejection and continuing to promote flow during diastole.[216] While compliant and elastic during youth, the aorta stiffens with aging as a result of the remodeling of the arterial wall.[217] Increased aortic stiffness, measured as carotid pulse wave velocity (cfPWV), may lead to insufficient flow wave dampening and a transmission of excessive pulsatile energy into the microvascular bed, particularly in high flow, low impendence organs such as the brain.[218] Increased aortic stiffness has been reported to be associated with cognitive decline and dementia.[12] Like other cardiovascular risk factors such as HbA1c, hypertension, total- and LDL-cholesterol,[219] cfPWV has been associated with WMH,[184,113,220,221,118,222,112] although fewer studies have examined associations of aortic stiffness with white matter microstructural integrity measured with DTI.[121,220,123-125] Among the latter, the results have been inconsistent, and most studies were based on small study samples. Although results from two extant population-based studies suggest that cfPWV is associated with lower fractional anisotropy, an index of white matter microstructural integrity, the associations between cfPWV and mean diffusivity (MD), another important index of white matter microstructural integrity, remains unknown. Additionally, the degree to which WMHs account for the associations between cfPWV and DTI measures needs to be further examined. Drawing on the large and well-characterized cohort of European Americans and African Americans in the Atherosclerosis Risk in Communities

Neurocognitive Study (ARIC-NCS), we aimed to test the hypothesis that higher aortic stiffness is associated with lower white matter microstructural integrity measured by DTI, in a cross-sectional analysis of data from community-dwelling older adults.

5.2. Methods

5.2.1. Study population

During 1987-1989, a total of 15,792 men and women aged 44 to 64 years were sampled to create a representative cohort of residents of four communities in the U.S. (Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland).[207] The present study is based on cross-sectional data for ARIC study cohort members who participated in the fifth examination of this cohort (2011-2013) and had data collected on aortic stiffness (measured as cfPWV) and white matter microstructural integrity (measured with DTI). All participants with evidence of cognitive impairment and a stratified random sample of cognitively normal participants were invited to complete a brain MRI scan (including DTI) as part of ARIC-NCS at visit 5.[223] The ARIC study protocols were approved by the institutional review boards at each site. All participants provided written informed consent.

To ensure high quality of cfPWV measurements, we excluded from analyses for participants with body mass index (BMI)$\geq$40kg/m^2 (n=57), participants with evidence of a major arrhythmia on the 12-lead ECG (MN code 8-1-3, 8-3-1, 8-3-2) (n=46), and participants with aortic aneurysm, aortic stenosis or aortic regurgitation (n=20). Individuals who self-identified as Asian or American Indian, and as black at the MN or MD centers were excluded due to small numbers (n=12). In addition, we excluded those with prevalent stroke (n=44).

5.2.2. Aortic stiffness

Aortic stiffness was assessed as carotid-femoral pulse wave velocity using the VP-1000 plus system (Omron Co., Ltd., Kyoto, Japan). The cfPWV was calculated using the following formula: path length (cm) = [carotid-femoral distance (cm) – (suprasternal notch – carotid distance (cm))]/transit time. A minimum of two measurements were taken per participant and the last two usable measurements (i.e., non-zero values) were averaged. Repeat visits conducted among a subset of participants at each field center approximately 4-8 weeks apart (n = 79; mean age: 75.7 years; 46 females) indicated that the intra-class correlation coefficients and 95% confidence intervals (CIs) for single measurements were 0.70 (0.59, 0.81) for cfPWV and approximately 0.82 for averaged cfPWV measurements, according to the Spearman-Brown formula.[224]

5.2.3. Neuroimaging information

DTI data was measured using 2.7 mm slices for Skyra and Verio scanners and 3 mm slices for Trio scanners.[225] Mean diffusivity (MD, mm^2/s) represents the average rate of diffusion independent of the directionality, and fractional anisotropy (FA, unitless) indicates the fraction of the tensor that can be assigned to anisotropic diffusion.[226,107] Higher MD and lower FA are thought to be independently related to damage in white matter microstructural integrity. Brain regions were defined by Lobar-22 atlas, which is based on the STAND400 template.[227] For each participant, regions of white matter were intersected tissue segmentations from T1-weighted and FLAIR images. Calculation of FA and MD was based on voxels with >50% probability of being white matter, including WMH regions. An upper cutoff of MD<0.002 mm^2/s was applied to exclude edge voxels that were primarily cerebrospinal fluid.[228] We averaged FAs and MDs, separately, across atlas regions and then took a weighted average, with weights based on the

number of voxels in each region of white matter, to create white matter FA and MD measures for regions of interest (ROIs), including frontal, temporal, occipital, and parietal lobes, the anterior and posterior corpus callosum, and an overall measure of all ROIs. White matter hyperintensities (WMH) volume was measured using FLAIR MRI scan and quantified using an algorithm developed at Mayo Clinic, and reported as cm^3.[229]

5.2.4. Covariates

All covariates are based on data collected at visit 1 or visit 5 of the ARIC cohort examinations. The covariates were selected for their associations with both aortic stiffness and white matter microstructural integrity, including age (visit 5, years), sex (men/women), race-center (black-Mississippi, black-North Carolina, white-North Carolina, white-Maryland, white-Minnesota), education (visit 1, below high school; high school/high school equivalent/vocational school; any college), *APOE* genotype (E4 allele ≥1/<1), smoking status (visit 5, ever/never), alcohol drinking status (visit 5, ever/never), body mass index (visit 5, kg/m^2), mean arterial pressure (visit 5, calculated as 1/3*systolic blood pressure + 2/3*diastolic blood pressure), diabetes (visit 5, yes/no, defined as fasting glucose >126 mg/dL, non-fasting glucose >200 mg/dL, self-reported history of diabetes diagnosis by a physician, or diabetes medication use), self-reported physical activity (visit 5, total minutes/week), heart rate (visit 5, beats per minute), and low-density lipoprotein (visit 5, mmol/dL).

5.2.5. Statistical analysis

cfPWV was examined continuously and dichotomized at the upper 25^{th} percentile to define elevated (cfPWV≥13.57m/s) vs. non-elevated (cfPWV<13.57m/s) levels of aortic stiffness. Participant characteristics at visit 5 were analyzed using T-test or chi-square tests. T-tests for FA

and MD by categories cfPWV were also conducted. Pearson correlations between FAs and MDs, as well as of cfPWV with FAs and MDs were estimated.

The ARIC-NCS MRI sampling weights, which was derived to represent all participants at visit 5, were applied in the analysis. Weighted linear regression models were used to assess the associations of cfPWV (both as a continuous variable, and dichotomized as elevated vs. non-elevated cfPWV) with z-scores of DTI measures of overall and regional white matter microstructural integrity (FA and MD). Four sets of analytic models were used. Model 1 was unadjusted; Model 2 was adjusted for WMH volumes alone to show to what extent WMH volumes accounted for the unadjusted association between cfPWV and DTI measures; Model 3 was adjusted for all covariates except WMH volumes (age, sex, race-center, education, *APOE* genotype, smoking status, alcohol drinking status, body mass index, mean arterial pressure, diabetes, heart rate, low-density lipoprotein); Model 4 was adjusted for all covariates. Beta (β) and 95% confidence intervals were used to summarize associations. All analyses were conducted using SAS 9.4 (Cary, NC, USA).

5.3. Results

5.3.1. Characteristics of participants

After exclusions, 1,484 participants remained in the analytic set (**Supplemental Figure 1**). A profile of the participants' characteristics is provided in **Table 1**. The mean age was 76 years, 40% were male, and 28.6% were black. Compared to participants with non-elevated cfPWV (cfPWV<13.57m/s), those with elevated cfPWV were older, more likely to be black, and less likely to have completed high school. In addition, participants with greater cfPWV were less likely to consume alcohol and spent less time engaging in leisure-time physical activities, while

being more likely to have diabetes and higher mean arterial pressure. The WMH volume was on average larger among those with elevated, as compared to non-elevated cfPWV.

The FAs of all regions were lower, and MDs of all regions were higher among participants excluded from analyses, as compared to those included (**Supplemental Table 1**). The FA and MD values overall and in all ROIs were approximately normally distributed. FA was negatively correlated with MD overall ($r=-0.75$, $p<0.0001$) (**Supplemental Table 2**). The volume of WMHs was negatively correlated with overall FA ($r=-0.45$, $p<0.0001$), and positively correlated with overall MD ($r=0.44$, $p<0.0001$).

5.3.2. Aortic stiffness and FA

The unadjusted linear regression models examining the association of incremental cfPWV with FAs (Model 1) indicated that each 1 m/s higher cfPWV was associated with lower FA overall and in all ROIs. When the models were adjusted for all covariates except WMHs volume (Model 3), the associations remained statistically significant for overall ($\beta=-0.03$, 95% CI: -0.05, -0.02) and all regions except Anterior corpus callosum (**Table 2**). The patterns of associations remained for overall as well as frontal lobe, temporal lobe and parietal lobe after further adjustment for WMH volume (Model 4).

In unadjusted models (Model 1) and models adjusted for WMH volumes only (Model 2), elevated cfPWV compared to non-elevated cfPWV was associated with lower FAs in all ROIs. After adjustment for demographic, lifestyle and clinical covariates (Model 3), the associations remained statistically significant for the overall measure ($\beta=-0.26$, 95% CI: -0.39, -0.14) and all regions (**Supplemental Table 3, Figure 1A**). The patterns of associations remained statistically significant after further adjusting for WMHs volume except for anterior corpus callosum and occipital lobe (Model 4).

5.3.3. Aortic stiffness and MD

The unadjusted linear regression models (Model 1) on incremental cfPWV and MDs indicated that each 1 m/s higher cfPWV was associated with higher MD in all ROIs and overall regions. When the models were adjusted for demographic, lifestyle, and clinical covariates (Model 3), the associations remained statistically significant for overall measure (β=0.03, 95% CI: 0.02, 0.04) and all regions (**Table 3**). The patterns of associations remained the same with Model 3 after further adjusted for WMHs volume (Model 4).

Elevated cfPWV was associated with higher MDs in unadjusted models (Model 1) for all ROIs. After adjustment for demographic, lifestyle and clinical covariates (Model 3), the associations remained statistically significant for overall measure (β=0.21, 95% CI: 0.11, 0.32) and all regions (**Supplemental Table 4, Figure 1B**). After further adjustment for WMH volume (Model 4), except for occipital lobe, all the associations remained.In this cross-sectional analysis of a sample of community-dwelling older white and black adults in the U.S., we found an association of greater aortic stiffness with lower cerebral white matter microstructural integrity (i.e., lower FAs and high MDs) overall and in different regions of the cerebrum. The associations were independent of potential confounders, including education and other demographic factors, lifestyle factors, and phenotypes related to vascular diseases (i.e., hypertension, diabetes). WMH volume partially accounts for the associations between aortic stiffness and lower cerebral white matter microstructural integrity, but associations remain after adjusting for WMH volume.

5.4. Discussion

The results of our cross-sectional study are consistent with prior cross-sectional studies,[123-125] although the effect sizes of associations in our study were smaller, which may be due to younger age of participants with lower aortic stiffness in the prior studies. However,

evidence from population-based studies is sparse. Our results agree with those of Maillard et al., who reported higher cfPWV to be associated with lower regional FA in a study of a young cohort composed of mostly white participants. The WMHs were not considered in the associations.[121] In the Health, Aging and Body Composition (Health ABC) Study of 303 older adults (mean age 82.9 years, 41% black), Rosano et al. reported that high cfPWV was correlated with low total brain FA, although the association was not statistically supported after adjustment for total WMH.[220] These findings differ from what we reported in our study. We attribute these disparate results to differences in study design, as well as different methods of measurement for cfPWV. The Health ABC Study was a cross-temporal analysis of cfPWV measured 10 years prior to the assessment of white matter lesions in association with white matter structural integrity. Although this study supports a temporal association between cfPWV and loss of white matter structural integrity, it does not directly assess how past aortic stiffness may be associated with later white matter integrity.

Hemodynamic factors likely play a role in the association between aortic stiffness and cerebral white matter integrity. The age-related process of aortic stiffening increases pulsatility, facilitating transmission of excessive pulse pressure into the cerebral circulation. This may trigger microvascular changes that limit flow, leading to ischemia and neural damage.[222,218]

Our results show that volume of WMHs only partially account for the associations between aortic stiffness and cerebral white matter microstructural integrity. Previous studies suggest that macrostructural and microstructural cerebral white matter degeneration reflect the same underlying pathophysiological changes,[203] but the fact that DTI indices remained correlated with PWV after adjusting for WMH volume suggest that the DTI indices may be more sensitive markers of loss of white matter integrity than WMH using conventional MRI tool.

Our study has public health relevance. Since DTI appears to detect white matter changes in an earlier stage than what can be observed through traditional MRI, FA and MD may be better indices of the impact of hemodynamic changes on the brain, facilitating early detection of pathological changes in white matter. Future research should also consider the potential for cfPWV as an important risk factor for loss of cerebral white matter microstructural integrity, with its downstream manifestations of cognitive decline and dementia. Based on our analytic sample, each 1 m/s increment in cfPWV was associated with a decrease in cerebral white matter microstructural integrity in a linear fashion, suggesting the absence of thresholds below which cfPWV is not associated with lower white matter integrity. Opportunities to reduce aortic stiffness across the range of the measurement should therefore be considered, not only among those with high cfPWV. Several studies have shown that aortic stiffness can be reduced via pharmacologic agents[230,56] and non-pharmacological interventions.[51-53] In addition, given the smaller effect sizes of the associations in our study, compared to those reported by previous studies based on data for young adults, efforts to reduce aortic stiffness may be most beneficial for brain health well before older adulthood, such as during midlife.

Our study has several strengths. The study's large population facilitates generalizing the results to similar populations of older adults. Furthermore, data collection was based on standardized protocols administered by trained personnel, and employed validated measurements for aortic stiffness, as well as white matter microstructural and macrostructural integrity.

The main limitation of our study is its cross-sectional design, which limits causal inferences regarding the association of aortic stiffness with cerebral white matter microstructural integrity among older adults, and possibilities that participants with white matter related disease (e.g. depression) may affect cfPWV with poor lifestyle cannot be excluded. Moreover, all

participants in this study had some degree of WMH, preventing the study of associations between cfPWV and DTI measures in the absence of WMH. We note however that our sensitivity analysis identified the difference in associations at high and low WMH volumes. Lastly, this study is restricted to older adults who were survivors from the start of the ARIC study subject to selection bias.

In conclusion, higher aortic stiffness is associated with lower cerebral white matter microstructural integrity among older adults. Future research should examine the longitudinal association of aortic stiffness with white matter microstructural integrity, as well as the potential opportunity for preservation of white matter microstructural integrity through the lowering of aortic stiffness.

Acknowledgement

The authors thank the staff and participants of the ARIC study for their important contributions.

Sources of Funding

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I). Neurocognitive data is collected by U012U01HL096812, 2U01HL096814, 2U01HL096899, 2U01HL096902, 2U01HL096917 from the NIH (NHLBI, NINDS, NIA and NIDCD), and with previous brain MRI examinations funded by R01-HL70825 from the NHLBI. Dr. Palta is supported by grant K99AG052830 from the National Institute of Aging.

Disclosures

None.

Table 1. Characteristics of the study participants at visit 5 of the ARIC study overall and by the upper 25th percentile of carotid-femoral pulse wave velocity (cfPWV; n=1,484)

	All (n=1,484)	Elevated stiffness cfPWV≥13.57m/s (n=372)	Non-elevated stiffness cfPWV<13.57m/s (n=1,112)
Age, year, mean ± SD	76.1±5.2	**78.0±5.2**	**75.5±5.1**
Sex, men, n (%)	597 (40.2)	162 (43.6)	435 (39.1)
Race, African Americans, n (%)	425 (28.6)	**156 (41.9)**	**269 (24.2)**
Center, n (%)			
Forsyth, NC	352 (23.7)	**82 (23.3)**	**270 (24.3)**
Jackson, MS	403 (27.2)	**152 (40.9)**	**251 (22.6)**
Minneapolis, MN	327 (22.0)	**53 (14.3)**	**274 (24.6)**
Washington, MD	402 (27.1)	**85 (22.9)**	**317 (28.5)**
Education, high school or above, n (%)			
Below high school	198 (13.2)	**76 (20.4)**	**122 (11.0)**
High school	612 (41.3)	**155 (41.7)**	**457 (41.2)**
College or above	672 (45.3)	**141 (37.9)**	**531 (47.9)**
Body mass index, kg/m^2, mean ± SD	27.7±4.5	27.5±4.7	27.7±4.4
Ever smoking, n (%)	785 (55.1)	191 (53.5)	594 (55.6)
Ever drinking, n (%)	1,119 (76.0)	**260 (70.3)**	**859 (78.0)**
Mean arterial pressure, mmHg, mean ± SD	87.8±11.4	**91.8±11.9**	**86.4±10.9**
Diabetes, n (%)	392 (26.7)	**133 (36.2)**	**259 (23.5)**
Heart rate, bpm, mean ± SD	64.5±11.0	**67.6±11.5**	**63.4±10.7**
Total physical activity, minutes/week, mean ± SD	180.9±176.6	**138.3±163.3**	**195.3±178.6**
Volume of white matter hyperintensities, cm^3, mean ± SD	16.4±16.4	**20.9±19.6**	**14.9±14.9**
APOE, n (%)			
APOE4 ≥1	1,003 (69.9)	254 (70.7)	749 (69.7)
APOE4 <1	431 (30.1)	105 (29.3)	326 (30.3)

* Bold indicates statistical significance. Hypertension is defined as systolic blood pressure≥140 mmHg, and/or diastolic blood pressure≤90 mmHg, and or antihypertensive medication use.

Table 2. Associations of carotid-femoral pulse wave velocity (cfPWV; per 1m/s increment) with fractional anisotropy (FA), estimated by linear regression (n=1,484)

Regions of FA	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 3 β (95% CI)	Model 4 (95% CI)
Anterior corpus callosum	**-0.04** **(-0.05, -0.02)**	**-0.03** **(-0.05, -0.01)**	-0.02 (-0.03, 0.001)	-0.01 (-0.03, 0.003)
Posterior corpus callosum	**-0.03** **(-0.04, -0.01)**	**-0.02** **(-0.03, -0.001)**	**-0.02** **(-0.04, -0.002)**	-0.02 (-0.03, 0.002)
Frontal lobe	**-0.06** **(-0.07, -0.04)**	**-0.03** **(-0.04, -0.02)**	**-0.03** **(-0.05, -0.01)**	**-0.02** **(-0.04, -0.01)**
Temporal lobe	**-0.03** **(-0.05, -0.01)**	-0.02 (-0.03, 0.0001)	**-0.04** **(-0.06, -0.02)**	**-0.03** **(-0.05, -0.02)**
Occipital lobe	**-0.03** **(-0.05, -0.01)**	**-0.02** **(-0.04, -0.003)**	**-0.02** **(-0.04, -0.003)**	-0.02 (-0.04, 0.0004)
Parietal lobe	**-0.04** **(-0.06, -0.02)**	-0.01 (-0.03, 0.002)	**-0.03** **(-0.04, -0.01)**	**-0.02** **(-0.03, -0.002)**
Overall	**-0.05** **(-0.07, -0.03)**	**-0.03** **(-0.04, -0.01)**	**-0.03** **(-0.05, -0.02)**	**-0.02** **(-0.04, -0.01)**

Bold indicates statistical significance. β is the difference (unadjusted for Model 1, adjusted for Model 2 to Model 4) of FAs for each 1 m/s cfPWV increment.

Model 1: Unadjusted.

Model 2: Adjusted for volume of white matter hyperintensities.

Model 3: Adjusted for age, sex, race-center, education, APOE genotype, ever smoking, ever drinking, body mass index, mean arterial pressure, diabetes, physical activity (total minutes/week), low-density lipoprotein cholesterol, heart rate

Model 4: Adjusted for factors included in Model 2 and Model 3.

Table 3**.** Associations of carotid-femoral pulse wave velocity (cfPWV; per 1 m/s increment) with mean diffusivity (MD), estimated by linear regression (n=1,484)

Regions of MD	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 3 β (95% CI)	Model 4 (95% CI)
Anterior corpus callosum	**0.04** **(0.03, 0.06)**	**0.04** **(0.02, 0.05)**	**0.02** **(0.01, 0.04)**	**0.02** **(0.01, 0.04)**
Posterior corpus callosum	**0.02** **(0.003, 0.04)**	0.01 (-0.003, 0.03)	**0.02** **(0.01, 0.04)**	**0.02** **(0.01, 0.04)**
Frontal lobe	**0.06** **(0.04, 0.07)**	**0.03** **(0.02, 0.04)**	**0.03** **(0.02, 0.05)**	**0.02** **(0.01, 0.04)**
Temporal lobe	**0.05** **(0.03, 0.06)**	**0.03** **(0.01, 0.04)**	**0.03** **(0.01, 0.04)**	**0.02** **(0.01, 0.04)**
Occipital lobe	**0.04** **(0.03, 0.06)**	**0.03** **(0.02, 0.05)**	**0.02** **(0.005, 0.03)**	**0.01** **(0.0001, 0.03)**
Parietal lobe	**0.04** **(0.03, 0.06)**	**0.02** **(0.003, 0.03)**	**0.02** **(0.01, 0.04)**	**0.02** **(0.003, 0.03)**
Overall	**0.05** **(0.04, 0.07)**	**0.03** **(0.01, 0.04)**	**0.03** **(0.02, 0.04)**	**0.02** **(0.01, 0.03)**

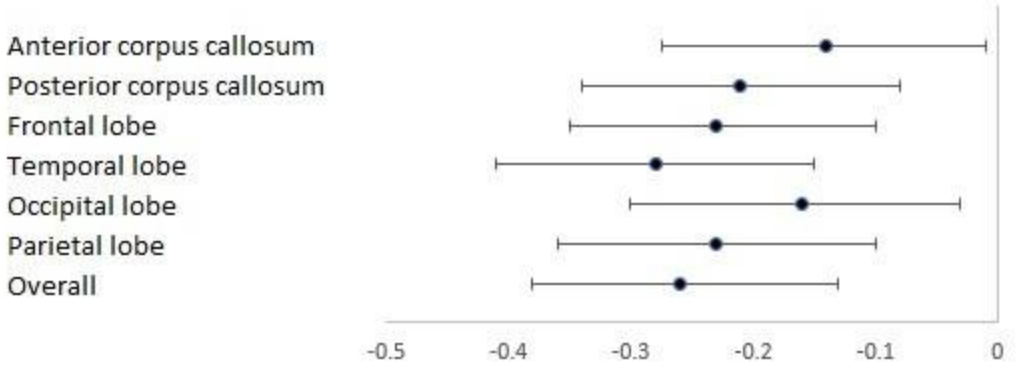
Bold indicates statistical significance. β is the difference (unadjusted for Model 1, adjusted for Model 2 to Model 4) of MDs for each 1m/s cfPWV increment.

Model 1: Unadjusted.

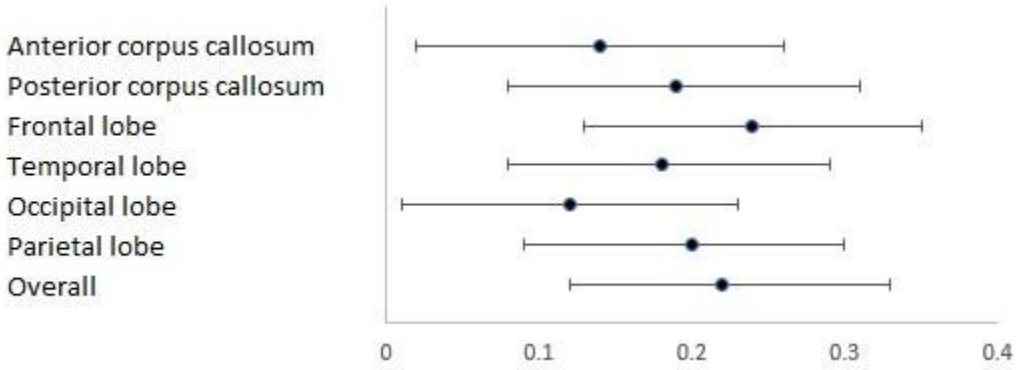
Model 2: Adjusted for volume of white matter hyperintensities.

Model 3: Adjusted for age, sex, race-center, education, APOE genotype, ever smoking, ever drinking, body mass index, mean arterial pressure, diabetes, physical activity (total minutes/week), low-density lipoprotein cholesterol, heart rate

Model 4: Adjusted for factors included in Model 2 and Model 3.

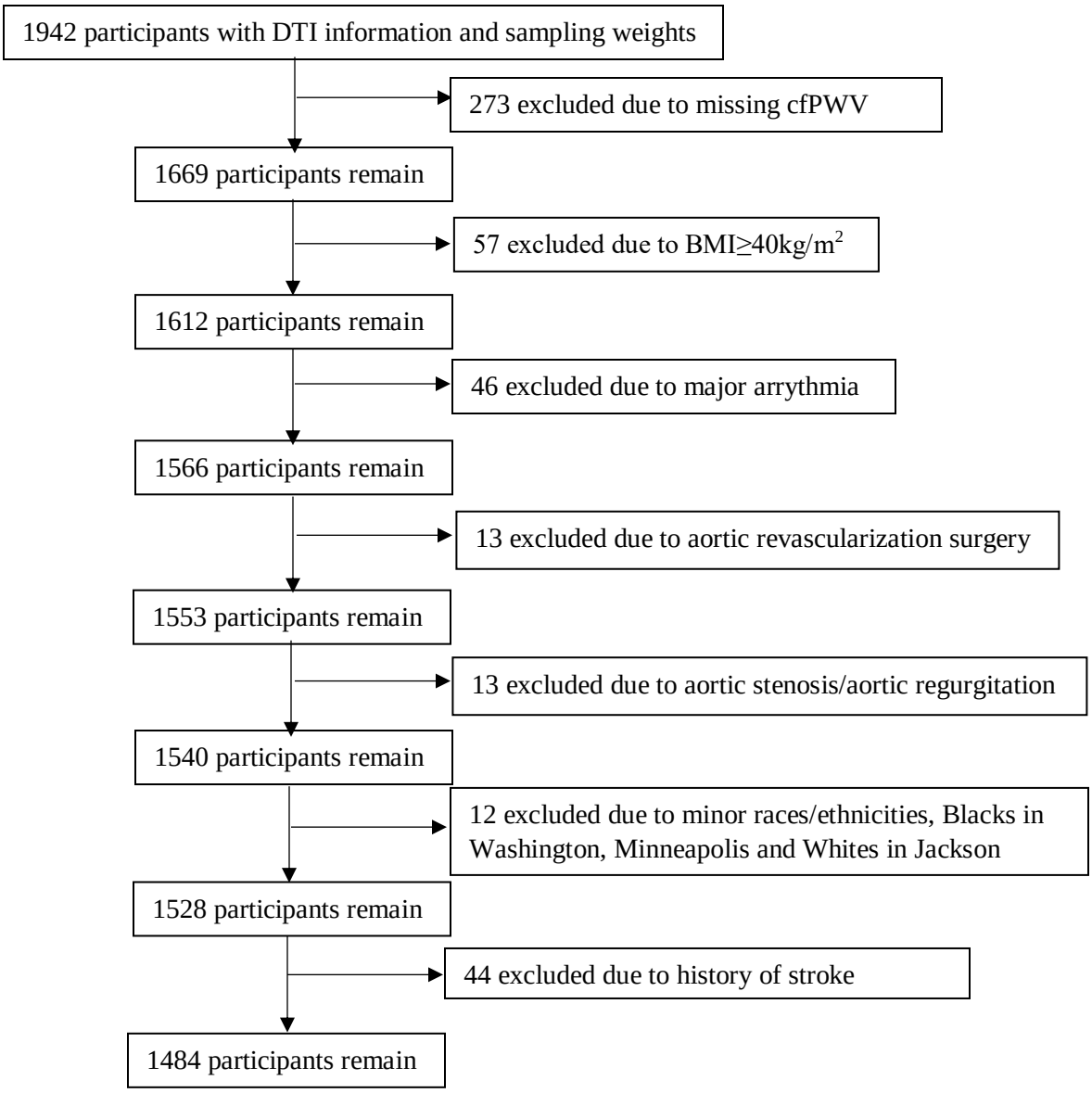


(A)



(B)

Figure 1**.** The adjusted difference of (A) FAs and (B) MDs by high and non-high carotid-femoral pulse wave velocity for overall bran region and specific regions of interest



Supplemental Figure 1**.** Flowchart of participant selection

Supplemental Table 1. Mean fractional anisotropy (FA) and mean diffusivity (MD) among included and excluded participants. ARIC study examination visit 5

	FA			MD (10^{-4} mm^2/s)		
Regions	Excluded (n=458)	Included (n=1,484)	Difference (SE)	Excluded (n=458)	Included (n=1,484)	Difference (SE)
Anterior corpus callosum	**0.407±0.06**	**0.424±0.06**	**-0.017 (0.003)**	**11.9±1.2**	**11.6±1.1**	**0.3 (0.06)**
Posterior corpus callosum	**0.559±0.07**	**0.578±0.06**	**-0.019 (0.003)**	**11.4±1.1**	**11.1±1.0**	**0.3 (0.06)**
Frontal lobe	**0.271±0.02**	**0.280±0.02**	**-0.009 (0.001)**	**8.8±0.6**	**8.6±0.5**	**0.3 (0.03)**
Temporal lobe	**0.275±0.02**	**0.283±0.02**	**-0.008 (0.001)**	**9.0±0.7**	**8.8±0.5**	**0.3 (0.03)**
Occipital lobe	**0.223±0.03**	**0.229±0.02**	**-0.007 (0.001)**	**9.0±0.7**	**8.8±0.6**	**0.2 (0.03)**
Parietal lobe	**0.290±0.03**	**0.300±0.02**	**-0.010 (0.001)**	**9.0±0.7**	**8.7±0.6**	**0.3 (0.03)**
Overall	**0.275±0.02**	**0.284±0.02**	**-0.009 (0.001)**	**9.0±0.6**	**8.7±0.5**	**0.3 (0.03)**

Bold indicates at $p<0.05$ from a t-test.

Supplemental Table 2. Correlations between FA and MD at different regions. ARIC study examination visit 5.

Regions	Correlation	P value
Frontal lobe	-0.75	<0.0001
Temporal lobe	-0.63	<0.0001
Occipital lobe	-0.68	<0.0001
Parietal lobe	-0.67	<0.0001
Anterior corpus callosum	-0.50	<0.0001
Posterior corpus callosum	-0.66	<0.0001
Overall	-0.75	<0.0001

Supplemental Table 3. Association of high cfPWV (upper 25th percentile) and z-scores of FA. Mean differences estimated by multivariable linear regression

Regions	Elevated cfPWV (cfPWV≥13.57 m/s)			
	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 3 β (95% CI)	Model 4 β (95% CI)
Anterior corpus callosum	**-0.33 (-0.46, -0.21)**	**-0.29 (-0.42, -0.16)**	**-0.14 (-0.27, -0.01)**	-0.13 (-0.26, 0.01)
Posterior corpus callosum	**-0.30 (-0.42, -0.18)**	**-0.23 (-0.35, -0.11)**	**-0.20 (-0.33, -0.08)**	**-0.17 (-0.30, -0.05)**
Frontal lobe	**-0.45 (-0.57, -0.33)**	**-0.28 (-0.39, -0.17)**	**-0.23 (-0.36, -0.11)**	**-0.16 (-0.27, -0.05)**
Temporal lobe	**-0.26 (-0.38, -0.13)**	**-0.16 (-0.28, -0.03)**	**-0.28 (-0.42, -0.15)**	**-0.24 (-0.37, -0.11)**
Occipital lobe	**-0.28 (-0.41, -0.15)**	**-0.21 (-0.34, -0.08)**	**-0.16 (-0.30, -0.02)**	-0.13 (-0.27, 0.002)
Parietal lobe	**-0.35 (-0.47, -0.23)**	**-0.17 (-0.28, -0.06)**	**-0.23 (-0.36, -0.11)**	**-0.16 (-0.27, -0.04)**
Overall	**-0.42 (-0.55, -0.30)**	**-0.26 (-0.37, -0.14)**	**-0.26 (-0.39, -0.14)**	**-0.19 (-0.31, -0.08)**

Bold indicates statistical significance. β is the difference (unadjusted for Model 1, adjusted for Model 2 to Model 4) of FAs between high and non-high cfPWV.

Model 1: Unadjusted.

Model 2: Adjusted for volume of white matter hyperintensities.

Model 3: Adjusted for age, sex, race-center, education, APOE genotype, ever smoking, ever drinking, body mass index, mean arterial pressure, diabetes, physical activity (total minutes/week), LDL-C, heart rate

Model 4: Adjusted for factors included in Model 2 and Model 3.

Supplemental Table 4. Association of high cfPWV (upper 25th percentile) and MDs. Mean differences estimated by multivariable linear regression.

Regions	Elevated cfPWV (cfPWV≥13.57 m/s)			
	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 3 β (95% CI)	Model 4 β (95% CI)
Anterior corpus callosum	**0.31 (0.19, 0.44)**	**0.28 (0.15, 0.40)**	**0.14 (0.02, 0.25)**	**0.13 (0.02, 0.25)**
Posterior corpus callosum	**0.21 (0.08, 0.34)**	**0.17 (0.05, 0.30)**	**0.19 (0.07, 0.30)**	**0.17 (0.05, 0.28)**
Frontal lobe	**0.46 (0.34, 0.59)**	**0.29 (0.19, 0.40)**	**0.24 (0.13, 0.35)**	**0.17 (0.08, 0.27)**
Temporal lobe	**0.35 (0.23, 0.47)**	**0.22 (0.11, 0.34)**	**0.17 (0.07, 0.28)**	**0.13 (0.03, 0.23)**
Occipital lobe	**0.37 (0.25, 0.49)**	**0.27 (0.15, 0.39)**	**0.12 (0.01, 0.23)**	0.08 (-0.02, 0.19)
Parietal lobe	**0.37 (0.24, 0.49)**	**0.20 (0.09, 0.31)**	**0.20 (0.09, 0.31)**	**0.13 (0.04, 0.23)**
Overall	**0.43 (0.31, 0.55)**	**0.27 (0.16, 0.38)**	**0.21 (0.11, 0.32)**	**0.15 (0.06, 0.24)**

Bold indicates statistical significance. β is the difference (unadjusted for Model 1, adjusted for Model 2 to Model 4) of MDs between high and non-high cfPWV.

Model 1: Unadjusted.

Model 2: Adjusted for volume of white matter hyperintensities.

Model 3: Adjusted for age, sex, race-center, education, APOE genotype, ever smoking, ever drinking, body mass index, mean arterial pressure, diabetes, physical activity (total minutes/week), LDL-C, heart rate

Model 4: Adjusted for factors included in Model 2 and Model 3.

CHAPTER VI. MANUSCRIPT II: AORTIC STIFFNESS AND DEPRESSIVE SYMPTOMS AMONG COMMUNITY-DWELLING OLDER ADULTS: THE ATHEROSCLEROSIS RISK IN COMMUNITIES NEUROCOGNITIVE STUDY

6.1. Introduction

Depression is a significant public health problem among older adults. Late-life depression, defined as a depressive episode occurring at age 60 years or older, is observed among 11% of American older adults [231]. Compared to depression among younger adults, the prevalence of late-life depression among older adults is lower; however, subsequent health outcomes associated with late-life depression are more severe [159]. Late-life depression is associated with increased risk of vascular dementia, Alzheimer's disease [183], all-cause and cardiovascular mortality [177]. In addition, studies have shown that late-life depression is associated with 47% to 51% higher total health care costs, as well as 43% to 52% higher outpatient costs [232] compared to those without late-life depression, which increases the public health burden of this condition.

As is suggested by the "vascular depression hypothesis" that cerebrovascular disease may predispose, precipitate, or perpetuate some late-life depressive syndromes [1], late-life depression may be attributed to structural abnormalities of the brain. This is supported by previous studies showing late-life depression, particularly late-onset depression is characterized with white matter hyperintensities (WMHs), manifestation of cerebral small vessel disease (CSVD) shown in magnetic resonance imaging (MRI) tools [160]. One of risk factors associated with WMHs is stiffening of aorta [222]. The elasticity of the aorta regulates the delivery of blood

supply to peripheral tissues, dampening sudden oscillations in blood pressure associated with systolic ejection [216]. While compliant and elastic during youth, stiffening of the aorta occurs with aging and the remodeling of the arterial wall [217]. Aortic stiffness increases pulsatility, which damages microvascular circulation, resulting in poor vasoreactivity and cerebral hypoperfusion and subsequent CSVD [184]. CSVD has been shown to impair the frontal and subcortical cerebral structures, which are related to mood regulation, a key feature of depression [1,185]. Therefore, aortic stiffness may be associated with late-life depression.

A small number of population-based studies have examined the associations of carotid-femoral pulse wave velocity (cfPWV), the gold standard measure of aortic stiffness [233], with late-life depression and depressive symptoms [234,192,194]. Two of these studies reported positive associations between cfPWV with depressive symptoms among older adults. However, these studies were based on a cross-sectional study designs and therefore are potentially open to reverse causality, since older adults with depressive symptoms may suffer from conditions (e.g., cardiovascular disease) that are likely to increase the stiffness of the aorta. It is therefore desirable to examine the association between aortic stiffness and depressive symptoms in a prospective cohort study.

Drawing on the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) data, we set out to extend the results from prior studies by both examining the cross-sectional associations of cfPWV with depressive symptoms in a biracial group of older adults, and the longitudinal associations of cfPWV with change of depressive symptoms and incident clinically significant depressive symptoms (CSDS) among older adults over the course of five years.

6.2. Methods

6.2.1. Study design and population

Our study participants are members of the ARIC cohort who participated in the fifth examination of this cohort (visit 5, 2011-2013), with measures of aortic stiffness (cfPWV) and depressive symptoms at visit 5, and/or measurement of depressive symptoms at visit 6 (2016-2018). At baseline, the ARIC cohort included a total of 15,792 participants aged 45 to 64 years sampled from four communities in the U.S. (Forsyth County, NC; Jackson, MS; suburbs of Minneapolis, MN; and Washington County, MD) in 1987-1989. A total of 6,538 cohort members attended visit 5, and 5,091 participants had information on both cfPWV and depressive symptoms at visit 5. To ensure high quality of cfPWV measurements, we excluded participants with body mass index (BMI)≥40kg/m^2 (n=149), participants with evidence of a major arrhythmia on the 12-lead ECG (MN code 8-1-3, 8-3-1, 8-3-2) (n=140), and participants with aortic aneurysm, aortic stenosis and aortic regurgitation (n=97). Individuals who self-identified as Asian or American Indian, and as African American at the MN or MD centers, were excluded because their small numbers precluded analysis (n=32). We further excluded participants with prevalent stroke at visit 5 (n=167). The total sample size at baseline after exclusion is 4,511, and after further exclusion of participants with CES-D score ≥9 (n=259) and participants who died prior to visit 6 (n=300), the sample size for longitudinal analysis is 3,952 (**Figure 2**).

6.2.2. Measurement of aortic stiffness

The cfPWV was measured using the VP-1000 plus system (Omron Co., Ltd., Kyoto, Japan) and calculated as [carotid-femoral distance – (suprasternal notch - carotid distance)]/transit time. A minimum of two measurements were taken per participant and the last two usable measurements (i.e., non-zero values) were averaged. Repeat visits conducted among a

subset of participants at each field center approximately 4 to 8 weeks later (n=79; mean age: 75.7 years; 46 females) indicated that the intra-class correlation coefficients and 95% confidence intervals (CIs) for single measurements were 0.70 (0.59, 0.81) for cfPWV and approximately 0.82 for averaged cfPWV measurements, according to the Spearman-Brown formula [224]. In the analysis, due to the lack of accepted clinically validated cut points, we modeled cfPWV continuously and dichotomized at the upper 25th percentile (cfPWV≥13.23 m/s) to define high aortic stiffness.

6.2.3. Measurement of depressive symptoms

Depressive symptoms were measured by the 11-item Centers for Epidemiologic Studies-Depression (CES-D) Scale at visit 5 and visit 6. The CES-D scale includes 11 depressive symptoms, including somatic complaints (appetite, sleep, effort, get going), depressed affect (depressed, lonely, sad), positive affect (happiness, enjoyment), and interpersonal problems (unfriendliness, dislike) [235]. Responses to each question are scored on a range from 0 to 2 points, with 2 points indicating the most severe. The total score ranges between 0 and 22. The reliability of the 11-item CES-D is high, with the Cronbach's alpha being 0.81 when compared to the original 20-item CES-D scale [235]. The CES-D scores were analyzed both continuously and categorically. A total CES-D score ≥9 was considered clinically significant depressive symptoms (CSDS) [235,236], which is suggestive of a major depressive disorder.

6.2.4. Other variables

All covariates are based on data collected at visit 1 or visit 5 of the ARIC cohort examination. The covariates were selected for their associations with both aortic stiffness and late-life depression, including age (years), sex (male/female), race-center (Black-Mississippi, Black-North Carolina, White-North Carolina, White-Maryland, White-Minnesota), education

(<high school, high school, college or above), smoking status (current/former/never), physical activity (total minutes/week), body mass index (kg/m^2), hypertension (systolic blood pressure ≥140mmHg, and/or diastolic blood pressure ≥90mmHg, and/or antihypertensive medication use), and diabetes (yes/no, defined as fasting glucose level ≥126 mg per 100 ml (7.0 mmol/l^{-1}), or use of antidiabetic medicine). Cognitive status (normal cognition, mild cognitive impairment, dementia) of participants was assessed at visit 5.

6.2.5. Statistical analysis

Participant characteristics at visit 5 were compared between those with high or non-high cfPWV using Student's t tests or chi-square tests. Continuous CES-D scores at both visits were converted to z-scores based on the mean (2.96) and standard deviation (2.91) of the CES-D scores at visit 5. Z-scores were also created for cfPWV based on mean (11.64 m/s) and standard deviation (3.14 m/s). We conducted both cross-sectional analyses for comparability with prior studies and longitudinal analyses to take full advantage of the prospective data available from the ARIC cohort. For cross-sectional analysis, multivariable linear regression models were used to assess the associations of cfPWV (continuous and binary) with z-score of depressive symptoms, with results presented as betas (βs) and 95% CIs. Multivariable logistic regression models were used to assess the associations of cfPWV (continuous and binary) with the odds of CSDS. Since adults with late-life depression may present with cognitive deficits [237], we conducted a sensitivity analysis of the cross-sectional associations among those participants with normal cognition at visit 5 (n=3,502).

In longitudinal analyses, participants with a total CES-D score ≥9 (clinically significant depressive symptoms) at the analytic baseline (visit 5) and participants who died before June 2015 were excluded (n=559). Due to the large proportion of loss to follow-up (approximately

40%) between visit 5 and visit 6, the method of multiple imputation by chained equations (MICE) was used to account for missing CES-D scores at visit 6 [238]. A total of 30 imputed datasets were created, with 40 iteration for each imputation. The variables used for imputation included covariates included in the models, visit 5 depressive symptoms and depression-related questions in the annual follow-up survey. The difference in z scores between two visits (visit 6 z-score – visit 5 z-score) was calculated following imputation. Multivariable linear regression models were then used to examine the associations of cfPWV (continuous and binary) with change in CES-D z-scores among those without clinically significant depressive symptoms at analysis baseline. The baseline values of CES-D z-score deserves consideration when assessing change over time, i.e., since a greater CES-D z-score allows smaller room for an increase. We therefore adjusted for baseline CES-D z-score in all models that examined the associations between cfPWV and change in depressive symptoms. Multivariable logistic regression models were used to examine the associations of cfPWV (continuous and binary) with incident CSDS among all participants after MICE, as well as complete cases with CES-D scores available at both visits. All analyses were conducted using SAS 9.4 (Cary, NC, USA).

6.3. Results

6.3.1. Characteristics of participants

The baseline characteristics of the participants included are provided in **Table 4**. The mean age was 75 years, 60% were female, and 79% were white. Clinically significant depressive symptoms were present among 259 (5.7%) participants. Compared to participants with non-high cfPWV (cfPWV<13.29m/s), those with high cfPWV (cfPWV≥13.29m/s) were older, more likely to be male and African American, were less likely to have completed high school, and had a

higher prevalence of hypertension and diabetes, lower body mass index, smaller amount of time for weekly physical activity, higher average CES-D score, and greater prevalence of CSDS.

6.3.2. Cross-sectional analysis

When considering a continuous measure of CES-D total z-score, the unadjusted linear regression models indicated that each standard deviation (SD, 3.14 m/s) higher in cfPWV was associated with a 0.10 SD higher total CES-D z-score (β=0.10, 95% CI: 0.07, 0.13). Similarly, relative to those with non-high cfPWV, those with high cfPWV had on average a 0.19 SD higher total CES-D z-score (β=0.19, 95% CI: 0.12, 0.26). The estimates were attenuated but remained elevated and statistically significant after adjustment for all covariates (for each SD higher cfPWV: β=0.05, 95% CI: 0.02, 0.08; for high cfPWV: β=0.07, 95% CI: 0.004, 0.15).
When considering a binary measure of CSDS, the unadjusted logistic regression models indicated that each SD higher cfPWV was associated with 1.24 times the odds of CSDS (OR=1.24, 95% CI: 1.10, 1.39). Similarly, relative to those with non-high cfPWV, those with high cfPWV had 1.65 times the odds of CSDS (OR=1.65, 95% CI: 1.26, 2.15). After adjustment for all covariates, associations were attenuated. Each SD higher cfPWV was marginally associated with 1.13 times the odds of CSDS (OR=1.13, 95% CI: 0.99, 1.30), and high cfPWV had 1.37 times the odds of CSDS (OR=1.37, 95% CI: 1.01, 1.85) (**Table 5**).

In the sensitivity analysis restricted to cognitively normal participants who were free of adjudicated MCI or dementia at visit 5, in the unadjusted models, a SD higher cfPWV was associated with 0.08 SD higher total CES-D z-score (β=0.08, 95% CI: 0.05, 0.11) and 1.20 times the odds of CSDS (OR=1.20, 95% CI: 1.04, 1.38). The binary measure of high (versus non-high) cfPWV was associated with 0.16 SD higher total CES-D z-score (β=0.16, 95% CI: 0.08, 0.23) and 1.53 times the odds of CSDS (OR=1.51, 95% CI: 1.11, 2.11). however, the associations were

not statistically supported after adjustment for all covariates (for each SD higher cfPWV: β=0.03, 95% CI: -0.01, 0.06, OR=1.05, 95% CI: 0.89, 1.24; for high cfPWV: β=0.04, 95% CI: -0.04, 0.12, OR=1.16, 95% CI: 0.80, 1.68) (**Supplemental Table 5**).

6.3.3. Longitudinal analysis

After excluding participants with CSDS at baseline and those who died prior to visit 6, 3,952 participants were included in the longitudinal analysis. Compared to those who attended visit 5 and also had a visit 6 CES-D score available, participants who did not have a CES-D score at visit 6 (those alive did not attend visit 6, or eligible for visit 6 but died) were older, had a smaller proportion of Black participants, smaller proportion of high school graduates, a lower body mass index, and lower reported leisure time physical activity, as well as a higher prevalence of hypertension and diabetes, and higher baseline CES-D scores (**Supplemental Table 2**). The mean CES-D score at visit 6 among complete cases was 0.02 standard deviations than visit 5 CES-D score, and the imputed results suggest that the mean CES-D score at visit 6 was 0.02 standard deviations higher than that at analysis baseline overall. Incident CSDS occurred among 3.1% of participants who had CES-D score<9 at analysis baseline, and 2.8% among complete cases.

The analysis based on complete case data did not show statistical significance in the associations of cfPWV with the 5-year change in depressive symptoms or with CSDS incidence, (**Supplemental Table 7**). Using imputed data, none of the linear regression or logistic regression models showed statistically significant association of higher cfPWV and elevated cfPWV with 5-year change in depressive symptoms and 5-year CSDS incidence. Compared to complete-case analysis, the effect sizes of association between each SD higher cfPWV and 5-year change in depressive symptoms were similar, and those of association between elevated cfPWV and 5-year

change in depressive symptoms become negative. The associations of each SD higher cfPWV and elevated cfPWV with 5-year incident CSDS showed a greater effect size with narrower 95% CIs (**Table 6**).

6.4. Discussion

In the present analysis of a cohort of community-dwelling older adults in the U.S., we found cross-sectional associations of higher and elevated aortic stiffness with higher depressive symptoms and prevalence of CSDS. The associations persisted after adjustment for potential confounders, including demographic and lifestyle factors, as well as risk factors for vascular diseases. However, among participants without significant depressive symptoms at analysis baseline, no significant prospective association was observed between aortic stiffness and change in depressive symptoms or in the probability of incident clinically significant depressive symptoms over an average of 5 years of follow-up.

There is a small number of prior population-based cross-sectional studies examining the association of cfPWV with depressive symptoms, which yields inconsistent results. van Sloten et al. reported that higher cfPWV was significantly associated with greater depressive symptoms measured with the 15-item Geriatric Depression Scale (GDS-15) in a sample of 2,058 older adults (mean age: 79.6 years, 59% women), while cfPWV was not associated with the odds of a dichotomous measure of depressive symptoms (defined as GDS-15≥6).[234] Tiemeier et al. found that a binary measure of high cfPWV (defined as cfPWV>15.2 m/s) vs. non-high cfPWV is not associated with higher odds of depressive symptoms (defined as 20-item CES-D≥16) after adjusting for all covariates, while it is associated with higher odds of a depressive disorder diagnosis according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria.[192] Onete et al. found that cfPWV is not associated with either major

depressive disorder (using the Mini-International Neuropsychiatric Interview) or depressive symptoms (dichotomized, defined as the Patient Health Questionnaire-9) in 1,399 men and women aged 60 years or older. [194] The results of our cross-sectional analysis were consistent with the previous finding that higher cfPWV and threshold-based high cfPWV were both associated with higher severity of depressive symptoms, and we also found that both higher and elevated cfPWV are associated with higher offs of CSDS. Given the limited studies, our study contributed to the evidence of the cross-sectional association between cfPWV and depressive symptoms among older adults.

This study is unique in its longitudinal examination of the association between aortic stiffness a and incidence of depressive symptoms, although we did not observe a statistically significant association of cfPWV with change in depressive symptoms and incident CSDS. The threshold-based identification of clinically significant depressive symptoms may not approximate major depressive disorders diagnosed according to DSM-IV criteria, as shown in the previously reported study [192]. Given the very little information on cfPWV and late-life depression, it is necessary that the cross-sectional and longitudinal associations between cfPWV and depressive symptoms among older adults be examined in other cohort studies, and it is desirable that future studies may examine the associations between cfPWV and risk of incident diagnosed depression among older adults.

The “vascular depression hypothesis” states that cerebrovascular disease may predispose, precipitate, or perpetuate some late-life depressive syndromes [1], suggesting that late-life depression may be attributed to structural abnormalities in the brain. This hypothesis is supported by previous studies showing that late-life depression, particularly late-onset depression (with its first occurrence after 60 or 65 years and older) is associated with white matter hyperintensities, a

manifestation of cerebral small vessel disease evidenced with magnetic resonance imaging [160]. Given that previous studies have found high (as compared to non-high) cfPWV to be associated with greater burden of white matter hyperintensities [222,220,113], aortic stiffness may represent a key hemodynamic mechanism for the occurrence of depressive symptoms among older adults. Our observations from cross-sectional analyses, suggestive of the association of cfPWV with CSDS among participants with normal cognitive status, favor the vascular hypothesis underlying the development of CSDS. Although we did not observe increased depressive symptoms and higher odds of incident CSDS, it does not necessarily mean vascular depression hypothesis is not true, and a cohort study in the future with formal diagnosis of depression and less attrition may help to test our hypothesis between higher cfPWV and greater risk of late-life depression, which is often featured as vascular depression.

Given the high prevalence of depressive symptoms among older adults and adverse outcomes associated with late-life depression, our results are of significance. Elevated cfPWV, defined by a population-based threshold, is associated with the presence of CSDS and greater depressive symptoms, suggesting that older adults with high aortic stiffness may have a propensity toward depression. Elevated cfPWV may be used as a marker to identify CSDS among older adults. Furthermore, each standard deviation increment in cfPWV was associated with higher depressive symptoms and CSDS among older adults, suggesting that the association of cfPWV with severity of depressive symptoms extends below the levels of cfPWV considered high.

A significant limitation of our study is the lack of clinical diagnoses of depression among older adults. We did however observe associations of cfPWV and depressive symptoms using a validated standardized scale. As a further limitation, our study is subject to a high proportion of

loss to follow-up, although we examined the longitudinal associations through the imputed data, which under the assumption of data missing at random conditional on observed covariates, would be expected to remove any bias from informative missing data. Despite these limitations, by using a prospective cohort study design with a large, biracial sample of older adults, and the gold standard measure for aortic stiffness, our study contributes new information to literature. In conclusion, high aortic stiffness is cross-sectionally associated with higher severity of depressive symptoms, but is not associated with 5-year change of depressive symptoms or incident CSDS in a sample of community-dwelling older adults. The longitudinal association between aortic stiffness and depressive symptoms among older adults warrants further investigation.

Acknowledgments

The authors appreciate the staff and participants of the ARIC study. The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C).

Disclosures

None.

Key words

Aortic stiffness; depressive symptoms; older adults

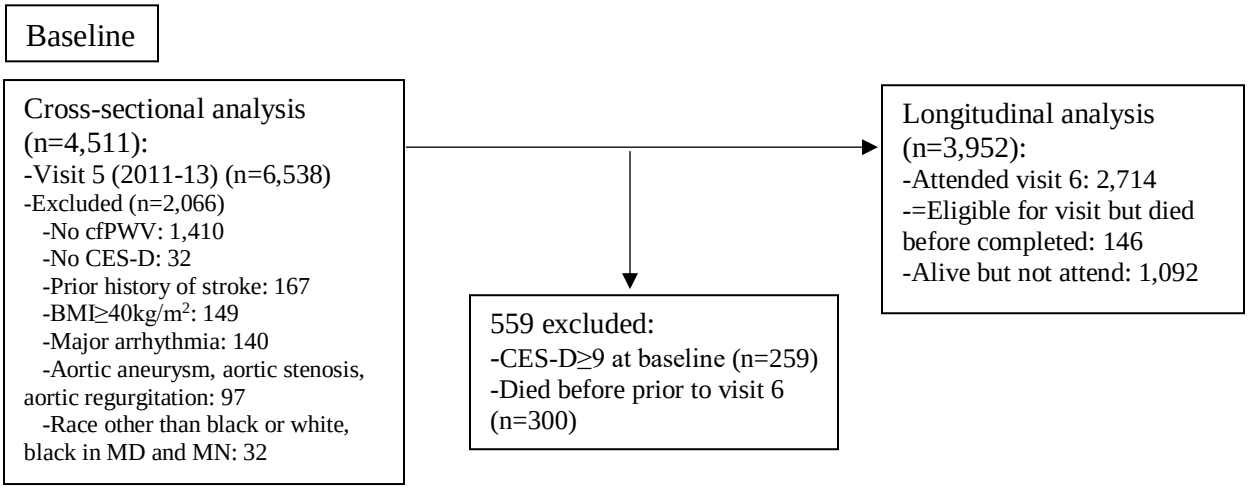


Figure 2. Flowchart of participants in the study, ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study). cfPWV: carotid-femoral pulse wave velocity; CES-D: Center for Epidemiological Studies-Depression; BMI: body mass index

Table 4. Characteristics of participants in the cross-sectional analysis, by cfPWV level. Visit 5 examination of the ARIC study (n=4,511)

	Overall (n=4,511)	Elevated cfPWV (cfPWV≥13.29m/s) (n=1,129)	Non-elevated cfPWV (cfPWV<13.29m/s) (n=3,382)
Age, years	75.2±5.0	**77.1±5.2**	**74.6±4.8**
Sex, male, n (%)	1,822 (40.4)	**493 (43.3)**	**1,329 (39.3)**
Race-center, n (%)			
Black-NC	58 (1.3)	**15 (1.3)**	**43 (1.3)**
Black-MS	922 (20.4)	**329 (29.1)**	**593 (17.5)**
White-NC	866 (19.2)	**195 (17.3)**	**671 (19.8)**
White-MD	1285 (28.5)	**315 (27.9)**	**970 (28.7)**
White-MN	1380 (30.6)	**275 (24.4)**	**1105 (32.7)**
Education, n (%)			
Below high school	571 (12.7)	**209 (18.5)**	**362 (10.7)**
High school	1,896 (42.1)	**477 (42.3)**	**1,419 (42.0)**
College or above	2,037 (45.2)	**443 (39.2)**	**1,594 (47.2)**
Body mass index, kg/m^2	27.8±4.5	**27.5±4.7**	**28.0±4.4**
Total physical activity, minutes/week	192.5±187.5	**157.1±177.9**	**204.4±189.1**
Smoking, n (%)			
Current	261 (6.2)	54 (5.2)	207 (6.6)
Former	2,098 (50.0)	506 (48.7)	1,592 (50.4)
Never	1,840 (43.8)	479 (46.1)	1,361 (43.1)
Hypertension, n (%)	3,220 (72.0)	**918 (81.8)**	**2,302 (68.7)**
Diabetes, n (%)	1,130 (25.3)	**408 (36.5)**	**722 (21.6)**
CES-D score	3.0±2.9	**3.3±3.1**	**2.8±2.8**
CES-D≥9, n (%)	259 (5.7)	**90 (8.0)**	**169 (5.0)**

Table 5. Cross-sectional associations of cfPWV with depressive symptoms and prevalence of clinically significant depressive symptoms. Visit 5 examination of the ARIC study (n=4,511)

Overall Depressive Symptoms		
	Per SD (3.14 m/s) higher Standardized β (95% CI)	Elevated cfPWV (cfPWV≥13.29m/s) vs. non-elevated cfPWV Standardized β (95% CI)
Model 1	**0.10 (0.07, 0.13)**	**0.19 (0.12, 0.26)**
Model 2	**0.05 (0.02, 0.08)**	**0.09 (0.02, 0.16)**
Model 3	**0.05 (0.02, 0.08)**	**0.07 (0.004, 0.15)**
Clinically Significant Depressive Symptoms		
	Per SD (3.14 m/s) higher OR (95% CI)	Elevated cfPWV (cfPWV≥13.29m/s) vs. non-elevated cfPWV OR (95% CI)
Model 1	**1.24 (1.10, 1.39)**	**1.65 (1.26, 2.15)**
Model 2	1.13 (0.99, 1.29)	**1.35 (1.00, 1.82)**
Model 3	1.13 (0.99, 1.30)	**1.37 (1.01, 1.85)**

SD: standard deviation; cfPWV: carotid-femoral pulse wave velocity; OR: odds ratio; CI: confidence interval.

Model 1: Unadjusted.

Model 2: Based on Model 1, adjusted for demographic and social factors (age (continuous), sex (male/female), race-center, education (below high school/high school/college or above), body mass index (kg/m^2), and lifestyle factors [smoking status (never/former/current), physical activity (minutes/week)].

Model 3: Based on Model 2, additionally adjusted for physical health conditions [hypertension (systolic blood pressure (SBP)≥140mmHg, and/or diastolic blood pressure (DBP)≥90mmHg, and/or taking antihypertensive medication), prevalent diabetes (fasting glucose≥126 mg/dL, and/or taking antidiabetic medication)].

Table 6. Associations of baseline cfPWV with change of depressive symptoms and incident clinically significant depressive symptoms over a period of 5 years. The ARIC study (n=3,952)

Change of Overall Depressive Symptoms		
	Per SD (3.14 m/s) higher Standardized β (95% CI)	Elevated cfPWV (cfPWV≥13.29m/s) vs. non-elevated cfPWV Standardized β (95% CI)
Model 1	0.02 (-0.01, 0.05)	0.04 (-0.03, 0.11)
Model 2	0.01 (-0.02, 0.04)	0.02 (-0.05, 0.09)
Model 3	0.01 (-0.02, 0.04)	0.02 (-0.05, 0.09)
Incident Clinically Significant Depressive Symptoms		
	Per SD (3.14 m/s) higher OR (95% CI)	Elevated cfPWV (cfPWV≥13.29m/s) vs. non-elevated cfPWV OR (95% CI)
Model 1	1.18 (0.98, 1.43)	1.32 (0.83, 2.08)
Model 2	1.11 (0.90, 1.36)	1.13 (0.70, 1.82)
Model 3	1.09 (0.88, 1.34)	1.08 (0.66, 1.77)

SD: standard deviation; cfPWV: carotid-femoral pulse wave velocity; OR: odds ratio; CI: confidence interval.

Model 1: Unadjusted (for incident clinically significant depressive symptoms); Adjusted for baseline total CES-D-11 score (for change of depressive symptoms).

Model 2: Based on Model 1, additionally adjusted for demographic and social factors (age (continuous), sex (male/female), race-center, education (below high school/high school/college or above), lifestyle factors [smoking status (never/former/current), body mass index (kg/m^2), physical activity (minutes/week)].

Model 3: Based on Model 2, additionally adjusted for physical health conditions [hypertension (systolic blood pressure (SBP)≥140mmHg, and/or diastolic blood pressure (DBP)≥90mmHg, and/or taking antihypertensive medication), prevalent diabetes (fasting glucose≥126 mg/dL, and/or taking antidiabetic medication)].

Supplemental Table 5. Cross-sectional associations of cfPWV with depressive symptoms and prevalence of clinically significant depressive symptoms at visit 5 of the ARIC study (n=3,502)

Overall Depressive Symptoms		
	Per SD (3.14m/s) higher β (95% CI)	High cfPWV (cfPWV≥13.29m/s) β (95% CI)
Model 1	**0.08 (0.05, 0.11)**	**0.16 (0.08, 0.23)**
Model 2	**0.04 (0.002, 0.07)**	0.05 (-0.03, 0.13)
Model 3	0.03 (-0.01, 0.06)	0.04 (-0.04, 0.12)
Clinically Significant Depressive Symptoms		
	Per SD (3.14 m/s) higher OR (95% CI)	High cfPWV (cfPWV≥13.29m/s) OR (95% CI)
Model 1	**1.20 (1.04, 1.38)**	**1.53 (1.11, 2.11)**
Model 2	1.06 (0.90, 1.24)	1.15 (0.80, 1.66)
Model 3	1.05 (0.89, 1.24)	1.16 (0.80, 1.68)

SD: standard deviation; cfPWV: carotid-femoral pulse wave velocity; OR: odds ratio; CI: confidence interval.

Model 1: Unadjusted.

Model 2: Adjusted for demographic and social factors (age (continuous), sex (male/female), race-center, education (below high school/high school/college or above), lifestyle factors [smoking status (never/former/current), body mass index (kg/m^2)].

Model 3: based on Model 2, additionally adjusted for physical health conditions [hypertension (systolic blood pressure (SBP)≥140mmHg, and/or diastolic blood pressure (DBP)≥90mmHg, and/or taking antihypertensive medication), prevalent diabetes (fasting glucose≥126 mg/dL, and/or taking antidiabetic medication), coronary heart disease (yes/no).

Supplemental Table 6. Baseline characteristics of participants for longitudinal analysis at visit 5 by attendance at visit 6 of the ARIC study (n=3,952)

	Overall (n=3,952)	Attended visit 6 (n=2,714)	Alive but not attended visit 6 (n=1,092)	Eligible for visit 6 but died (n=146)
cfPWV, m/s	11.6±2.9	11.3±2.8	11.8±3.1	12.4±3.2
cfPWV≥13.29 m/s, n (%)	939 (23.8)	578 (21.3)	313 (28.7)	48 (32.9)
Age, year	75.0±4.9	74.4±4.7	76.1±5.1	78.8±5.3
Sex, male, n (%)	1,595 (40.4)	1,106 (40.8)	413 (37.8)	76 (52.1)
Race, black, n (%)	816 (20.7)	587 (21.6)	194 (17.8)	35 (24.0)
Education, n (%)				
Below high school	441 (11.2)	269 (9.9)	143 (13.1)	29 (19.9)
High school	1,653 (41.9)	1,119 (41.3)	470 (43.1)	64 (43.8)
College or above	1,852 (46.9)	1,322 (48.8)	477 (43.8)	53 (36.3)
Body mass index, kg/m^2	27.9±4.4	28.0±4.4	27.7±4.5	26.6±4.4
Smoking, n (%)				
Current	205 (5.6)	138 (5.4)	61 (6.3)	6 (4.4)
Former	1,832 (49.7)	1,304 (50.6)	455 (46.8)	73 (53.3)
Never	1,648 (44.7)	1,134 (44.0)	456 (46.9)	58 (42.3)
Physical activity, minutes/week	201.0±189.6	210.8±191.9	185.3±185.0	136.9±158.2
Hypertension, n (%)	2,800 (71.4)	1,890 (70.1)	792 (73.2)	118 (81.9)
Diabetes, n (%)	941 (24.0)	605 (22.5)	291 (27.0)	45 (30.8)
CES-D score (visit 5)	2.4±2.1	2.3±2.1	2.6±2.2	3.0±2.3

Supplemental Table 7. Associations of baseline cfPWV with change of depressive symptoms and incident clinically significant depressive symptoms over a period of 5 years in the ARIC study among complete cases (n=2,580)

Change of Overall Depressive Symptoms		
	Per SD (2.90 m/s) higher β (95% CI)	High cfPWV (cfPWV≥13.23m/s) β (95% CI)
Model 1	0.03 (-0.01, 0.06)	0.04 (-0.03, 0.11)
Model 2	0.02 (-0.01, 0.05)	0.04 (-0.03, 0.12)
Model 3	0.02 (-0.02, 0.05)	0.04 (-0.04, 0.11)
Incident Clinically Significant Depressive Symptoms		
	Per SD (2.90 m/s) higher OR (95% CI)	High cfPWV (cfPWV≥13.23m/s) OR (95% CI)
Model 1	1.18 (0.93, 1.49)	1.24 (0.71, 2.15)
Model 2	1.14 (0.88, 1.47)	1.19 (0.67, 2.14)
Model 3	1.13 (0.87, 1.47)	1.16 (0.65, 2.10)

SD: standard deviation; cfPWV: carotid-femoral pulse wave velocity; OR: odds ratio; CI: confidence interval.

Model 1: Adjusted for baseline total CES-D-11 score.

Model 2: Based on Model 1, additionally adjusted for demographic and social factors (age (continuous), sex (male/female), race-center, education (below high school/high school/college or above), lifestyle factors [smoking status (never/former/current), body mass index (kg/m^2)].

Model 3: Based on Model 2, additionally adjusted for physical health conditions [hypertension (systolic blood pressure (SBP)≥140mmHg, and/or diastolic blood pressure (DBP)≥90mmHg, and/or taking antihypertensive medication), prevalent diabetes (fasting glucose≥126 mg/dL, and/or taking antidiabetic medication), coronary heart disease (yes/no).

CHAPTER VII. CONCLUSIONS

7.1. Recapitulation of aims

Late-life depression, defined as episodes of depressive disorder occurring at the age of 65 years or older has become a public health burden.[239] The vascular depression hypothesis suggests that late-life depression may be attributed to cerebrovascular disease,[1] which is supported by the presence of white matter hyperintensities (WMHs) as shown on magnetic resonance imaging (MRI).[240] Although considered a surrogate marker for white matter pathology, WMHs shown on MRI do not capture the microstructural pathology of white matter due to low sensitivity. Diffusion tensor imaging (DTI) on the other hand detects pathology of white matter microstructural integrity both within WMHs and in normal-appearing white matter. Aortic stiffness, a hallmark of aging,[241] is a risk factor of WMHs.[242,222] but few population-based studies have examined the association between aortic stiffness and white matter microstructural integrity assessed with DTI. Moreover, aortic stiffness may be associated with late-life depression, given the associations between aortic stiffness and WMHs, as well as that between WMH and late-life depression. Only a few studies have addressed this topic, all based on cross-sectional study designs. Therefore, the goal of the dissertation was to study the associations of aortic stiffness with white matter microstructural integrity and depressive symptoms among older adults. To achieve this goal, two aims were proposed:

Specific Aim 1, to study the cross-sectional relationship of aortic stiffness with white matter microstructural integrity in older adults.

Specific Aim 2, to study the cross-sectional and longitudinal relationship of aortic stiffness with depressive symptoms in older adults.

Analysis was conducted based on the fifth (2011-2013) and sixth visit (2016-2018) of Atherosclerosis Risk in Communities (ARIC) study, a large biracial prospective cohort of adults (aged 45 to 66 years at visit 1, 1985-1987) in four U.S. communities. Aortic stiffness was assessed as carotid-femoral pulse wave velocity (cfPWV) at visit 5, and white matter microstructural integrity was measured using DTI at visit 5. Depressive symptoms were assessed using the 11-item Center for Epidemiologic Studies Depression Scale (CES-D). Variables of demographic, lifestyle and physical health factors were available at visit 1 or visit 5 for majority of participants.

For Aim 1, the cross-sectional associations of cfPWV with DTI measures (fractional anisotropy, mean diffusivity) were assessed among a group of older adults composed of participants with evidence of cognitive impairment and a stratified random sample of cognitively normal participants from the ARIC study. The analysis assessed potential confounding by demographic, lifestyle and physical health factors.

For Aim 2, cross-sectional associations of cfPWV with depressive symptoms and clinically significant depressive symptoms (CES-D score ≥9) at visit 5, as well as longitudinal associations of cfPWV with change of depressive symptoms from visit 5 to visit 6 and incident clinically significant depressive symptoms at visit 6 were assessed among participants free of clinically significant depressive symptoms at visit 5. The analysis assessed potential confounding by demographic, lifestyle and physical health factors.

7.2. Main findings

For Aim 1, a total of 1,484 participants remained in the analytic set, with the mean age of 76 years, 40% male, 28.6% black. The FA and MD values were normally distributed. FA was negatively correlated with MD overall ($r=-0.75$, $p<0.0001$). Participants with elevated cfPWV were older, more likely to be black, and less likely to have completed high school. In addition, participants with greater cfPWV were less likely to consume alcohol and spent less time engaging in leisure-time physical activities, while being more likely to have hypertension and diabetes, as well as greater WMH volume. Each 1 m/s higher cfPWV was associated with 0.03 standard deviations lower of overall FA (95% confidence interval (CI): -0.05, -0.02) and 0.03 standard deviations higher of overall MD (95% CI: 0.02, 0.04). High cfPWV (upper 25^{th} percentile) was associated with 0.26 standard deviations lower of FA (95% CI: -0.39, -0.14) and 0.21 standard deviations higher overall MD (95% CI: 0.11, 0.32). Similar associations were observed at individual regions of interest (anterior corpus callosum, posterior corpus callosum, frontal lobe, temporal lobe, occipital lobe and parietal lobe).

For Aim 2, a total of 4,511 examinees at baseline were included in the cross-sectional analysis. Participants with high cfPWV were older, more likely to be male and African American, were less likely to have completed high school, and had a higher prevalence of hypertension and diabetes, lower body mass index, less time spent on weekly physical activity, higher average CES-D score, and greater prevalence of clinically significant depressive symptoms. Each standard deviation (3.14 m/s) increment in cfPWV was associated with 0.05 standard deviation higher total CES-D score (95% CI: 0.02, 0.08), and associated with 1.13 times the odds of clinically significant depressive symptoms at visit 5. High cfPWV (defined at the upper 25^{th} percentile) was associated with 0.07 standard deviation higher total CES-D score

(95% CI: 0.004, 0.15) and 1.37 times the odds of clinically significant depressive symptoms (95% CI: 1.01, 1.85) among older adults at visit 5. In the longitudinal analysis, each standard deviation (3.14 m/s) higher in cfPWV and high cfPWV (upper 25th percentile) were associated with higher total CES-D score and higher odds of incident clinically significant depressive symptoms among older adults, although these associations were not statistically significant.

7.3. Strengths

The analysis conducted for Aim 1 represents the largest population-based study of the association between aortic stiffness and white matter microstructural integrity among older adults. The data collection for this study was based on standardized protocols administered by trained personnel, and employed validated measurements for aortic stiffness (cfPWV), as well as white matter microstructural (FA, MD) and macrostructural integrity (WMHs).

The study conducted for Aim 2 is the only population-based prospective study on aortic stiffness and depressive symptoms among older adults with repeated measures of depressive symptoms. The large sample size and gold standard measurement of aortic stiffness are further strengths of the study.

7.4. Limitations

For the study conducted for Aim 1, the main limitation is its cross-sectional design, which limits causal inferences regarding the association of aortic stiffness with cerebral white matter microstructural integrity among older adults, and allows for the possibility of reverse causality. However, it is improbable that WMH or white matter-related disease (e.g. depression) would affect cfPWV. As a further limitation, effectively all participants in this study had some degree of WMH, precluding a study of associations between cfPWV and DTI measures in the absence of WMH. We note however that our sensitivity analysis identified differences in associations at

high and low WMH volumes. Lastly, this study is restricted to older adults, thus survivors who are sufficiently engaged, healthy and vigorous to attend an examination at a facility of the ARIC study. These characteristics are to be considered in generalizing our results.

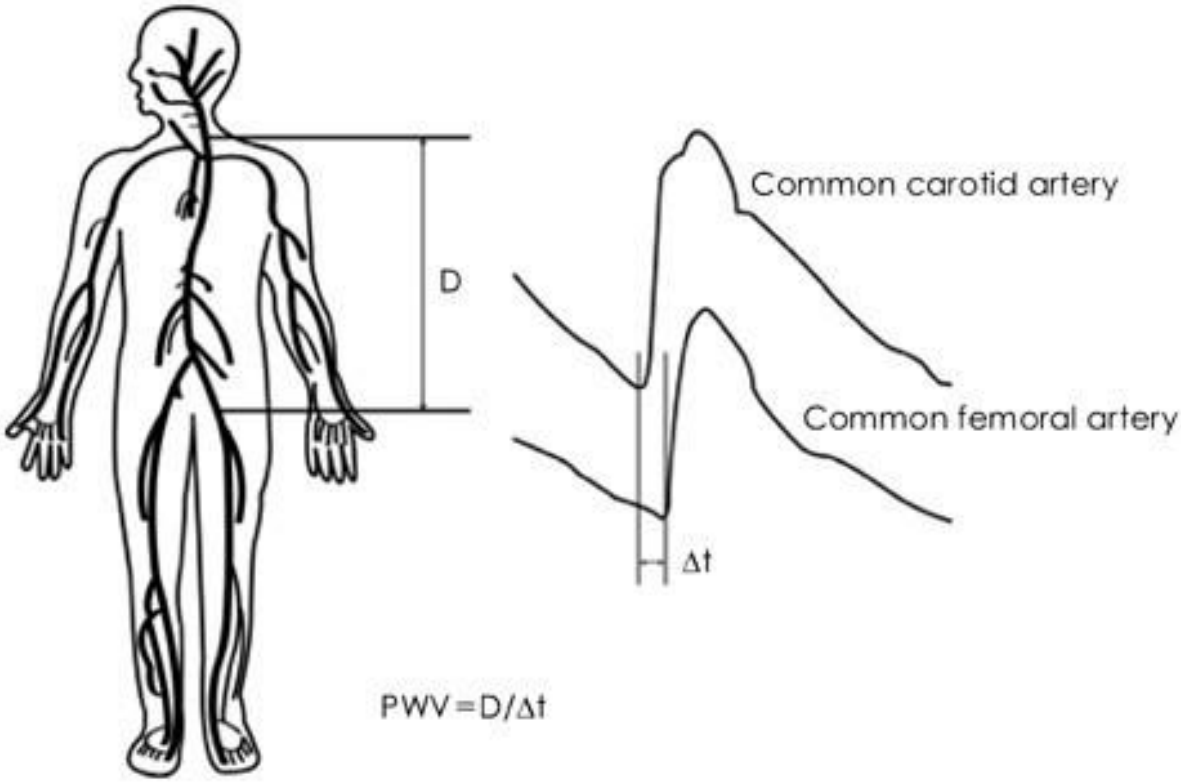
For the study conducted for Aim 2, a significant limitation of our study is the lack of clinical diagnoses of depression among older adults. We did however observe associations of cfPWV and depressive symptoms using a validated standardized scale. As a further limitation, our study is subject to a high degree of loss to follow-up. To assess its potential impact and correct for selection bias we imputed the missing data, which may reflect the true associations between aortic stiffness and depressive symptoms among older adults in the population.

7.5. Overall conclusions

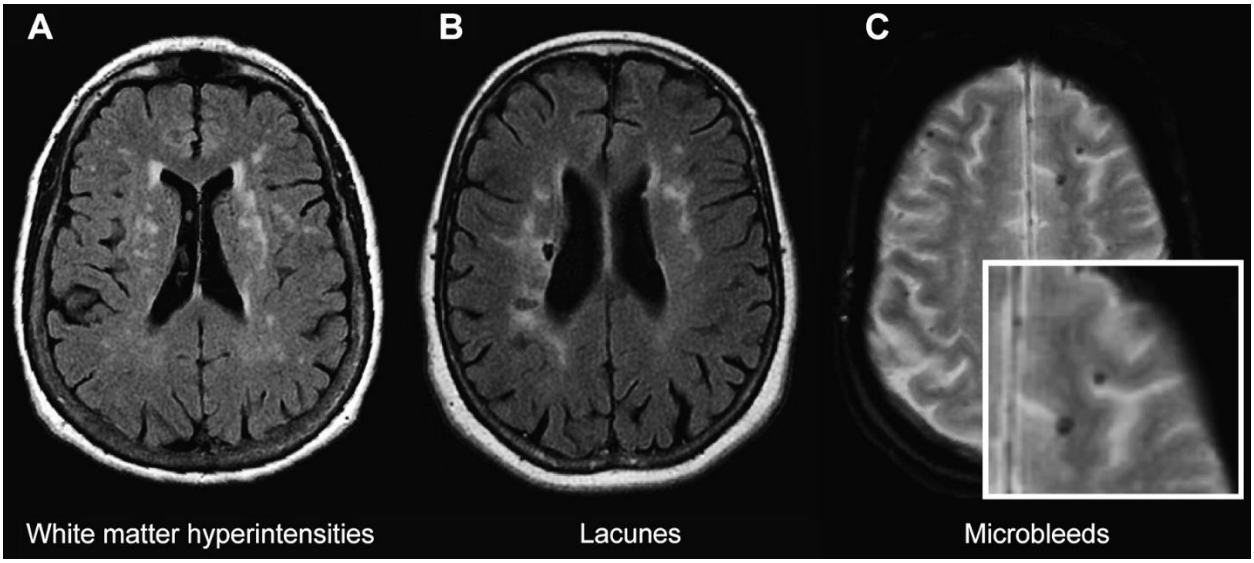
Results of our study suggest that higher aortic stiffness is associated with lower cerebral white matter microstructural integrity among older adults. Further, high aortic stiffness is cross-sectionally associated with higher severity of depressive symptoms and higher odds of clinically significant depressive symptoms, but is not significantly associated with 5-year change of depressive symptoms or incident, clinically significant depressive symptoms in a sample of community-dwelling older adults.

Future research should consider the longitudinal associations of aortic stiffness with white matter microstructural integrity, as well as the potential opportunity for preservation of white matter microstructural integrity through the lowering of aortic stiffness. Given the limited information available, the longitudinal association between aortic stiffness and depressive symptoms among older adults warrants further investigation.

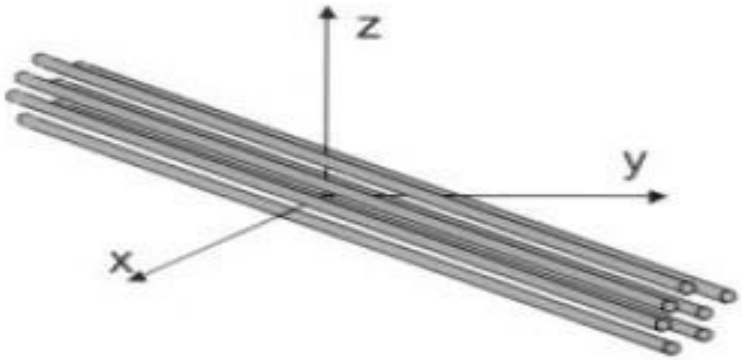
APPENDIX 1: MEASUREMENT OF CAROTID-FEMORAL PULSE WAVE VELOCITY. SOURCE: RHEE (2008)[243]



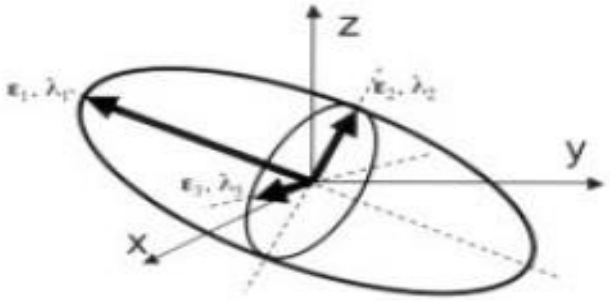
APPENDIX 2: MRI IMAGES OF CEREBRAL SMALL VESSEL DISEASE, INCLUDING (A) WHITE MATTER HYPERINTENSITIES (B) LACUNES (C) MICROBLEEDS. SOURCE: INZITARI (2009)[244]



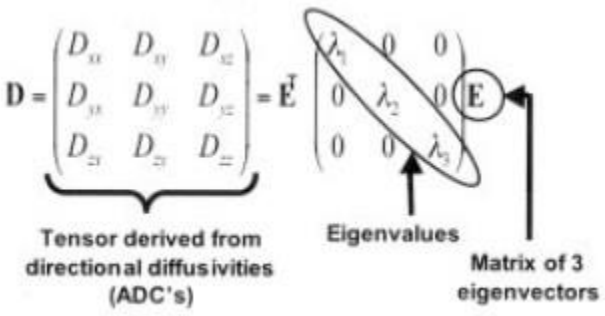
APPENDIX 3: PHYSICS OF DTI. SOURCE: JELLISON (2004)[96]



(A)



(B)



(C)

APPENDIX 4: ITEMS OF DIFFERENT VERSIONS OF CES-D SCALES

	20-item	10-item	8-item	11-item	12-item
I was bothered by things that usually don't bother me.	X	X			
I did not feel like eating; my appetite was poor	X			X	X
I felt that I could not shake off the blues even with help from my family or friends.	X				X
I felt I was just as good as other people.	X				
I had trouble keeping my mind on what I was doing.	X	X			X
I felt depressed.	X	X	X	X	X
I felt that everything I did was an effort.	X	X	X	X	X
I felt hopeful about the future.	X	X			X
I thought my life had been a failure.	X				
I felt fearful.	X	X			
My sleep was restless.	X	X	X	X	X
I was happy.	X	X	X	X	X
I talked less than usual.	X				
I felt lonely.	X	X	X	X	X
People were unfriendly.	X			X	
I enjoyed life.	X		X	X	X
I had crying spells.	X				X
I felt sad.	X		X	X	
I felt that people disliked me.	X			X	X
I could not get "going."	X	X	X	X	

REFERENCES

1. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M (1997) 'Vascular depression' hypothesis. Archives of general psychiatry 54 (10):915-922

2. London GM, Pannier B (2010) Arterial functions: how to interpret the complex physiology. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 25 (12):3815-3823. doi:10.1093/ndt/gfq614

3. Wang D, Wang Z, Zhang L, Wang Y (2017) Roles of Cells from the Arterial Vessel Wall in Atherosclerosis. Mediators Inflamm 2017:8135934-8135934. doi:10.1155/2017/8135934

4. Frantz C, Stewart KM, Weaver VM (2010) The extracellular matrix at a glance. J Cell Sci 123 (Pt 24):4195-4200. doi:10.1242/jcs.023820

5. Milan A, Tosello F, Fabbri A, Vairo A, Leone D, Chiarlo M, Covella M, Veglio F (2011) Arterial stiffness: from physiology to clinical implications. High blood pressure & cardiovascular prevention : the official journal of the Italian Society of Hypertension 18 (1):1-12. doi:10.2165/11588020-000000000-00000

6. Eble JA, Niland S (2009) The extracellular matrix of blood vessels. Current pharmaceutical design 15 (12):1385-1400

7. Shirwany NA, Zou MH (2010) Arterial stiffness: a brief review. Acta pharmacologica Sinica 31 (10):1267-1276. doi:10.1038/aps.2010.123

8. Zieman SJ, Melenovsky V, Kass DA (2005) Mechanisms, pathophysiology, and therapy of arterial stiffness. Arteriosclerosis, thrombosis, and vascular biology 25 (5):932-943. doi:10.1161/01.atv.0000160548.78317.29

9. Izzo JL, Jr., Shykoff BE (2001) Arterial stiffness: clinical relevance, measurement, and treatment. Reviews in cardiovascular medicine 2 (1):29-34, 37-40

10. van Varik BJ, Rennenberg RJMW, Reutelingsperger CP, Kroon AA, de Leeuw PW, Schurgers LJ (2012) Mechanisms of arterial remodeling: lessons from genetic diseases. Front Genet 3:290-290. doi:10.3389/fgene.2012.00290

11. Quinn U, Tomlinson LA, Cockcroft JR (2012) Arterial stiffness. JRSM Cardiovascular Disease 1 (6):cvd.2012.012024. doi:10.1258/cvd.2012.012024

12. Avolio A (2013) Arterial Stiffness. Pulse (Basel) 1 (1):14-28. doi:10.1159/000348620

13. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H (2006) Expert consensus document on arterial stiffness: methodological issues and clinical applications. European heart journal 27 (21):2588-2605. doi:10.1093/eurheartj/ehl254

14. Palombo C, Kozakova M (2016) Arterial stiffness, atherosclerosis and cardiovascular risk: Pathophysiologic mechanisms and emerging clinical indications. Vascular pharmacology 77:1-7. doi:10.1016/j.vph.2015.11.083

15. Mudau M, Genis A, Lochner A, Strijdom H (2012) Endothelial dysfunction: the early predictor of atherosclerosis. Cardiovasc J Afr 23 (4):222-231. doi:10.5830/CVJA-2011-068

16. Zhang Y, Agnoletti D, Xu Y, Wang JG, Blacher J, Safar ME (2014) Carotid-femoral pulse wave velocity in the elderly. Journal of hypertension 32 (8):1572-1576; discussion 1576. doi:10.1097/hjh.0000000000000187

17. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D (2004) Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension (Dallas, Tex : 1979) 43 (6):1239-1245. doi:10.1161/01.HYP.0000128420.01881.aa

18. Berard E, Bongard V, Ruidavets JB, Amar J, Ferrieres J (2013) Pulse wave velocity, pulse pressure and number of carotid or femoral plaques improve prediction of cardiovascular death in a population at low risk. Journal of human hypertension 27 (9):529-534. doi:10.1038/jhh.2013.8

19. Inoue N, Maeda R, Kawakami H, Shokawa T, Yamamoto H, Ito C, Sasaki H (2009) Aortic pulse wave velocity predicts cardiovascular mortality in middle-aged and elderly Japanese men. Circulation journal : official journal of the Japanese Circulation Society 73 (3):549-553

20. Shokawa T, Imazu M, Yamamoto H, Toyofuku M, Tasaki N, Okimoto T, Yamane K, Kohno N (2005) Pulse wave velocity predicts cardiovascular mortality: findings from the Hawaii-Los Angeles-Hiroshima study. Circulation journal : official journal of the Japanese Circulation Society 69 (3):259-264

21. Meaume S, Benetos A, Henry OF, Rudnichi A, Safar ME (2001) Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. Arteriosclerosis, thrombosis, and vascular biology 21 (12):2046-2050

22. Duman OO, Goldeli O, Gursul E, Baris N, Ozpelit E, Simsek MA (2015) The value of aortic pulse wave velocity in predicting coronary artery disease diagnosis and severity. Acta cardiologica 70 (3):315-322. doi:10.2143/ac.70.3.3080636

23. Lim HE, Park CG, Shin SH, Ahn JC, Seo HS, Oh DJ (2004) Aortic pulse wave velocity as an independent marker of coronary artery disease. Blood pressure 13 (6):369-375

24. Pereira T, Maldonado J, Pereira L, Conde J (2013) Aortic stiffness is an independent predictor of stroke in hypertensive patients. Arquivos brasileiros de cardiologia 100 (5):437-443. doi:10.5935/abc.20130079

25. Zhong Q, Hu MJ, Cui YJ, Liang L, Zhou MM, Yang YW, Huang F (2017) Carotid-Femoral Pulse Wave Velocity in the Prediction of Cardiovascular Events and Mortality: An Updated Systematic Review and Meta-Analysis. Angiology:3319717742544. doi:10.1177/0003319717742544

26. Pase MP, Herbert A, Grima NA, Pipingas A, O'Rourke MF (2012) Arterial stiffness as a cause of cognitive decline and dementia: a systematic review and meta-analysis. Internal medicine journal 42 (7):808-815. doi:10.1111/j.1445-5994.2011.02645.x

27. Pase MP, Beiser A, Himali JJ, Tsao C, Satizabal CL, Vasan RS, Seshadri S, Mitchell GF (2016) Aortic Stiffness and the Risk of Incident Mild Cognitive Impairment and Dementia. Stroke 47 (9):2256-2261. doi:10.1161/strokeaha.116.013508

28. Meyer ML, Palta P, Tanaka H, Deal JA, Wright J, Knopman DS, Griswold ME, Mosley TH, Heiss G (2017) Association of Central Arterial Stiffness and Pressure Pulsatility with Mild Cognitive Impairment and Dementia: The Atherosclerosis Risk in Communities Study-Neurocognitive Study (ARIC-NCS). Journal of Alzheimer's disease : JAD 57 (1):195-204. doi:10.3233/jad-161041

29. Nilsson ED, Elmstahl S, Minthon L, Pihlsgard M, Nilsson PM, Hansson O, Nagga K (2017) No independent association between pulse wave velocity and dementia: a population-based, prospective study. Journal of hypertension 35 (12):2462-2467. doi:10.1097/hjh.0000000000001480

30. Mitchell GF, Guo CY, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D (2007) Cross-sectional correlates of increased aortic stiffness in the community: the Framingham Heart Study. Circulation 115 (20):2628-2636. doi:10.1161/circulationaha.106.667733

31. Mitchell GF (2014) Arterial stiffness and hypertension: chicken or egg? Hypertension (Dallas, Tex : 1979) 64 (2):210-214. doi:10.1161/HYPERTENSIONAHA.114.03449

32. Dernellis J, Panaretou M (2005) Aortic stiffness is an independent predictor of progression to hypertension in nonhypertensive subjects. Hypertension (Dallas, Tex : 1979) 45 (3):426-431. doi:10.1161/01.hyp.0000157818.58878.93

33. Liao D, Arnett DK, Tyroler HA, Riley WA, Chambless LE, Szklo M, Heiss G (1999) Arterial stiffness and the development of hypertension. The ARIC study. Hypertension (Dallas, Tex : 1979) 34 (2):201-206

34. Najjar SS, Scuteri A, Shetty V, Wright JG, Muller DC, Fleg JL, Spurgeon HP, Ferrucci L, Lakatta EG (2008) Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. Journal of the American College of Cardiology 51 (14):1377-1383. doi:10.1016/j.jacc.2007.10.065

35. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS, Mitchell GF (2012) Aortic stiffness, blood pressure progression, and incident hypertension. Jama 308 (9):875-881. doi:10.1001/2012.jama.10503

36. El Khoudary SR, Barinas-Mitchell E, White J, Sutton-Tyrrell K, Kuller LH, Curb JD, Shin C, Ueshima H, Masaki K, Evans RW, Miura K, Edmundowicz D, Sekikawa A (2012) Adiponectin, systolic blood pressure, and alcohol consumption are associated with more aortic stiffness progression among apparently healthy men. Atherosclerosis 225 (2):475-480. doi:10.1016/j.atherosclerosis.2012.09.015

37. AlGhatrif M, Strait JB, Morrell CH, Canepa M, Wright J, Elango P, Scuteri A, Najjar SS, Ferrucci L, Lakatta EG (2013) Longitudinal trajectories of arterial stiffness and the role of blood pressure: the Baltimore Longitudinal Study of Aging. Hypertension (Dallas, Tex : 1979) 62 (5):934-941. doi:10.1161/hypertensionaha.113.01445

38. Birru MS, Matthews KA, Thurston RC, Brooks MM, Ibrahim S, Barinas-Mitchell E, Janssen I, Sutton-Tyrrell K (2011) African-American ethnicity and cardiovascular risk factors are related to aortic pulse-wave velocity progression. American journal of hypertension 24 (7):809-815. doi:10.1038/ajh.2011.57

39. Strain WD, Chaturvedi N, Dockery F, Shiff R, Shore AC, Bulpitt CJ, Rajkumar C (2006) Increased arterial stiffness in Europeans and African Caribbeans with type 2 diabetes cannot be accounted for by conventional cardiovascular risk factors. American journal of hypertension 19 (9):889-896. doi:10.1016/j.amjhyper.2006.01.009

40. McEniery CM, Wilkinson IB, Johansen NB, Witte DR, Singh-Manoux A, Kivimaki M, Tabak AG, Brunner EJ, Shipley MJ (2017) Nondiabetic Glucometabolic Status and Progression of Aortic Stiffness: The Whitehall II Study. Diabetes care 40 (4):599-606. doi:10.2337/dc16-1773

41. Li P, Wang L, Liu C (2017) Overweightness, obesity and arterial stiffness in healthy subjects: a systematic review and meta-analysis of literature studies. Postgraduate medicine 129 (2):224-230. doi:10.1080/00325481.2017.1268903

42. Petersen KS, Blanch N, Keogh JB, Clifton PM (2015) Effect of weight loss on pulse wave velocity: systematic review and meta-analysis. Arteriosclerosis, thrombosis, and vascular biology 35 (1):243-252. doi:10.1161/atvbaha.114.304798

43. Whelton SP, Blankstein R, Al–Mallah MH, Lima JAC, Bluemke DA, Hundley WG, Polak JF, Blumenthal RS, Nasir K, Blaha MJ (2013) Association of resting heart rate with carotid and aortic arterial stiffness: Multi-Ethnic Study of Atherosclerosis (MESA). Hypertension (Dallas, Tex : 1979) 62 (3):10.1161/HYPERTENSIONAHA.1113.01605. doi:10.1161/HYPERTENSIONAHA.113.01605

44. Albaladejo P, Asmar R, Safar M, Benetos A (2000) Association between 24-hour ambulatory heart rate and arterial stiffness. Journal of human hypertension 14 (2):137-141

45. Wilkinson I, Cockcroft JR (2007) Cholesterol, lipids and arterial stiffness. Advances in cardiology 44:261-277. doi:10.1159/000096747

46. Wang F, Ye P, Luo L, Xiao W, Qi L, Bian S, Wu H, Sheng L, Xiao T, Xu R (2011) Association of serum lipids with arterial stiffness in a population-based study in Beijing. European journal of clinical investigation 41 (9):929-936. doi:10.1111/j.1365-2362.2011.02481.x

47. Wang X, Du Y, Fan L, Ye P, Yuan Y, Lu X, Wang F, Zeng Q (2013) Relationships between HDL-C, hs-CRP, with central arterial stiffness in apparently healthy people undergoing a general health examination. PloS one 8 (12):e81778. doi:10.1371/journal.pone.0081778

48. Wang X, Ye P, Cao R, Yang X, Xiao W, Zhang Y, Bai Y, Wu H (2016) Triglycerides are a predictive factor for arterial stiffness: a community-based 4.8-year prospective study. Lipids in health and disease 15:97. doi:10.1186/s12944-016-0266-8

49. McVeigh GE, Brennan GM, Cohn JN, Finkelstein SM, Hayes RJ, Johnston GD (1994) Fish oil improves arterial compliance in non-insulin-dependent diabetes mellitus. Arteriosclerosis and thrombosis : a journal of vascular biology 14 (9):1425-1429

50. Nestel PJ, Pomeroy SE, Sasahara T, Yamashita T, Liang YL, Dart AM, Jennings GL, Abbey M, Cameron JD (1997) Arterial compliance in obese subjects is improved with dietary plant n-3 fatty acid from flaxseed oil despite increased LDL oxidizability. Arteriosclerosis, thrombosis, and vascular biology 17 (6):1163-1170

51. Ashor AW, Lara J, Siervo M, Celis-Morales C, Mathers JC (2014) Effects of Exercise Modalities on Arterial Stiffness and Wave Reflection: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. PloS one 9 (10):e110034. doi:10.1371/journal.pone.0110034

52. Nordstrand N, Gjevestad E, Hertel JK, Johnson LK, Saltvedt E, Roislien J, Hjelmesaeth J (2013) Arterial stiffness, lifestyle intervention and a low-calorie diet in morbidly obese patients-a nonrandomized clinical trial. Obesity (Silver Spring, Md) 21 (4):690-697. doi:10.1002/oby.20099

53. Jatoi NA, Jerrard-Dunne P, Feely J, Mahmud A (2007) Impact of smoking and smoking cessation on arterial stiffness and aortic wave reflection in hypertension. Hypertension (Dallas, Tex : 1979) 49 (5):981-985. doi:10.1161/hypertensionaha.107.087338

54. Lee HY, Oh BH (2010) Aging and arterial stiffness. Circulation journal : official journal of the Japanese Circulation Society 74 (11):2257-2262

55. Chen X, Huang B, Liu M, Li X (2015) Effects of different types of antihypertensive agents on arterial stiffness: a systematic review and meta-analysis of randomized controlled trials. Journal of Thoracic Disease 7 (12):2339-2347. doi:10.3978/j.issn.2072-1439.2015.12.58

56. Upala S, Wirunsawanya K, Jaruvongvanich V, Sanguankeo A (2017) Effects of statin therapy on arterial stiffness: A systematic review and meta-analysis of randomized controlled trial. International journal of cardiology 227:338-341. doi:10.1016/j.ijcard.2016.11.073

57. Mayfield (2018) Anatomy of the Brain. https://mayfieldclinic.com/pe-anatbrain.htm. Accessed 07/06 2019

58. Joutel A, Faraci FM (2014) Cerebral small vessel disease: insights and opportunities from mouse models of collagen IV-related small vessel disease and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Stroke 45 (4):1215-1221. doi:10.1161/strokeaha.113.002878

59. Cipolla M (2009) The Cerebral Circulation. Chapter 2, Anatomy and Ultrastructure. San Rafael (CA): Morgan & Claypool Life Sciences,

60. Serlin Y, Shelef I, Knyazer B, Friedman A (2015) Anatomy and physiology of the blood-brain barrier. Semin Cell Dev Biol 38:2-6. doi:10.1016/j.semcdb.2015.01.002

61. Wardlaw JM, Valdes Hernandez MC, Munoz-Maniega S (2015) What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. Journal of the American Heart Association 4 (6):001140. doi:10.1161/jaha.114.001140

62. Salamon N (2014) Neuroimaging of cerebral small vessel disease. Brain pathology (Zurich, Switzerland) 24 (5):519-524. doi:10.1111/bpa.12179

63. Shibuya M, Leite CDC, Lucato LT (2017) Neuroimaging in cerebral small vessel disease: Update and new concepts. Dementia & neuropsychologia 11 (4):336-342. doi:10.1590/1980-57642016dn11-040002

64. Pantoni L (2010) Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. The Lancet Neurology 9 (7):689-701. doi:10.1016/s1474-4422(10)70104-6

65. Wardlaw JM, Smith C, Dichgans M (2013) Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. The Lancet Neurology 12 (5):483-497. doi:10.1016/s1474-4422(13)70060-7

66. Rincon F, Wright CB (2014) Current pathophysiological concepts in cerebral small vessel disease. Frontiers in aging neuroscience 6:24. doi:10.3389/fnagi.2014.00024

67. Blair GW, Hernandez MV, Thrippleton MJ, Doubal FN, Wardlaw JM (2017) Advanced Neuroimaging of Cerebral Small Vessel Disease. Curr Treat Options Cardiovasc Med 19 (7):56-56. doi:10.1007/s11936-017-0555-1

68. Patel B, Markus HS (2011) Magnetic resonance imaging in cerebral small vessel disease and its use as a surrogate disease marker. International journal of stroke : official journal of the International Stroke Society 6 (1):47-59. doi:10.1111/j.1747-4949.2010.00552.x

69. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, Black SE, Brayne C, Breteler M, Chabriat H, Decarli C, de Leeuw FE, Doubal F, Duering M, Fox NC, Greenberg S, Hachinski V, Kilimann I, Mok V, Oostenbrugge R, Pantoni L, Speck O, Stephan BC, Teipel S, Viswanathan A, Werring D, Chen C, Smith C, van Buchem M, Norrving B, Gorelick PB, Dichgans M (2013) Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. The Lancet Neurology 12 (8):822-838. doi:10.1016/s1474-4422(13)70124-8

70. Sudlow CL, Warlow CP (1997) Comparable studies of the incidence of stroke and its pathological types: results from an international collaboration. International Stroke Incidence Collaboration. Stroke 28 (3):491-499

71. Vermeer SE, Longstreth WT, Jr., Koudstaal PJ (2007) Silent brain infarcts: a systematic review. The Lancet Neurology 6 (7):611-619. doi:10.1016/s1474-4422(07)70170-9

72. Bryan RN, Wells SW, Miller TJ, Elster AD, Jungreis CA, Poirier VC, Lind BK, Manolio TA (1997) Infarctlike lesions in the brain: prevalence and anatomic characteristics at MR imaging of the elderly--data from the Cardiovascular Health Study. Radiology 202 (1):47-54. doi:10.1148/radiology.202.1.8988191

73. Daneman R, Prat A The blood-brain barrier. Cold Spring Harb Perspect Biol 7 (1):a020412-a020412. doi:10.1101/cshperspect.a020412

74. Moran C, Phan TG, Srikanth VK (2012) Cerebral small vessel disease: a review of clinical, radiological, and histopathological phenotypes. International journal of stroke : official journal of the International Stroke Society 7 (1):36-46. doi:10.1111/j.1747-4949.2011.00725.x

75. Soderlund H, Nyberg L, Adolfsson R, Nilsson LG, Launer LJ (2003) High prevalence of white matter hyperintensities in normal aging: relation to blood pressure and cognition. Cortex; a journal devoted to the study of the nervous system and behavior 39 (4-5):1093-1105

76. de Leeuw FE, de Groot JC, Achten E, Oudkerk M, Ramos L, Heijboer R, Hofman A, Jolles J, van Gijn J, Breteler M (2001) Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. Journal of Neurology, Neurosurgery, and Psychiatry 70 (1):9-14. doi:10.1136/jnnp.70.1.9

77. Enzinger C, Fazekas F, Ropele S, Schmidt R (2007) Progression of cerebral white matter lesions -- clinical and radiological considerations. Journal of the neurological sciences 257 (1-2):5-10. doi:10.1016/j.jns.2007.01.018

78. Young VG, Halliday GM, Kril JJ (2008) Neuropathologic correlates of white matter hyperintensities. Neurology 71 (11):804-811. doi:10.1212/01.wnl.0000319691.50117.54

79. Vernooij MW, van der Lugt A, Ikram MA, Wielopolski PA, Niessen WJ, Hofman A, Krestin GP, Breteler MM (2008) Prevalence and risk factors of cerebral microbleeds: the Rotterdam Scan Study. Neurology 70 (14):1208-1214. doi:10.1212/01.wnl.0000307750.41970.d9

80. Cordonnier C, Al-Shahi Salman R, Wardlaw J (2007) Spontaneous brain microbleeds: systematic review, subgroup analyses and standards for study design and reporting. Brain : a journal of neurology 130 (Pt 8):1988-2003. doi:10.1093/brain/awl387

81. Sepehry AA, Lang D, Hsiung GY, Rauscher A (2016) Prevalence of Brain Microbleeds in Alzheimer Disease: A Systematic Review and Meta-Analysis on the Influence of Neuroimaging Techniques. AJNR American journal of neuroradiology 37 (2):215-222. doi:10.3174/ajnr.A4525

82. Poels MM, Vernooij MW, Ikram MA, Hofman A, Krestin GP, van der Lugt A, Breteler MM (2010) Prevalence and risk factors of cerebral microbleeds: an update of the Rotterdam scan study. Stroke 41 (10 Suppl):S103-106. doi:10.1161/strokeaha.110.595181

83. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, Launer LJ, Van Buchem MA, Breteler MM (2009) Cerebral microbleeds: a guide to detection and interpretation. The Lancet Neurology 8 (2):165-174. doi:10.1016/s1474-4422(09)70013-4

84. Grinberg LT, Thal DR (2010) Vascular pathology in the aged human brain. Acta neuropathologica 119 (3):277-290. doi:10.1007/s00401-010-0652-7

85. Prabhakaran S, Wright CB, Yoshita M, Delapaz R, Brown T, DeCarli C, Sacco RL (2008) Prevalence and determinants of subclinical brain infarction: the Northern Manhattan Study. Neurology 70 (6):425-430. doi:10.1212/01.wnl.0000277521.66947.e5

86. Grueter BE, Schulz UG (2012) Age-related cerebral white matter disease (leukoaraiosis): a review. Postgraduate medical journal 88 (1036):79-87. doi:10.1136/postgradmedj-2011-130307

87. Rasband MN (2016) Glial Contributions to Neural Function and Disease. Mol Cell Proteomics 15 (2):355-361. doi:10.1074/mcp.R115.053744

88. Sarbu N, Shih RY, Jones RV, Horkayne-Szakaly I, Oleaga L, Smirniotopoulos JG (2016) White Matter Diseases with Radiologic-Pathologic Correlation. RadioGraphics 36 (5):1426-1447. doi:10.1148/rg.2016160031

89. Siegel GJ (1999) Basic neurochemistry: molecular, cellular and medical aspects. vol V360 SIEb.

90. Murphy ML, Frodl T (2011) Meta-analysis of diffusion tensor imaging studies shows altered fractional anisotropy occurring in distinct brain areas in association with depression. Biology of Mood & Anxiety Disorders 1:3-3. doi:10.1186/2045-5380-1-3

91. Choudhri AF, Chin EM, Blitz AM, Gandhi D (2014) Diffusion tensor imaging of cerebral white matter: technique, anatomy, and pathologic patterns. Radiologic clinics of North America 52 (2):413-425. doi:10.1016/j.rcl.2013.11.005

92. O'Donnell LJ, Westin C-F (2011) An introduction to diffusion tensor image analysis. Neurosurgery clinics of North America 22 (2):185-viii. doi:10.1016/j.nec.2010.12.004

93. Mukherjee P, Berman JI, Chung SW, Hess CP, Henry RG (2008) Diffusion tensor MR imaging and fiber tractography: theoretic underpinnings. AJNR American journal of neuroradiology 29 (4):632-641. doi:10.3174/ajnr.A1051

94. Acosta-Cabronero J, Nestor PJ (2014) Diffusion tensor imaging in Alzheimer's disease: insights into the limbic-diencephalic network and methodological considerations. Frontiers in aging neuroscience 6 (266). doi:10.3389/fnagi.2014.00266

95. Alexander AL, Lee JE, Lazar M, Field AS (2007) Diffusion tensor imaging of the brain. Neurotherapeutics 4 (3):316-329. doi:10.1016/j.nurt.2007.05.011

96. Jellison BJ, Field AS, Medow J, Lazar M, Salamat MS, Alexander AL (2004) Diffusion tensor imaging of cerebral white matter: a pictorial review of physics, fiber tract anatomy, and tumor imaging patterns. AJNR American journal of neuroradiology 25 (3):356-369

97. O'Sullivan M (2008) Leukoaraiosis. Practical neurology 8 (1):26-38. doi:10.1136/jnnp.2007.139428

98. Chao LL, Decarli C, Kriger S, Truran D, Zhang Y, Laxamana J, Villeneuve S, Jagust WJ, Sanossian N, Mack WJ, Chui HC, Weiner MW (2013) Associations between white matter hyperintensities and beta amyloid on integrity of projection, association, and limbic fiber tracts measured with diffusion tensor MRI. PloS one 8 (6):e65175. doi:10.1371/journal.pone.0065175

99. Wang L, Goldstein FC, Levey AI, Lah JJ, Meltzer CC, Holder CA, Mao H (2011) White Matter Hyperintensities and Changes in White Matter Integrity in Patients with Alzheimer's Disease. Neuroradiology 53 (5):373-381. doi:10.1007/s00234-010-0806-2

100. Maniega SM, Valdés Hernández MC, Clayden JD, Royle NA, Murray C, Morris Z, Aribisala BS, Gow AJ, Starr JM, Bastin ME, Deary IJ, Wardlaw JM (2015) White matter hyperintensities and normal-appearing white matter integrity in the aging brain. Neurobiology of Aging 36 (2):909-918. doi:10.1016/j.neurobiolaging.2014.07.048

101. Watson C, Busovaca E, Foley JM, Allen IE, Schwarz CG, Jahanshad N, Nir TM, Esmaeili-Firidouni P, Milanini B, Rosen H, Carmichael OT, Thompson PM, Valcour VG (2017) White matter hyperintensities correlate to cognition and fiber tract integrity in older adults with HIV. Journal of neurovirology 23 (3):422-429. doi:10.1007/s13365-016-0509-5

102. Zhong G, Zhang R, Jiaerken Y, Yu X, Zhou Y, Liu C, Lin L, Tong L, Lou M (2017) Better Correlation of Cognitive Function to White Matter Integrity than to Blood Supply in Subjects with Leukoaraiosis. Frontiers in aging neuroscience 9:185. doi:10.3389/fnagi.2017.00185

103. van Norden AG, van Uden IW, de Laat KF, van Dijk EJ, de Leeuw FE (2012) Cognitive function in small vessel disease: the additional value of diffusion tensor imaging to conventional magnetic resonance imaging: the RUN DMC study. Journal of Alzheimer's disease : JAD 32 (3):667-676. doi:10.3233/jad-2012-120784

104. Shimony JS, Sheline YI, D'Angelo G, Epstein AA, Benzinger TLS, Mintun MA, McKinstry RC, Snyder AZ (2009) DIFFUSE MICROSTRUCTURAL ABNORMALITIES OF NORMAL APPEARING WHITE MATTER IN LATE LIFE DEPRESSION: A DIFFUSION TENSOR IMAGING STUDY. Biological psychiatry 66 (3):245-252. doi:10.1016/j.biopsych.2009.02.032

105. Yang Q, Huang X, Hong N, Yu X (2007) White matter microstructural abnormalities in late-life depression. International psychogeriatrics 19 (4):757-766. doi:10.1017/s1041610207004875

106. Nobuhara K, Okugawa G, Sugimoto T, Minami T, Tamagaki C, Takase K, Saito Y, Sawada S, Kinoshita T (2006) Frontal white matter anisotropy and symptom severity of late-life depression: a magnetic resonance diffusion tensor imaging study. Journal of Neurology, Neurosurgery, and Psychiatry 77 (1):120-122. doi:10.1136/jnnp.2004.055129

107. Power MC, Tingle JV, Reid RI, Huang J, Sharrett AR, Coresh J, Griswold M, Kantarci K, Jack CR, Jr., Knopman D, Gottesman RF, Mosley TH (2017) Midlife and Late-Life Vascular Risk Factors and White Matter Microstructural Integrity: The Atherosclerosis Risk in Communities Neurocognitive Study. Journal of the American Heart Association 6 (5). doi:10.1161/jaha.117.005608

108. Wang R, Fratiglioni L, Laukka EJ, Lövdén M, Kalpouzos G, Keller L, Graff C, Salami A, Bäckman L, Qiu C (2015) Effects of vascular risk factors and APOE ε4 on white matter integrity and cognitive decline. Neurology 84 (11):1128-1135. doi:10.1212/WNL.0000000000001379

109. Gons RA, de Laat KF, van Norden AG, van Oudheusden LJ, van Uden IW, Norris DG, Zwiers MP, de Leeuw FE (2010) Hypertension and cerebral diffusion tensor imaging in small vessel disease. Stroke 41 (12):2801-2806. doi:10.1161/strokeaha.110.597237

110. Gons RA, van Norden AG, de Laat KF, van Oudheusden LJ, van Uden IW, Zwiers MP, Norris DG, de Leeuw FE (2011) Cigarette smoking is associated with reduced microstructural integrity of cerebral white matter. Brain : a journal of neurology 134 (Pt 7):2116-2124. doi:10.1093/brain/awr145

111. Gons RA, Tuladhar AM, de Laat KF, van Norden AG, van Dijk EJ, Norris DG, Zwiers MP, de Leeuw FE (2013) Physical activity is related to the structural integrity of cerebral white matter. Neurology 81 (11):971-976. doi:10.1212/WNL.0b013e3182a43e33

112. Henskens LH, Kroon AA, van Oostenbrugge RJ, Gronenschild EH, Fuss-Lejeune MM, Hofman PA, Lodder J, de Leeuw PW (2008) Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. Hypertension (Dallas, Tex : 1979) 52 (6):1120-1126. doi:10.1161/hypertensionaha.108.119024

113. King KS, Chen KX, Hulsey KM, McColl RW, Weiner MF, Nakonezny PA, Peshock RM (2013) White matter hyperintensities: use of aortic arch pulse wave velocity to predict volume independent of other cardiovascular risk factors. Radiology 267 (3):709-717. doi:10.1148/radiol.13121598

114. Poels MM, Zaccai K, Verwoert GC, Vernooij MW, Hofman A, van der Lugt A, Witteman JC, Breteler MM, Mattace-Raso FU, Ikram MA (2012) Arterial stiffness and cerebral small vessel disease: the Rotterdam Scan Study. Stroke 43 (10):2637-2642. doi:10.1161/strokeaha.111.642264

115. van Sloten TT, Mitchell GF, Sigurdsson S, van Buchem MA, Jonsson PV, Garcia ME, Harris TB, Henry RMA, Levey AS, Stehouwer CDA, Gudnason V, Launer LJ (2016) Associations between arterial stiffness, depressive symptoms and cerebral small vessel disease: cross-sectional findings from the AGES-Reykjavik Study. Journal of Psychiatry & Neuroscience : JPN 41 (3):162-168. doi:10.1503/jpn.140334

116. Tsao CW, Seshadri S, Beiser AS, Westwood AJ, Decarli C, Au R, Himali JJ, Hamburg NM, Vita JA, Levy D, Larson MG, Benjamin EJ, Wolf PA, Vasan RS, Mitchell GF (2013) Relations of arterial stiffness and endothelial function to brain aging in the community. Neurology 81 (11):984-991. doi:10.1212/WNL.0b013e3182a43e1c

117. Laugesen E, Høyem P, Stausbøl-Grøn B, Mikkelsen A, Thrysøe S, Erlandsen M, Christiansen JS, Knudsen ST, Hansen KW, Kim WY, Hansen TK, Poulsen PL (2013) Carotid-Femoral Pulse Wave Velocity Is Associated With Cerebral White Matter Lesions in Type 2 Diabetes. Diabetes care 36 (3):722-728. doi:10.2337/dc12-0942

118. Gustavsson AM, Stomrud E, Abul-Kasim K, Minthon L, Nilsson PM, Hansson O, Nagga K (2015) Cerebral Microbleeds and White Matter Hyperintensities in Cognitively Healthy Elderly: A Cross-Sectional Cohort Study Evaluating the Effect of Arterial Stiffness. Cerebrovascular diseases extra 5 (2):41-51. doi:10.1159/000377710

119. van Elderen SG, Brandts A, Westenberg JJ, van der Grond J, Tamsma JT, van Buchem MA, Romijn JA, Kroft LJ, Smit JW, de Roos A (2010) Aortic stiffness is associated with cardiac function and cerebral small vessel disease in patients with type 1 diabetes mellitus: assessment by magnetic resonance imaging. European radiology 20 (5):1132-1138. doi:10.1007/s00330-009-1655-4

120. Rosano C, Watson N, Chang Y, Newman AB, Aizenstein HJ, Du Y, Venkatraman V, Harris TB, Barinas-Mitchell E, Sutton-Tyrrell K (2013) AORTIC PULSE WAVE VELOCITY PREDICTS FOCAL WHITE MATTER HYPERINTENSITIES IN A BIRACIAL COHORT OF OLDER ADULTS. Hypertension (Dallas, Tex : 1979) 61 (1):160-165. doi:10.1161/HYPERTENSIONAHA.112.198069

121. Maillard P, Mitchell GF, Himali JJ, Beiser A, Tsao CW, Pase MP, Satizabal CL, Vasan RS, Seshadri S, DeCarli C (2016) Effects of Arterial Stiffness on Brain Integrity in Young Adults From the Framingham Heart Study. Stroke 47 (4):1030-1036. doi:10.1161/strokeaha.116.012949

122. Maillard P, Mitchell GF, Himali JJ, Beiser A, Fletcher E, Tsao CW, Pase MP, Satizabal CL, Vasan RS, Seshadri S, DeCarli C (2017) Aortic Stiffness, Increased White Matter Free Water, and Altered Microstructural Integrity: A Continuum of Injury. Stroke. doi:10.1161/strokeaha.116.016321

123. Tarumi T, de Jong DL, Zhu DC, Tseng BY, Liu J, Hill C, Riley J, Womack KB, Kerwin DR, Lu H, Munro Cullum C, Zhang R (2015) Central artery stiffness, baroreflex sensitivity, and brain white matter neuronal fiber integrity in older adults. NeuroImage 110:162-170. doi:10.1016/j.neuroimage.2015.01.041

124. Sala M, van den Berg-Huysmans A, van der Grond J, Huisman M, Brandts A, Westenberg JJ, de Roos A (2016) Aortic Arch Stiffness Is Associated With Incipient Brain Injury in Patients With Hypertension. Am J Hypertens 29 (6):705-712. doi:10.1093/ajh/hpv161

125. Tjeerdema N, Van Schinkel LD, Westenberg JJ, Van Elderen SG, Van Buchem MA, Smit JW, Van der Grond J, De Roos A (2014) Aortic stiffness is associated with white matter integrity in patients with type 1 diabetes. European radiology 24 (9):2031-2037. doi:10.1007/s00330-014-3179-9

126. APA (2019) Depression. Accessed 07/06 2019

127. Richards D (2011) Prevalence and clinical course of depression: a review. Clinical psychology review 31 (7):1117-1125. doi:10.1016/j.cpr.2011.07.004

128. Kennedy SH (2008) Core symptoms of major depressive disorder: relevance to diagnosis and treatment. Dialogues in clinical neuroscience 10 (3):271-277

129. Saito M, Iwata N, Kawakami N, Matsuyama Y, World Mental Health Japan – C, Ono Y, Nakane Y, Nakamura Y, Tachimori H, Uda H, Nakane H, Watanabe M, Naganuma Y, Furukawa TA, Hata Y, Kobayashi M, Miyake Y, Takeshima T, Kikkawa T (2010) Evaluation of the DSM-IV and ICD-10 criteria for depressive disorders in a community population in Japan using item response theory. International journal of methods in psychiatric research 19 (4):211-222. doi:10.1002/mpr.320

130. Sajatovic M, Chen P, Young RC (2015) Chapter Nine - Rating Scales in Bipolar Disorder A2 - Tohen, Mauricio. In: Bowden CL, Nierenberg AA, Geddes JR (eds) Clinical Trial Design Challenges in Mood Disorders. Academic Press, San Diego, pp 105-136. doi:https://doi.org/10.1016/B978-0-12-405170-6.00009-9

131. Jackson-Koku G (2016) Beck Depression Inventory. Occupational medicine (Oxford, England) 66 (2):174-175. doi:10.1093/occmed/kqv087

132. Smarr KL, Keefer AL (2011) Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire-9 (PHQ-9). Arthritis Care Res (Hoboken) 63 Suppl 11:S454-466. doi:10.1002/acr.20556

133. Beck AT, Steer RA, Brown GK (1987) BDI-FastScreen for medical patients: manual. Psychological Corporation,

134. Beck AT, Steer RA, Carbin MG (1988) Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. Clinical psychology review 8 (1):77-100. doi:https://doi.org/10.1016/0272-7358(88)90050-5

135. Beck AT, Steer RA, Brown GK (1996) Beck depression inventory-II. San Antonio 78 (2):490-498

136. Radloff LS (1977) The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Applied Psychological Measurement 1 (3):385-401. doi:10.1177/014662167700100306

137. Gaynes BN, Asher G, Gartlehner G, Hoffman V, Green J, Boland E, Lux L, Weber RP, Randolph C, Bann C (2018) Definition of treatment-resistant depression in the Medicare population.

138. Orme JG, Reis J, Herz EJ (1986) Factorial and discriminant validity of the Center for Epidemiological Studies Depression (CES-D) scale. Journal of clinical psychology 42 (1):28-33

139. Missinne S, Vandeviver C, Van de Velde S, Bracke P (2014) Measurement equivalence of the CES-D 8 depression-scale among the ageing population in eleven European countries. Social science research 46:38-47. doi:10.1016/j.ssresearch.2014.02.006

140. Andresen EM, Byers K, Friary J, Kosloski K, Montgomery R (2013) Performance of the 10-item Center for Epidemiologic Studies Depression scale for caregiving research. SAGE Open Medicine 1:2050312113514576. doi:10.1177/2050312113514576

141. Gellis ZD (2010) Assessment of a Brief CES-D Measure for Depression in Homebound Medically Ill Older Adults. Journal of gerontological social work 53 (4):289-303. doi:10.1080/01634371003741417

142. Poulin C, Hand D, Boudreau B (2005) Validity of a 12-item version of the CES-D used in the National Longitudinal Study of Children and Youth. Chronic diseases in Canada 26 (2-3):65-72

143. Assari S, Moazen-Zadeh E (2016) Confirmatory Factor Analysis of the 12-Item Center for Epidemiologic Studies Depression Scale among Blacks and Whites. Frontiers in Psychiatry 7:178. doi:10.3389/fpsyt.2016.00178

144. Brink TL, Yesavage JA, Lum O, Heersema PH, Adey M, Rose TL (1982) Screening tests for geriatric depression. Clinical Gerontologist: The Journal of Aging and Mental Health 1 (1):37-43. doi:10.1300/J018v01n01_06

145. Marc LG, Raue PJ, Bruce ML (2008) Screening performance of the 15-item geriatric depression scale in a diverse elderly home care population. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 16 (11):914-921. doi:10.1097/JGP.0b013e318186bd67

146. Stiles PG, McGarrahan JF (1998) The Geriatric Depression Scale: A comprehensive review. Journal of Clinical Geropsychology 4 (2):89-110

147. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta psychiatrica Scandinavica 67 (6):361-370

148. Bjelland I, Dahl AA, Haug TT, Neckelmann D (2002) The validity of the Hospital Anxiety and Depression Scale. An updated literature review. Journal of psychosomatic research 52 (2):69-77

149. Blazer DG (2003) Depression in late life: review and commentary. The journals of gerontology Series A, Biological sciences and medical sciences 58 (3):249-265

150. Dillon C, Allegri RF, Serrano CM, Iturry M, Salgado P, Glaser FB, Taragano FE (2009) Late- versus early-onset geriatric depression in a memory research center. Neuropsychiatric disease and treatment 5:517-526

151. Blazer D, Burchett B, Service C, George LK (1991) The association of age and depression among the elderly: an epidemiologic exploration. Journal of gerontology 46 (6):M210-215

152. Snowden LR (2003) Bias in Mental Health Assessment and Intervention: Theory and Evidence. American Journal of Public Health 93 (2):239-243. doi:10.2105/AJPH.93.2.239

153. Schulz R, Beach SR, Ives DG, Martire LM, Ariyo AA, Kop WJ (2000) Association between depression and mortality in older adults: the Cardiovascular Health Study. Archives of internal medicine 160 (12):1761-1768

154. Vannoy SD, Duberstein P, Cukrowicz K, Lin E, Fan MY, Unutzer J (2007) The relationship between suicide ideation and late-life depression. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 15 (12):1024-1033. doi:10.1097/JGP.0b013e3180cc2bf1

155. Koenig HG, George LK (1998) Depression and physical disability outcomes in depressed medically ill hospitalized older adults. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 6 (3):230-247

156. Sivertsen H, Bjorklof GH, Engedal K, Selbaek G, Helvik AS (2015) Depression and Quality of Life in Older Persons: A Review. Dementia and geriatric cognitive disorders 40 (5-6):311-339. doi:10.1159/000437299

157. Blazer D, Williams CD (1980) Epidemiology of dysphoria and depression in an elderly population. The American journal of psychiatry 137 (4):439-444. doi:10.1176/ajp.137.4.439

158. Alexopoulos GS, Bruce ML, Silbersweig D, Kalayam B, Stern E (1999) Vascular depression: a new view of late-onset depression. Dialogues in clinical neuroscience 1 (2):68-80

159. Aizenstein HJ, Baskys A, Boldrini M, Butters MA, Diniz BS, Jaiswal MK, Jellinger KA, Kruglov LS, Meshandin IA, Mijajlovic MD, Niklewski G, Pospos S, Raju K, Richter K, Steffens DC, Taylor WD, Tene O (2016) Vascular depression consensus report - a critical update. BMC medicine 14 (1):161. doi:10.1186/s12916-016-0720-5

160. Herrmann LL, Le Masurier M, Ebmeier KP (2008) White matter hyperintensities in late life depression: a systematic review. Journal of neurology, neurosurgery, and psychiatry 79 (6):619-624. doi:10.1136/jnnp.2007.124651

161. Tham MW, Woon PS, Sum MY, Lee TS, Sim K (2011) White matter abnormalities in major depression: evidence from post-mortem, neuroimaging and genetic studies. Journal of affective disorders 132 (1-2):26-36. doi:10.1016/j.jad.2010.09.013

162. Wen MC, Steffens DC, Chen MK, Zainal NH (2014) Diffusion tensor imaging studies in late-life depression: systematic review and meta-analysis. International journal of geriatric psychiatry 29 (12):1173-1184. doi:10.1002/gps.4129

163. Lippi G, Montagnana M, Favaloro EJ, Franchini M (2009) Mental depression and cardiovascular disease: a multifaceted, bidirectional association. Seminars in thrombosis and hemostasis 35 (3):325-336. doi:10.1055/s-0029-1222611

164. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A (2007) Depression and the risk for cardiovascular diseases: systematic review and meta analysis. International journal of geriatric psychiatry 22 (7):613-626. doi:10.1002/gps.1723

165. Kendler KS, Gardner CO, Fiske A, Gatz M (2009) Major depression and coronary artery disease in the Swedish twin registry: phenotypic, genetic, and environmental sources of comorbidity. Archives of general psychiatry 66 (8):857-863. doi:10.1001/archgenpsychiatry.2009.94

166. Naismith SL, Norrie LM, Mowszowski L, Hickie IB (2012) The neurobiology of depression in later-life: clinical, neuropsychological, neuroimaging and pathophysiological features. Progress in neurobiology 98 (1):99-143. doi:10.1016/j.pneurobio.2012.05.009

167. Long J, Duan G, Tian W, Wang L, Su P, Zhang W, Lan J, Zhang H (2015) Hypertension and risk of depression in the elderly: a meta-analysis of prospective cohort studies. Journal of human hypertension 29 (8):478-482. doi:10.1038/jhh.2014.112

168. Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Yoon JS (2006) Vascular risk factors and incident late-life depression in a Korean population. The British journal of psychiatry : the journal of mental science 189:26-30. doi:10.1192/bjp.bp.105.015032

169. Bisschop MI, Kriegsman DM, Deeg DJ, Beekman AT, van Tilburg W (2004) The longitudinal relation between chronic diseases and depression in older persons in the community: the Longitudinal Aging Study Amsterdam. Journal of clinical epidemiology 57 (2):187-194. doi:10.1016/j.jclinepi.2003.01.001

170. Maraldi C, Volpato S, Penninx BW, Yaffe K, Simonsick EM, Strotmeyer ES, Cesari M, Kritchevsky SB, Perry S, Ayonayon HN, Pahor M (2007) Diabetes mellitus, glycemic control, and incident depressive symptoms among 70- to 79-year-old persons: the health, aging, and body composition study. Archives of internal medicine 167 (11):1137-1144. doi:10.1001/archinte.167.11.1137

171. de Jonge P, Roy JF, Saz P, Marcos G, Lobo A (2006) Prevalent and incident depression in community-dwelling elderly persons with diabetes mellitus: results from the ZARADEMP project. Diabetologia 49 (11):2627-2633. doi:10.1007/s00125-006-0442-x

172. Luijendijk HJ, Stricker BH, Hofman A, Witteman JC, Tiemeier H (2008) Cerebrovascular risk factors and incident depression in community-dwelling elderly. Acta psychiatrica Scandinavica 118 (2):139-148. doi:10.1111/j.1600-0447.2008.01189.x

173. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, Zitman FG (2010) Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Archives of general psychiatry 67 (3):220-229. doi:10.1001/archgenpsychiatry.2010.2

174. Almeida OP, Pfaff JJ (2005) Depression and smoking amongst older general practice patients. Journal of affective disorders 86 (2-3):317-321. doi:10.1016/j.jad.2005.02.014

175. Lam TH, Li ZB, Ho SY, Chan WM, Ho KS, Li MP, Leung GM (2004) Smoking and depressive symptoms in Chinese elderly in Hong Kong. Acta psychiatrica Scandinavica 110 (3):195-200. doi:10.1111/j.1600-0447.2004.00342.x

176. van Gool CH, Kempen GI, Penninx BW, Deeg DJ, Beekman AT, van Eijk JT (2003) Relationship between changes in depressive symptoms and unhealthy lifestyles in late middle aged and older persons: results from the Longitudinal Aging Study Amsterdam. Age and ageing 32 (1):81-87

177. Wei J, Hou R, Zhang X, Xu H, Xie L, Chandrasekar EK, Ying M, Goodman M (2019) The association of late-life depression with all-cause and cardiovascular mortality among community-dwelling older adults: systematic review and meta-analysis. The British Journal of Psychiatry:1-7. doi:10.1192/bjp.2019.74

178. Cullum S, Metcalfe C, Todd C, Brayne C (2008) Does depression predict adverse outcomes for older medical inpatients? A prospective cohort study of individuals screened for a trial. Age and ageing 37 (6):690-695. doi:10.1093/ageing/afn193

179. Liang X, Margolis KL, Hendryx M, Reeves K, Wassertheil-Smoller S, Weitlauf J, Danhauer SC, Chlebowski RT, Caan B, Qi L, Lane D, Lavasani S, Luo J (2017) Effect of depression before breast cancer diagnosis on mortality among postmenopausal women. Cancer 123 (16):3107-3115. doi:10.1002/cncr.30688

180. Dias F, Teixeira AL, Guimaraes HC, Barbosa MT, Resende EPF, Beato RG, Carmona KC, Caramelli P (2017) Cognitive performance of community-dwelling oldest-old individuals with major depression: the Pieta study. International psychogeriatrics 29 (9):1507-1513. doi:10.1017/s1041610217000850

181. O'Shea DM, Fieo RA, Hamilton JL, Zahodne LB, Manly JJ, Stern Y (2015) Examining the association between late-life depressive symptoms, cognitive function, and brain volumes in the context of cognitive reserve. International journal of geriatric psychiatry 30 (6):614-622. doi:10.1002/gps.4192

182. Hamilton JL, Brickman AM, Lang R, Byrd GS, Haines JL, Pericak-Vance MA, Manly JJ (2014) Relationship between depressive symptoms and cognition in older, non-demented African Americans. Journal of the International Neuropsychological Society : JINS 20 (7):756-763. doi:10.1017/s1355617714000423

183. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF, 3rd (2013) Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. The British journal of psychiatry : the journal of mental science 202 (5):329-335. doi:10.1192/bjp.bp.112.118307

184. van Sloten TT, Protogerou AD, Henry RM, Schram MT, Launer LJ, Stehouwer CD (2015) Association between arterial stiffness, cerebral small vessel disease and cognitive impairment: A systematic review and meta-analysis. Neuroscience and biobehavioral reviews 53:121-130. doi:10.1016/j.neubiorev.2015.03.011

185. Krishnan KR, Hays JC, Blazer DG (1997) MRI-defined vascular depression. The American journal of psychiatry 154 (4):497-501. doi:10.1176/ajp.154.4.497

186. Iliff JJ, Wang M, Zeppenfeld DM, Venkataraman A, Plog BA, Liao Y, Deane R, Nedergaard M (2013) Cerebral arterial pulsation drives paravascular CSF-interstitial fluid exchange in the murine brain. The Journal of neuroscience : the official journal of the Society for Neuroscience 33 (46):18190-18199. doi:10.1523/jneurosci.1592-13.2013

187. Hughes TM, Kuller LH, Barinas-Mitchell EJ, Mackey RH, McDade EM, Klunk WE, Aizenstein HJ, Cohen AD, Snitz BE, Mathis CA, Dekosky ST, Lopez OL (2013) Pulse wave velocity is associated with beta-amyloid deposition in the brains of very elderly adults. Neurology 81 (19):1711-1718. doi:10.1212/01.wnl.0000435301.64776.37

188. Hughes TM, Kuller LH, Barinas-Mitchell EJ, McDade EM, Klunk WE, Cohen AD, Mathis CA, Dekosky ST, Price JC, Lopez OL (2014) Arterial stiffness and beta-amyloid progression in nondemented elderly adults. JAMA neurology 71 (5):562-568. doi:10.1001/jamaneurol.2014.186

189. Murphy MP, LeVine H (2010) Alzheimer’s Disease and the β-Amyloid Peptide. Journal of Alzheimer's disease : JAD 19 (1):311. doi:10.3233/JAD-2010-1221

190. Holmes SE, Esterlis I, Mazure CM, Lim YY, Ames D, Rainey-Smith S, Martins RN, Salvado O, Dore V, Villemagne VL, Rowe CC, Laws SM, Masters CL, Maruff P, Pietrzak RH (2016) beta-Amyloid, APOE and BDNF Genotype, and Depressive and Anxiety Symptoms in Cognitively Normal Older Women and Men. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 24 (12):1191-1195. doi:10.1016/j.jagp.2016.08.007

191. Harrington KD, Gould E, Lim YY, Ames D, Pietrzak RH, Rembach A, Rainey-Smith S, Martins RN, Salvado O, Villemagne VL, Rowe CC, Masters CL, Maruff P (2017) Amyloid burden and incident depressive symptoms in cognitively normal older adults. International journal of geriatric psychiatry 32 (4):455-463. doi:10.1002/gps.4489

192. Tiemeier H, Breteler MM, van Popele NM, Hofman A, Witteman JC (2003) Late-life depression is associated with arterial stiffness: a population-based study. Journal of the American Geriatrics Society 51 (8):1105-1110

193. Paranthaman R, Greenstein AS, Burns AS, Cruickshank JK, Heagerty AM, Jackson A, Malik RA, Scott ML, Baldwin RC (2010) Vascular function in older adults with depressive disorder. Biological psychiatry 68 (2):133-139. doi:10.1016/j.biopsych.2010.04.017

194. Onete V, Henry RM, Sep SJS, Koster A, van der Kallen CJ, Dagnelie PC, Schaper N, Kohler S, Reesink K, Stehouwer CDA, Schram MT (2017) Arterial stiffness is associated with depression in middle-aged men - the Maastricht Study. Journal of psychiatry & neuroscience : JPN 42 (6):160246. doi:10.1503/jpn.160246

195. Fiske A, Wetherell JL, Gatz M (2009) Depression in older adults. Annual review of clinical psychology 5:363-389. doi:10.1146/annurev.clinpsy.032408.153621

196. Kennedy GJ (1995) The geriatric syndrome of late-life depression. Psychiatric services (Washington, DC) 46 (1):43-48. doi:10.1176/ps.46.1.43

197. Qiu WQ, Himali JJ, Wolf PA, DeCarli DC, Beiser A, Au R (2017) Effects of white matter integrity and brain volumes on late life depression in the Framingham Heart Study. International journal of geriatric psychiatry 32 (2):214-221. doi:10.1002/gps.4469

198. Oosterman JM, Sergeant JA, Weinstein HC, Scherder EJ (2004) Timed executive functions and white matter in aging with and without cardiovascular risk factors. Reviews in the neurosciences 15 (6):439-462

199. O'Sullivan M, Morris RG, Huckstep B, Jones DK, Williams SC, Markus HS (2004) Diffusion tensor MRI correlates with executive dysfunction in patients with ischaemic leukoaraiosis. Journal of neurology, neurosurgery, and psychiatry 75 (3):441-447

200. Madden DJ, Bennett IJ, Song AW (2009) Cerebral white matter integrity and cognitive aging: contributions from diffusion tensor imaging. Neuropsychology review 19 (4):415-435. doi:10.1007/s11065-009-9113-2

201. Pasi M, van Uden IW, Tuladhar AM, de Leeuw FE, Pantoni L (2016) White Matter Microstructural Damage on Diffusion Tensor Imaging in Cerebral Small Vessel Disease: Clinical Consequences. Stroke 47 (6):1679-1684. doi:10.1161/strokeaha.115.012065

202. de Groot M, Ikram MA, Akoudad S, Krestin GP, Hofman A, van der Lugt A, Niessen WJ, Vernooij MW (2015) Tract-specific white matter degeneration in aging: the Rotterdam Study. Alzheimer's & dementia : the journal of the Alzheimer's Association 11 (3):321-330. doi:10.1016/j.jalz.2014.06.011

203. Pelletier A, Periot O, Dilharreguy B, Hiba B, Bordessoules M, Chanraud S, Peres K, Amieva H, Dartigues JF, Allard M, Catheline G (2015) Age-Related Modifications of Diffusion Tensor Imaging Parameters and White Matter Hyperintensities as Inter-Dependent Processes. Frontiers in aging neuroscience 7:255. doi:10.3389/fnagi.2015.00255

204. Maniega SM, Valdes Hernandez MC, Clayden JD, Royle NA, Murray C, Morris Z, Aribisala BS, Gow AJ, Starr JM, Bastin ME, Deary IJ, Wardlaw JM (2015) White matter hyperintensities and normal-appearing white matter integrity in the aging brain. Neurobiology of aging 36 (2):909-918. doi:10.1016/j.neurobiolaging.2014.07.048

205. Vernooij MW, de Groot M, van der Lugt A, Ikram MA, Krestin GP, Hofman A, Niessen WJ, Breteler MM (2008) White matter atrophy and lesion formation explain the loss of structural integrity of white matter in aging. NeuroImage 43 (3):470-477. doi:10.1016/j.neuroimage.2008.07.052

206. Maillard P, Fletcher E, Lockhart SN, Roach AE, Reed B, Mungas D, DeCarli C, Carmichael OT (2014) White matter hyperintensities and their penumbra lie along a continuum of injury in the aging brain. Stroke 45 (6):1721-1726. doi:10.1161/strokeaha.113.004084

207. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators (1989). American journal of epidemiology 129 (4):687-702

208. Podolec P, Kopec G, Podolec J, Wilkolek P, Krochin M, Rubis P, Cwynar M, Grodzicki T, Zmudka K, Tracz W (2007) Aortic pulse wave velocity and carotid-femoral pulse wave velocity: similarities and discrepancies. Hypertension research : official journal of the Japanese Society of Hypertension 30 (12):1151-1158. doi:10.1291/hypres.30.1151

209. Meyer ML, Tanaka H, Palta P, Cheng S, Gouskova N, Aguilar D, Heiss G (2016) Correlates of Segmental Pulse Wave Velocity in Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study. American journal of hypertension 29 (1):114-122. doi:10.1093/ajh/hpv079

210. Meyer ML, Tanaka H, Palta P, Patel MD, Camplain R, Couper D, Cheng S, Al Qunaibet A, Poon AK, Heiss G (2016) Repeatability of Central and Peripheral Pulse Wave Velocity Measures: The Atherosclerosis Risk in Communities (ARIC) Study. American journal of hypertension 29 (4):470-475. doi:10.1093/ajh/hpv127

211. Knopman DS, Griswold ME, Lirette ST, Gottesman RF, Kantarci K, Sharrett AR, Jack CR, Graff-Radford J, Schneider ALC, Windham BG, Coker LH, Albert MS, Mosley TH, the ANI (2015) Vascular imaging abnormalities and cognition: Mediation by Cortical Volume in non-demented persons: ARIC-NCS Study. Stroke; a journal of cerebral circulation 46 (2):433-440. doi:10.1161/STROKEAHA.114.007847

212. Oishi K, Zilles K, Amunts K, Faria A, Jiang H, Li X, Akhter K, Hua K, Woods R, Toga AW, Pike GB, Rosa-Neto P, Evans A, Zhang J, Huang H, Miller MI, van Zijl PC, Mazziotta J, Mori S (2008) Human brain white matter atlas: identification and assignment of common anatomical structures in superficial white matter. NeuroImage 43 (3):447-457. doi:10.1016/j.neuroimage.2008.07.009

213. ARIC (2017) Visit 6 Manual 17 ARIC Neurocognitive Exam https://www2.cscc.unc.edu/aric/sites/default/files/public/manuals/ARIC%20MOP17%20170405.pdf.

214. Bos D, Wolters FJ, Darweesh SKL, Vernooij MW, de Wolf F, Ikram MA, Hofman A (2018) Cerebral small vessel disease and the risk of dementia: A systematic review and meta-analysis of population-based evidence. Alzheimer's & dementia : the journal of the Alzheimer's Association 14 (11):1482-1492. doi:10.1016/j.jalz.2018.04.007

215. Maillard P, Fletcher E, Harvey D, Carmichael O, Reed B, Mungas D, DeCarli C (2011) White matter hyperintensity penumbra. Stroke 42 (7):1917-1922. doi:10.1161/strokeaha.110.609768

216. Sethi S, Rivera O, Oliveros R, Chilton R (2014) Aortic stiffness: pathophysiology, clinical implications, and approach to treatment. Integrated blood pressure control 7:29-34. doi:10.2147/IBPC.S59535

217. Kucharska-Newton AM, Stoner L, Meyer ML (2019) Determinants of Vascular Age: An Epidemiological Perspective. Clinical chemistry 65 (1):108-118. doi:10.1373/clinchem.2018.287623

218. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ (2011) Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility--Reykjavik study. Brain : a journal of neurology 134 (Pt 11):3398-3407. doi:10.1093/brain/awr253

219. Murray AD, Staff RT, Shenkin SD, Deary IJ, Starr JM, Whalley LJ (2005) Brain white matter hyperintensities: relative importance of vascular risk factors in nondemented elderly people. Radiology 237 (1):251-257. doi:10.1148/radiol.2371041496

220. Rosano C, Watson N, Chang Y, Newman AB, Aizenstein HJ, Du Y, Venkatraman V, Harris TB, Barinas-Mitchell E, Sutton-Tyrrell K (2013) Aortic pulse wave velocity predicts focal white matter hyperintensities in a biracial cohort of older adults. Hypertension (Dallas, Tex : 1979) 61 (1):160-165. doi:10.1161/hypertensionaha.112.198069

221. Tap L, van Opbroek A, Niessen WJ, Smits M, Mattace-Raso FU (2018) Aortic stiffness and brain integrity in elderly patients with cognitive and functional complaints. Clinical interventions in aging 13:2161-2167. doi:10.2147/cia.s181437

222. Palta P, Sharrett AR, Wei J, Meyer ML, Kucharska-Newton A, Power MC, Deal JA, Jack CR, Knopman D, Wright J, Griswold M, Tanaka H, Mosley TH, Heiss G (2019) Central Arterial Stiffness Is Associated With Structural Brain Damage and Poorer Cognitive Performance: The ARIC Study. Journal of the American Heart Association 8 (2):e011045. doi:10.1161/jaha.118.011045

223. Knopman DS, Griswold ME, Lirette ST, Gottesman RF, Kantarci K, Sharrett AR, Jack CR, Jr., Graff-Radford J, Schneider AL, Windham BG, Coker LH, Albert MS, Mosley TH, Jr. (2015) Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: atherosclerosis risk in communities-neurocognitive study. Stroke 46 (2):433-440. doi:10.1161/strokeaha.114.007847

224. Meyer ML, Tanaka H, Palta P, Patel MD, Camplain R, Couper D, Cheng S, Al Qunaibet A, Poon AK, Heiss G (2016) Repeatability of Central and Peripheral Pulse Wave Velocity Measures: The Atherosclerosis Risk in Communities (ARIC) Study. American journal of hypertension 29 (4):470-475. doi:10.1093/ajh/hpv127

225. Schneider ALC, Selvin E, Sharrett AR, Griswold M, Coresh J, Jack CR, Knopman D, Mosley T, Gottesman RF (2017) Diabetes, Prediabetes, and Brain Volumes and Subclinical Cerebrovascular Disease on MRI: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). Diabetes care 40 (11):1514. doi:10.2337/dc17-1185

226. Madden DJ, Bennett IJ, Burzynska A, Potter GG, Chen NK, Song AW (2012) Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. Biochimica et biophysica acta 1822 (3):386-400. doi:10.1016/j.bbadis.2011.08.003

227. Vemuri P, Gunter JL, Senjem ML, Whitwell JL, Kantarci K, Knopman DS, Boeve BF, Petersen RC, Jack CR, Jr. (2008) Alzheimer's disease diagnosis in individual subjects using structural MR images: validation studies. NeuroImage 39 (3):1186-1197. doi:10.1016/j.neuroimage.2007.09.073

228. Walker KA, Power MC, Hoogeveen RC, Folsom AR, Ballantyne CM, Knopman DS, Windham BG, Selvin E, Jack CR, Jr., Gottesman RF (2017) Midlife Systemic Inflammation, Late-Life White Matter Integrity, and Cerebral Small Vessel Disease: The Atherosclerosis Risk in Communities Study. Stroke 48 (12):3196-3202. doi:10.1161/strokeaha.117.018675

229. Raz L, Jayachandran M, Tosakulwong N, Lesnick TG, Wille SM, Murphy MC, Senjem ML, Gunter JL, Vemuri P, Jack CR, Jr., Miller VM, Kantarci K (2013) Thrombogenic microvesicles and white matter hyperintensities in postmenopausal women. Neurology 80 (10):911-918. doi:10.1212/WNL.0b013e3182840c9f

230. Chen X, Huang B, Liu M, Li X (2015) Effects of different types of antihypertensive agents on arterial stiffness: a systematic review and meta-analysis of randomized controlled trials. Journal of thoracic disease 7 (12):2339-2347. doi:10.3978/j.issn.2072-1439.2015.12.58

231. Steffens DC, Fisher GG, Langa KM, Potter GG, Plassman BL (2009) Prevalence of depression among older Americans: the Aging, Demographics and Memory Study. International psychogeriatrics 21 (5):879-888. doi:10.1017/s1041610209990044

232. Katon WJ, Lin E, Russo J, Unutzer J (2003) Increased medical costs of a population-based sample of depressed elderly patients. Archives of general psychiatry 60 (9):897-903. doi:10.1001/archpsyc.60.9.897

233. Cavalcante JL, Lima JA, Redheuil A, Al-Mallah MH (2011) Aortic stiffness: current understanding and future directions. Journal of the American College of Cardiology 57 (14):1511-1522. doi:10.1016/j.jacc.2010.12.017

234. van Sloten TT, Mitchell GF, Sigurdsson S, van Buchem MA, Jonsson PV, Garcia ME, Harris TB, Henry RM, Levey AS, Stehouwer CD, Gudnason V, Launer LJ (2016) Associations between arterial stiffness, depressive symptoms and cerebral small vessel disease: cross-sectional findings from the AGES-Reykjavik Study. Journal of psychiatry & neuroscience : JPN 41 (3):162-168

235. Kohout FJ, Berkman LF, Evans DA, Cornoni-Huntley J (1993) Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. Journal of aging and health 5 (2):179-193. doi:10.1177/089826439300500202

236. Torres E (2012) Psychometric properties of the Center for Epidemiologic Studies Depression Scale in African American and Black Caribbean US adults. Issues in mental health nursing 33 (10):687-696. doi:10.3109/01612840.2012.697534

237. Wilkins CH, Mathews J, Sheline YI (2009) Late life depression with cognitive impairment: evaluation and treatment. Clinical interventions in aging 4:51-57

238. Azur MJ, Stuart EA, Frangakis C, Leaf PJ (2011) Multiple imputation by chained equations: what is it and how does it work? International journal of methods in psychiatric research 20 (1):40-49. doi:10.1002/mpr.329

239. Fiske A, Wetherell JL, Gatz M (2009) Depression in older adults. Annual review of clinical psychology 5:363-389. doi:10.1146/annurev.clinpsy.032408.153621

240. Culang-Reinlieb ME, Johnert LC, Brickman AM, Steffens DC, Garcon E, Sneed JR (2011) MRI-defined vascular depression: a review of the construct. International journal of geriatric psychiatry 26 (11):1101-1108. doi:10.1002/gps.2668

241. Nilsson PM (2014) Hemodynamic Aging as the Consequence of Structural Changes Associated with Early Vascular Aging (EVA). Aging Dis 5 (2):109-113. doi:10.14336/AD.2014.0500109

242. Tsao CW, Himali JJ, Beiser AS, Larson MG, DeCarli C, Vasan RS, Mitchell GF, Seshadri S (2016) Association of arterial stiffness with progression of subclinical brain and cognitive disease. Neurology 86 (7):619-626. doi:10.1212/WNL.0000000000002368

243. Rhee M-Y, Lee H-Y, Park JB (2008) Measurements of Arterial Stiffness: Methodological Aspects. Korean Circ J 38 (7):343-350

244. Inzitari D, Pracucci G, Poggesi A, Carlucci G, Barkhof F, Chabriat H, Erkinjuntti T, Fazekas F, Ferro JM, Hennerici M, Langhorne P, O'Brien J, Scheltens P, Visser MC, Wahlund LO, Waldemar G, Wallin A, Pantoni L (2009) Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort. BMJ (Clinical research ed) 339:b2477. doi:10.1136/bmj.b2477