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CEREBROVASCULAR RISK FACTORS, ARTERIOLAR SCLEROSIS, AND COGNITIVE DECLINE IN THE KENTUCKY APPALACHIAN "STROKE-BELT"

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CEREBROVASCULAR RISK FACTORS, ARTERIOLAR SCLEROSIS, AND COGNITIVE DECLINE IN THE KENTUCKY APPALACHIAN "STROKE-BELT."

Thesis

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science in the College of
Medicine at the University of Kentucky

By
Omar M. Al-Janabi

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ABSTRACT OF THESIS

CEREBROVASCULAR DISEASE RISK FACTORS, ARTERIOLAR SCLEROSIS, AND COGNITIVE DECLINE IN THE KENTUCKY APPALACHIAN "STROKE-BELT."

The relationship between cerebrovascular disease (CVD) risk factors and cognitive impairment or dementia has been widely studied with significant variability in findings between groups. We hypothesized that chronic small vessel injury in the form of arteriolar sclerosis, measured quantitatively using MRI to measure total white matter hyperintensity (WMH) volumes, would identify specific association of CVD risk factors and patterns of cognitive decline, associated with mild cognitive impairment of the cerebrovascular type, that represent the core features of vascular cognitive impairment in our cohort.

A Cross-sectional analysis of clinical and quantitative MRI data on 114 subjects with normal cognitive function (n=52) and mild cognitive impairment (MCI; n=62) was performed. Quantitative total WMH volumes were examined in relation to potentially causative CVD risk factors and resultant test scores across cognitive domains using linear regression models adjusted for age, gender, and education.

Among CVD risk factors analyzed, age ($p< 0.001$), education ($p= 0.003$), hypertension ($p= 0.012$), and hyperlipidemia ($p= 0.008$) demonstrated the strongest associations with WMH volumes. Conversely, diabetes, smoking, history of heart attacks, atrial fibrillation, and history of stroke that have shown associations with CVD pathology on imaging in other studies were not statistically associated with increased WMH in this cohort. WMH volumes were associated with decrease performance on the Trial Making Test type A & B and long delayed free recall on the California Verbal Learning Test.

Our findings suggest similarities and yet differences in comparison to other studies. Hypertension and hyperlipidemia appear to represent common shared risks across geographically disparate groups. Our findings, like others, suggest CVD pathology impact processing speed and executive function and provide further evidence for CVD effects on short-term memory in those at risk for cognitive decline and the future development of dementia in our cohort.

Key Words: Arteriolar Sclerosis, Hypertension, Hyperlipidemia, vascular cognitive impairment, dementia.

Author's signature: Omar M. Al-Janabi

Date: April 6th, 2016

CEREBROVASCULAR RISK FACTORS, ARTERIOLAR SCLEROSIS, AND COGNITIVE DECLINE IN THE KENTUCKY APPALACHIAN "STROKE-BELT."

By

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Date: April 25th, 2016

Dedication

This work is dedicated to all patients who fight vascular dementia and to their outstanding families who are making strenuous efforts to overcome the difficulties of their patients' lives.

Acknowledgments

I would like to thank Dr. Gregory A. Jicha my wonderful advisor from the bottom of my heart. I am grateful for the opportunity to work in his lab on this important project. Ongoing advice and guidance have had a clear impact in enriching my research experience and have contributed to my success in this important stage of my career. I promise him to be a successful researcher in the field of behavioral neurology in the near future.

I would also like to thank Dr. Charles D. Smith, my co-advisor, for his help. His guidance had a significant impact in enriching my background in measuring WMH volumes using a magnetic resonance imaging.

Thank you so much to my awesome DGS Dr. Joe Springer for your help and support throughout this process.

Finally, I would like to thank my great parents, my lovely wife Yamama, my son Abdul Aziz, my daughter Rose, and my son Ahmed for their unlimited support and patience.

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List of Abbreviations

Aβ	Amyloid Beta protein
AD	Alzheimer's disease
AF	Atrial Fibrillation
APOE ε	Apolipoprotein E Epsilon ε allele
AS	Arteriolar Sclerosis
BBB	Blood Brain Barrier
CDR	Clinical Dementia Rating
CVD	Cerebrovascular Disease
CVLT	California Verbal Learning Test
DM	Diabetes Mellitus
DSST	Digit Symbols Substitution Test
FRS	Framingham Risk Score
HIS	Hachinski Ischemic Score
HLD	Hyperlipidemia
HTN	Hypertension
LDFRC	Long Delayed Free Recall Correct
MCI	Mild Cognitive Impairment
MI	Myocardial Infarction
MMSE	Mini Mental State Exam
SVD	Small Vessel Disease
SVI	Small Vessel Ischemic changes
TMT-A	Trail Making Test type A
TMT-B	Trail Making Test type B
T-WMH	Total White Matter Hyperintensity
VaD	Vascular Dementia
WMH	White Matter Hyperintensity
WML	White Matter Lesion

1. Introduction:

This thesis describes and reports on an investigation of risk factors for and cognitive sequelae of cerebral small vessel disease (arteriolar sclerosis). Arteriolar sclerosis (AS) is a subtype of cerebral small vessel ischemic disease that is characterized pathologically by the narrowing of the lumen, thickening of the blood vessels' walls, and hyaline deposition. For the purpose of this investigation and discussion, lipohyalinosis is included under the rubric of AS. In addition to these changes, the tunica media layer loses its smooth muscle cells (Leonardo Pantoni, 2010). AS has been found to be associated with age and hypertension (HTN) (Furuta, Ishii, Nishihara, & Horie, 1991).

Cerebral small vessel disease is a broad term used to describe all pathological conditions that affect cerebral small arteries, arterioles, venules and capillaries. To better understand cerebral small vessel disease, it is essential to know the subtypes of this disease. According to Leonardo Pantoni, cerebral small vessel disease can be subdivided into six main subtypes. First, there is arteriolar sclerosis which is also called vascular risk factor and age-related cerebral small vessel disease. The second subtype is cerebral amyloid angiopathy which is further divided into sporadic or hereditary. Pantoni identifies the heterogeneous category of genetic causes of small vessel disease, such as cerebral autosomal dominant arteriopathy with subcortical ischemic stroke and leukoencephalopathy (CADASIL), as a third subtype. The fourth subtype is inflammatory or immune-mediated small vessel disease such as vasculitis associated with systemic lupus erythematosus. Fifth, there is venous collagenosis. Finally, other causes exist such as post-radiation angiopathy (Leonardo Pantoni, 2010).

Cerebrovascular disease (CVD) risk factors contribute to vascular dementia (Gorelick, Counts, & Nyenhuis; Leonardo Pantoni, 2010). Its incidence is found to be six to ten times more than that of stroke (Thompson & Hakim, 2009). Furthermore, CVD risk factors are associated with asymptomatic ischemic or hemorrhagic infarcts that are visualized as hyperintense lesions on T2 magnetic resonance imaging (MRI). Small vessel disease is manifest as subcortical and periventricular (WMH) (de Leeuw et al., 2001). Seventeen percent of elderly people, aged 65 and up, are found to have cognitive decline associated with and presumably caused by cerebral small vessel disease (Heiss, 2016; Ighodaro et al., 2016; Leary & Saver, 2003). Cerebral small vessel disease prevalence increases with age in addition to increases seen with an increasing burden of CVD risk factors (Thompson & Hakim, 2009).

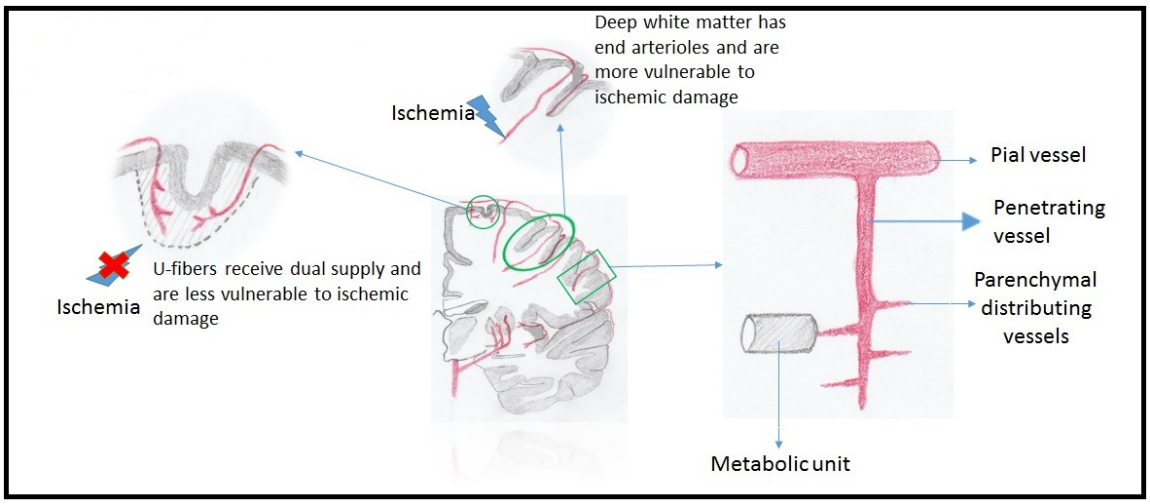
1.1 Pathogenesis of CVD and arteriolar sclerosis:

Much is known regarding pathogenesis and mechanisms by which discrete risk factors produce arteriolar sclerotic changes, which ultimately will affect cognition. To understand how cerebrovascular risk factors lead to AS, it is important to understand the normal anatomy and physiology of cerebral blood vessels.

Anatomy of cerebral blood vessels: Arising from the pial surface as branches from subarachnoid vessels are the penetrating arteries, branched at a right angle with the brain surface toward the surface of the lateral ventricles. These vessels range from 20-50mm in length, and their origin caliber ranges from 100-200μm. Each penetrating artery sends out short divisions (distributing vessels) that are perpendicular to it to supply a metabolic unit. Furthermore, ventriculofugal vessels (15mm length) are branches of subependymal arteries derived from the choroidal or rami striati. Ventriculofugal vessels supply part of the thalamus, internal capsule, and a portion of the basal

ganglia. There is little or no anastomosis between branches originating from the subependymal vessels and those originating at the brain surface. For this reason, periventricular and deep subcortical white matter are considered a watershed area that is prone to damage by ischemia (Leonardo Pantoni, 2010; L. Pantoni & Garcia, 1997) (Figure 1.1).

Figure 1.1. Cerebral white matter blood vessel and white matter areas that are vulnerable to ischemic damage.



Factors that affect blood flow in cerebral arterioles: Many factors will affect the blood flow in cerebral arterioles. First, the tortuosity and complexity of small arteries or arterioles will result in the reduction of cerebral blood flow (i.e. worsen with age and other cerebrovascular risk factors). As a result of such blood flow reduction, white matter lesion (WML) are ultimately formed (Spangler, Challa, Moody, & Bell, 1994).

Second, depending on how many sources there are per small artery or arteriole, they may have single, dual, or triple sources of blood. Obviously, areas with dual or triple sources (like the subcortical U-fibers) will be less vulnerable to damage by ischemic changes. Areas with a single source, however, will be affected to a great extent by ischemia (D M Moody, Bell, & Challa, 1990) (Figure 1.1)

Third, the adventitial layer of the subcortical and deep white matter arteries may be affected by aging, HTN and other CVD risk factors leading to AS (Nonaka et al., 2003).

There are five common mechanisms that lead to WMH:

I. Ischemia:

A. Chronic ischemia: reduction in cerebral blood flow due to narrowing or obstruction of small arteries and arterioles in subcortical and deep white matter regions (arteriolar sclerosis) results in ischemia especially if those arterioles have only a single source of blood (D M Moody et al., 1990). Chronic ischemia leads to the death of oligodendrocytes contributing to myelinolysis (Mike O'Sullivan, 2008; L. Pantoni, 2002; Leonardo Pantoni, 2010). This chronic ischemic injury will lead to the formation of incomplete lacunar infarcts (Leonardo Pantoni, 2010). Incomplete lacunae are defined as areas of selective

neuronal or axonal necrosis. These lesions spare the vascular tissue and the glial components of the affected areas (Lammie, Brannan, & Wardlaw, 1998).

B. Acute ischemia: this will result from acute obstruction of cerebral small arteries and arterioles. Acute ischemia will result in the formation of complete lacunar infarcts (Leonardo Pantoni, 2010). Deep white matter lacunes can occur in regions of WMH.

II. Disruption of Blood-Brain Barriers (BBB): The most accepted non-ischemic theory explaining WMH focuses on damage to the BBB. BBB breakdown results in white matter damage caused by the toxic effect of extravasated proteins such as fibrinogen, albumin and IgG and resultant inflammatory changes. Ischemic changes may occur simultaneously with BBB damage, but the relative causality is poorly understood (Mike O'Sullivan, 2008; L. Pantoni, 2002; Leonardo Pantoni, 2010).

III. Endothelial Damage: Both ischemias due to hypoperfusion and BBB disruption can lead to the loss of endothelial integrity (Mike O'Sullivan, 2008). Also, toxic effects of homocysteine on endothelial cells may contribute to endothelial damage (Hassan et al., 2004). As a result of endothelial damage, nitric oxide is reduced, which negatively affects cerebral blood flow and through interference with autoregulatory mechanisms of cerebral white matter small vessels (Khan, Porteous, Hassan, & Markus, 2007; M. O'Sullivan et al., 2002; Terborg, Gora, Weiller, & Röther, 2000). Supporting evidence for this mechanism include observed elevated levels of endothelial dysfunction markers such as intercellular adhesion molecule 1 (ICAM1), thrombomodulin (TM), tissue factor (TF) and tissue factor pathway inhibitor (TFPI) (Hassan et al., 2003).

IV. Amyloid β: The Aβ deposition and level correlates with the severity of arteriosclerotic disease (Mike O'Sullivan, 2008). Cerebral Amyloid Angiopathy (CAA) which is characterized by the accumulation of Aβ protein in the walls of small-medium sized blood vessels and capillaries. In severe CAA, blood vessels' walls may be damaged causing leakage of blood into the surrounding brain tissue (Leonardo Pantoni, 2010). CAA was found to be associated with intracerebral hemorrhage, and subcortical WML, and can be commonly seen in elderly subjects with Alzheimer's disease, Down's syndrome and cerebral small vessel disease (Azmin, Osman, Mukari, & Sahathevan, 2015; Esiri et al., 2015).

V. Genetics: Many genetic risk factors may play a role in cerebral small vessel disease such as cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL) (L. Pantoni, 2002). Many other hereditary diseases lead to cerebral small vessel disease including cerebral autosomal recessive arteriopathy with subcortical infarct and leukoencephalopathy (CARASIL), Fabry's disease, hereditary extensive vascular leukoencephalopathy (HEVL), and mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) (Leonardo Pantoni, 2010). Furthermore, ABCC9 Hippocampal Sclerosis-Aging risk genotype has been found to be associated with a reduction in the cerebral blood flow (Ighodaro et al., 2016). Finally, APOE ε4 was found to have a role in the microvascular changes of the brain that ultimately lead to AS (Yip et al., 2005). There is a strong association between the APO E ε4 genotype and atherosclerosis in addition to cerebral blood vessels structural changes such as amyloid angiopathy (due to increased Aβ deposition). The latter is found to be associated with increased risk of WML. The ultimate effect of APO E ε4 is decreased cerebral blood flow which results in ischemic damage to vulnerable areas and cognitive decline (Hofman et al., 1997).

1.2. How Do Cerebrovascular Risk Factors Lead to Arteriolar Sclerotic Disease and Ultimately Affect Cognition?

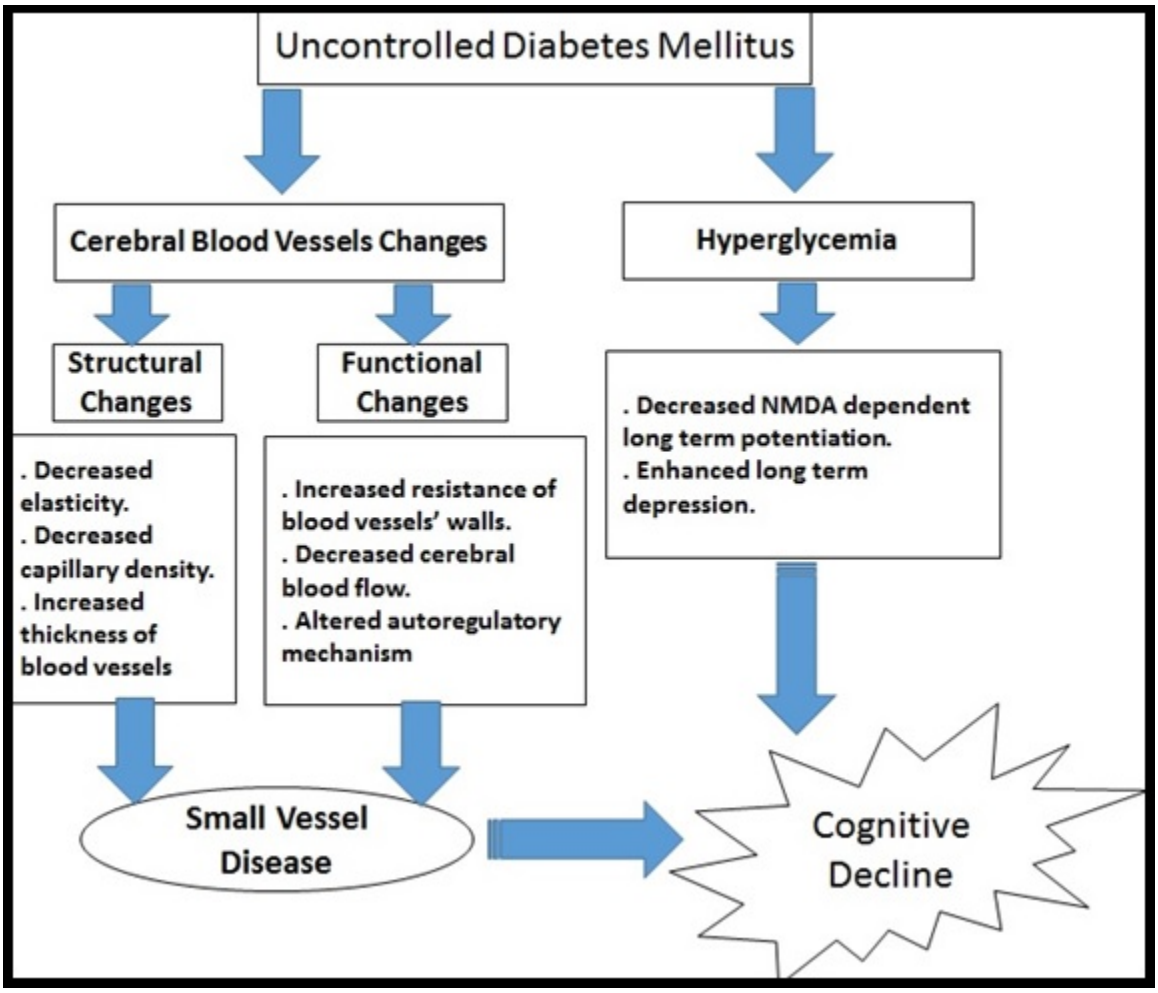
Many cerebrovascular risk factors increase arteriolar sclerotic injury, which in turn can lead to cognitive decline and dementia. CVD risk factors include but are not limited to HTN, diabetes mellitus (DM), and hypercholesterolemia. According to the Rotterdam Study, an extensive multi-year epidemiologic longitudinal study of brain aging begun in 1990, advanced age, female gender, HTN and smoking contributed to cerebral small vessel disease (van Dijk et al., 2008). Patients with higher CVD risk burden were more prone to have small vessel ischemic changes at autopsy than their counterparts (Bangen et al., 2015). CVD risk factors can be aggregated into a risk score that is meaningful for AS and eventual cognitive decline. The Framingham stroke risk score (R. B. D'Agostino, Wolf, Belanger, & Kannel, 1994), reflects the aggregate of many CVD risk factors and has been shown to be associated with impaired cognition (Elias et al., 2004). CVD risk factors in midlife are strongly associated with the development of late-life dementia (Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005). Higher aggregate CVD risk factors at baseline are associated with poorer cognitive performance at follow up. The impact of CVD risk factors on cognition may preferentially affect specific cognitive domain performance, such as executive function (Lo & Jagust, 2012). The following sections discuss specific CVD risk factors in detail.

1.2. A. Diabetes Mellitus (DM):

Uncontrolled DM can have a devastating effect on cerebral blood vessels and blood flow. Cerebral blood vessels undergo a progressive aging process that is accelerated by DM. This process involves functional and structural changes in the cerebral blood vessels including decreased elasticity, decreased capillary density, and the thickening of the blood vessels' basement membranes due to the accumulation of Aβ. These changes lead to increased resistance to cerebral blood flow. DM can also change the autoregulatory response of cerebral blood vessels resulting in cerebral ischemia (A. M. A. Brands, Kessels, de Haan, Kappelle, & Biessels, 2004) (Figure 1.2).

Uncontrolled DM can also result in the loss of neuronal plasticity secondary to reduced expression of NMDA-dependent long-term potentiation (LTP) in the hippocampus. LTP reduction was strongly associated with hyperglycemia. In addition to reducing LTP expression, long-term depression (LTD) expression was enhanced in diabetic mice (Gispen & Biessels, 2000). Furthermore, uncontrolled DM patients were found to have a slowed mental function, memory loss, and learning problems that ultimately lead to cognitive decline. The extent of cognitive decline in diabetic patients range from mild to moderate and are found to be associated with small vessel disease (A. M. Brands, Biessels, de Haan, Kappelle, & Kessels, 2005). DM affects cognition and has a variable effect on specific cognitive domains including processing speed, attention, memory, language, and general intelligence (van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009). However, there are mechanisms other than AS that contribute to cognitive impairment and to experimental observations such as reduced hippocampal LTP (Figure 1.2).

Figure 1.2. The mechanisms by which uncontrolled diabetes mellitus causes arteriolar sclerosis and cognitive decline.



1.2. B. Hypertension (HTN):

Uncontrolled HTN is arguably the most common risk factors associated with stroke, CVD, cognitive decline, and dementia. HTN is defined as blood pressure level of more than 120/80 mmHg and divided into three stages of severity according to the American Society of HTN (ASH). The relationship between HTN and cognition is not clearly understood, the relationship between HTN and AS is strongly influenced by age (Gąsecki, Kwarciany, Nyka, & Narkiewicz, 2013).

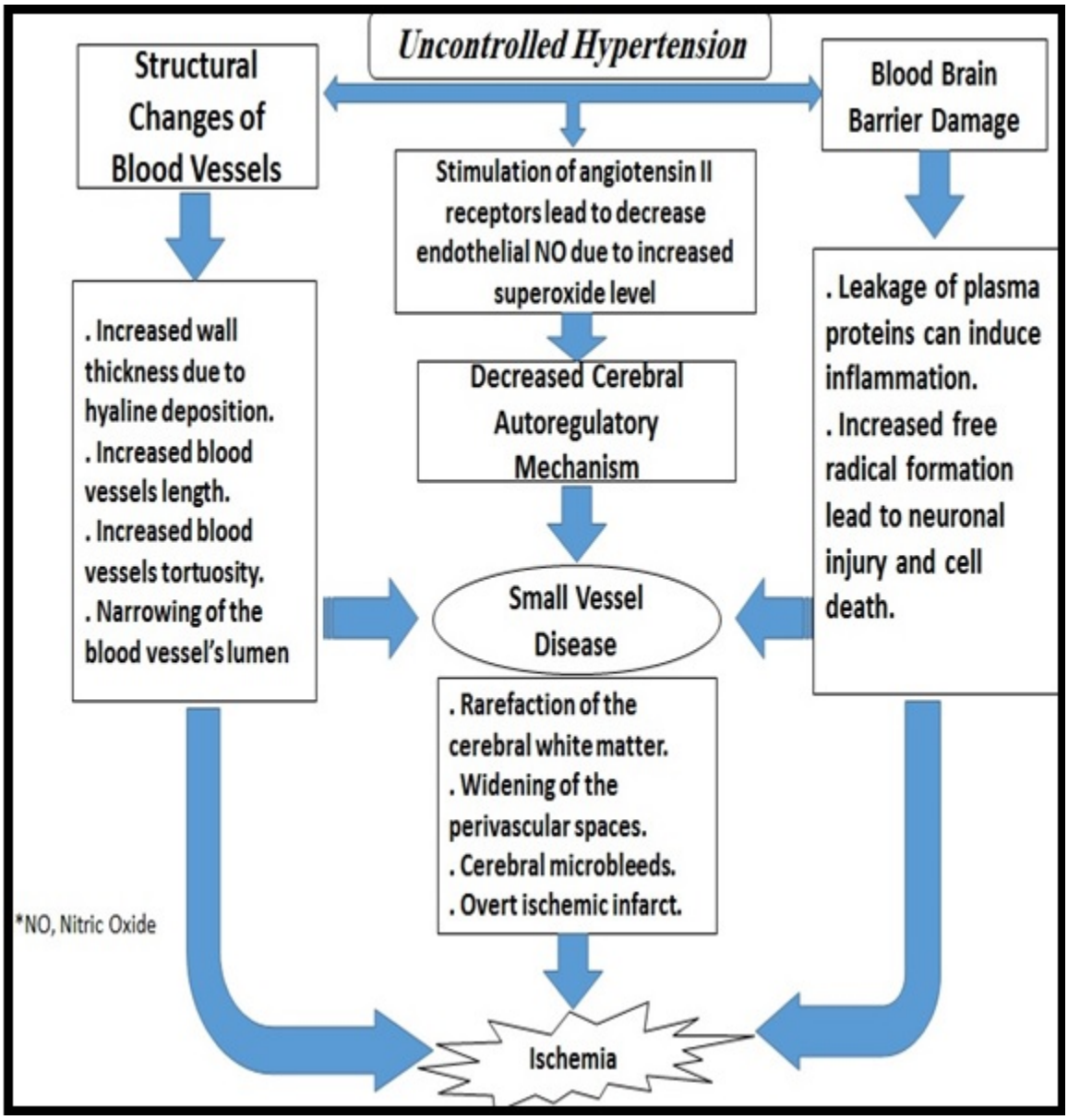
1.2. B.1. The mechanism by which uncontrolled HTN induces formation of arteriolar sclerosis:

Uncontrolled HTN causes thickening of cerebral blood vessels' basement membranes, leading to reduced cerebral blood flow (Gąsecki et al., 2013) and cerebral small vessel disease (SVD). Pathologically HTN leads to white matter rarefaction, widening of perivascular spaces, cerebral microbleeds, and overt ischemic infarcts (Tzourio, Laurent, & Debette, 2014).(Figure 1.3)

Subcortical and deep white matter regions of the brain are especially vulnerable to ischemic damage caused by HTN because these areas are supplied by end arterioles with few anastomoses (L. Pantoni, 2002; Tzourio et al., 2014). Diminished cerebral autoregulation (Paulson, Strandgaard, & Edvinsson, 1990) may be secondary to stimulation of angiotensin II receptors, leading to endothelial dysfunction and nitric oxide (NO) reduction (Nickenig & Harrison, 2002). Also, structural changes (increased hyalinization, increased length, tortuosity and narrowing of cerebral blood vessels) caused by uncontrolled HTN further diminish cerebral blood flow (D. M. Moody, Santamore, & Bell, 1991). HTN is strongly associated with an increase in frontal lobe WML (Gąsecki et al., 2013).

Uncontrolled HTN also results in damage to the BBB as a result of mechanical tear and shear of blood vessels' walls, promoting leakage of plasma proteins that can induce inflammatory responses leading to local tissue damage in affected areas (L. Pantoni, 2002; Tzourio et al., 2014). Protein deposition as a result of BBB breakdown can also increase free radical formation resulting in neuronal injury and cell death due to oxidative stress, (Duron & Hanon, 2008) ultimately leading to cognitive decline.

Figure 1.3. The mechanisms by which uncontrolled hypertension cause arteriolar sclerosis and cognitive decline.



1.2 B.2. Midlife vs. Late life HTN:

HTN's effects on the brain are determined by many factors that include patient specific characteristics, time at which the diagnosis of HTN was made, duration of disease, degree of blood pressure elevation and severity of the disease (continuous or episodic). The earlier in life HTN begins, the more severe, and the longer duration of exposure to high blood pressure, the more sever the resultant damage to the brain will be (Tzourio et al., 2014). Uncontrolled midlife HTN increases risk of dementia in late-life. Targeting HTN earlier in midlife may help reducing deterioration of cognitive function (L. J. Launer, Masaki, Petrovitch, Foley, & Havlik, 1995). The Honolulu-Asia Aging Study (n=7878), found that 27% of patients with midlife HTN and 17% of patients with pre HTN later develop cognitive decline (Lenore J. Launer et al., 2010).

On the other hand, late-life HTN may not be associated with cognitive decline. In fact, low systolic blood pressure can result in a cognitive decline in elderly (low diastolic pressure effect was not significant in this study) (Mahoney, Verghese, Goldin, Lipton, & Holtzer, 2010). Muller Majon et.al. reported that lower late-life diastolic pressure with a history of midlife HTN was associated with cognitive decline (Muller et al., 2014). This can be explained by the fact that midlife HTN causes vascular changes that then require sustained HTN to allow for sufficient cerebral blood flow in late-life.

HTN is associated with global cognitive decline as well as decline in specific cognitive domains including, memory, processing speed, cognitive flexibility, attention, and perception. Language impairment was not associated with HTN in this study (van den Berg et al., 2009).

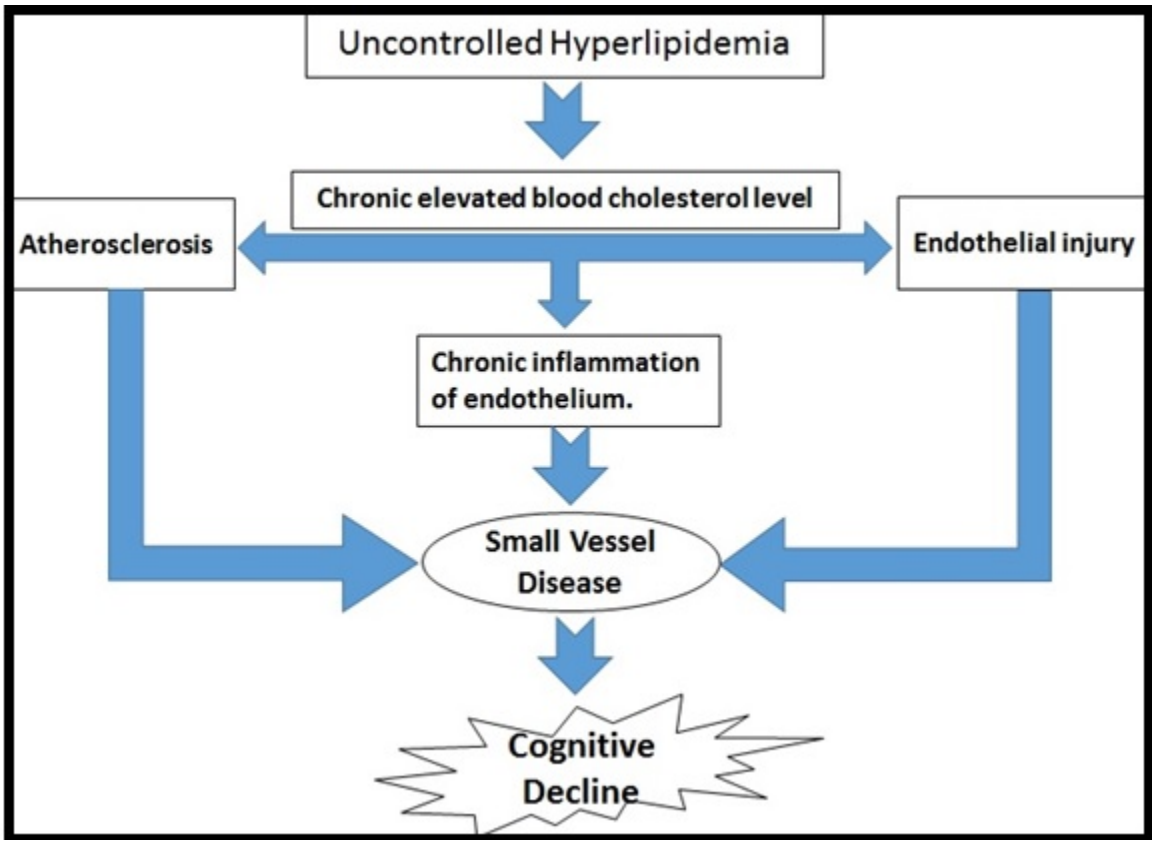
1.2. C. Hyperlipidemia (HLD):

HLD is defined as high levels of plasma cholesterol (> 200 mg/dl) (Stapleton, Goodwill, James, Brock, & Frisbee, 2010), or triglycerides, or both (Murchison, 1985). AS is found to be strongly associated with intimal thickening in patients with large vessels disease (e.g., carotid stenosis) (Ben-Assayag et al., 2012) and is more prevalent in men than in women (Pico et al., 2002). Cholesterol constitutes a central component of the atheroma that accumulate in blood vessel walls. Chronic elevated cholesterol levels can lead to chronic inflammation resulting in endothelial injury and atherosclerosis (Goldschmidt-Clermont, Dong, Seo, & Velazquez, 2012). These changes further lead to platelet adhesion and release of platelet-derived growth factor (PDGF), activating smooth muscle migration, proliferation, and foam cell formation (Munro & Cotran, 1988). Atherosclerosis is strongly associated with small vessel disease (SVD), ischemic heart disease (IHD), and overt stroke. (Figure 1.4)

According to Kaechang Park et al., hypertriglyceridemia (which is defined as an elevated blood triglyceride level > 150 mg/dL (Pejic & Lee, 2006)), was found to be strongly associated with increased WMH volume (Park et al., 2007); however, Jordi Jimenez-Conde et al. reported that HLD can be protective in cerebral small vessel disease (Jimenez-Conde et al., 2010a). The latter finding is controversial. The authors have postulated that cholesterol stabilization of microvasculature leads to a reduction in intracerebral hemorrhage and microbleeds that might otherwise worsen WMH burden. In support of this hypothesis, the same study found that active statin therapy reduced the impact of HLD on WMH, rendering it statistically insignificant (Jimenez-Conde et al., 2010b).

HLD was found to preferentially affect cognition in the domains of memory and processing speed (van den Berg et al., 2009).

Figure 1.4. The mechanisms by which uncontrolled hyperlipidemia cause arteriolar sclerosis and cognitive decline. Large vessel disease is also associated with hyperlipidemia and with stroke (occlusive or embolic), cardiac and renal dysfunction, and chronic hypoperfusion (not emphasized in this figure).



1.2. D. Age:

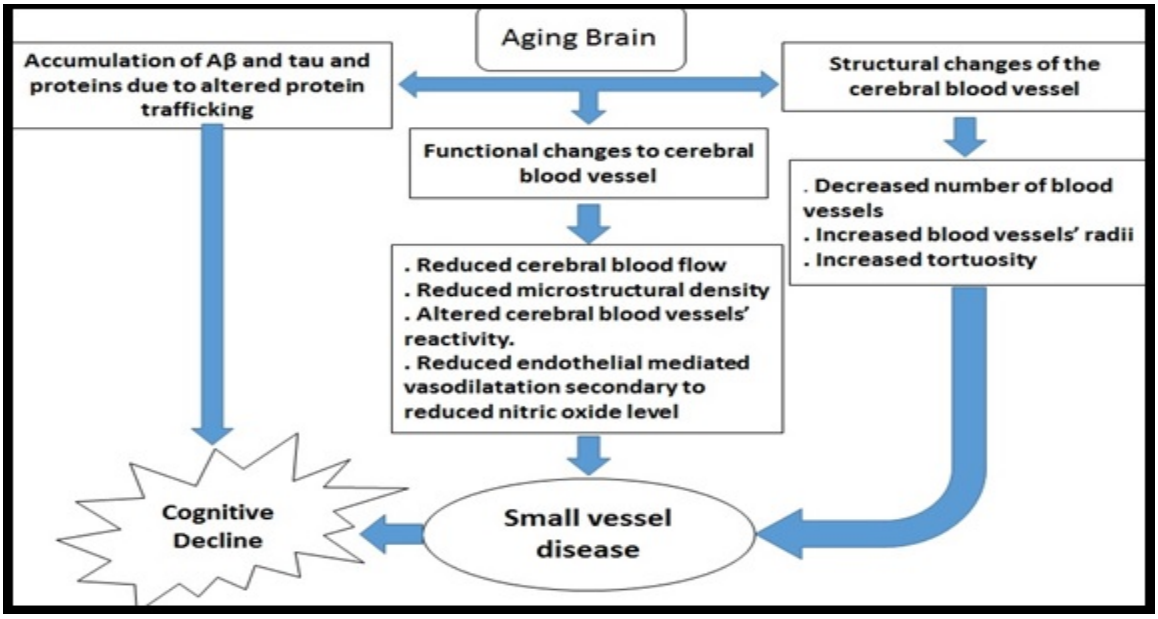
Aging affects the structure of gray matter, white matter, and cerebral blood vessels. Structural changes to cerebral blood vessels as a result of advanced age include: decreased number of blood vessels, increased blood vessels' radii, and increased tortuosity of blood vessels (Bullitt et al., 2010). Functional consequences of these changes in the aging brain include: reduced cerebral blood flow (Martin, Friston, Colebatch, & Frackowiak, 1991), reduced microstructural density (Sonntag, Lynch, Cooney, & Hutchins, 1997), altered cerebral blood vessels' reactivity, and reduced endothelial mediated vasodilator activity due to decreased nitric oxide level (Sonntag WE, 2007) (Figure 1.5).

The effects of aging on the brain include: 1) alterations in the protein trafficking and processing that can lead to increased accumulation of Aβ, tau, and α-synuclein, 2) impaired mitochondrial function leading to increased neuronal vulnerability to damage by oxidative stress, and 3) DNA damage repair capacity is reduced leading to (Yankner, Lu, & Loerch, 2008). These effects result in overall reduced integrity of white matter (Gąsecki et al., 2013) resulting in decreased network efficiency (Faith M. Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009). The prefrontal cortex is preferentially affected more severely by the aging process.

Aging and cognition:

Aging affects global cognition but specifically has the greatest impact on executive function (explained by reduced volume of prefrontal cortex), processing speed, and working memory (F. M. Gunning-Dixon & Raz, 2000). Verbal memory performance has also been shown to decline to some degree as a result of the aging process (Yankner et al., 2008).

Figure 1.5. The mechanisms by which normal aging causes arteriolar sclerosis contributing to cognitive decline

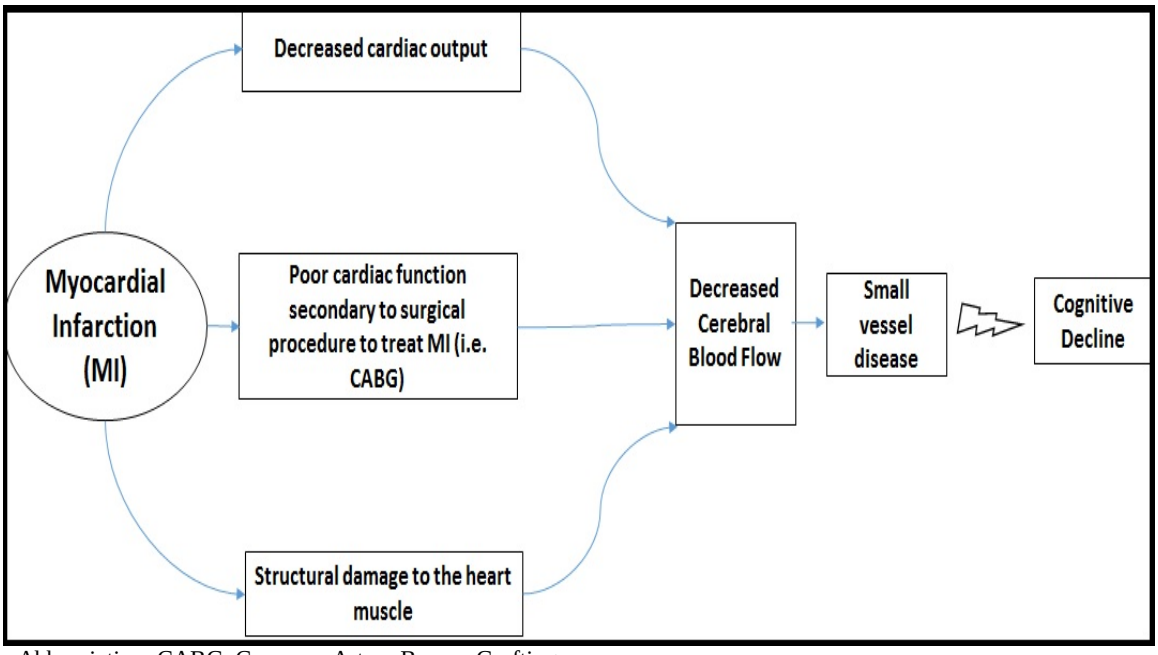


1.2. E. Cardiac disease (congestive heart failure, myocardial infarction, and atrial fibrillation):

I. Myocardial Infarction (MI):

Myocardial infarction is one of the leading causes of death in the US (Mozaffarian et al., 2016). The mechanism by which MI affects cognition is believed to be cerebral hypoperfusion secondary to diminished cardiac function sometimes compounded by temporary interruptions during cardiac surgery (CABG) (Volonghi, Pendlebury, Welch, Mehta, & Rothwell, 2013). Cardiac output reduction due to structural damage of the heart can lead to systemic hypoperfusion, reduction of cerebral blood flow, and ischemic damage to brain areas important for cognitive performance (Eggermont et al., 2012) (Figure 1.6).

Figure 1.6. The mechanisms by which myocardial infarction may be linked with cognitive decline, emphasizing small vessel disease effects.



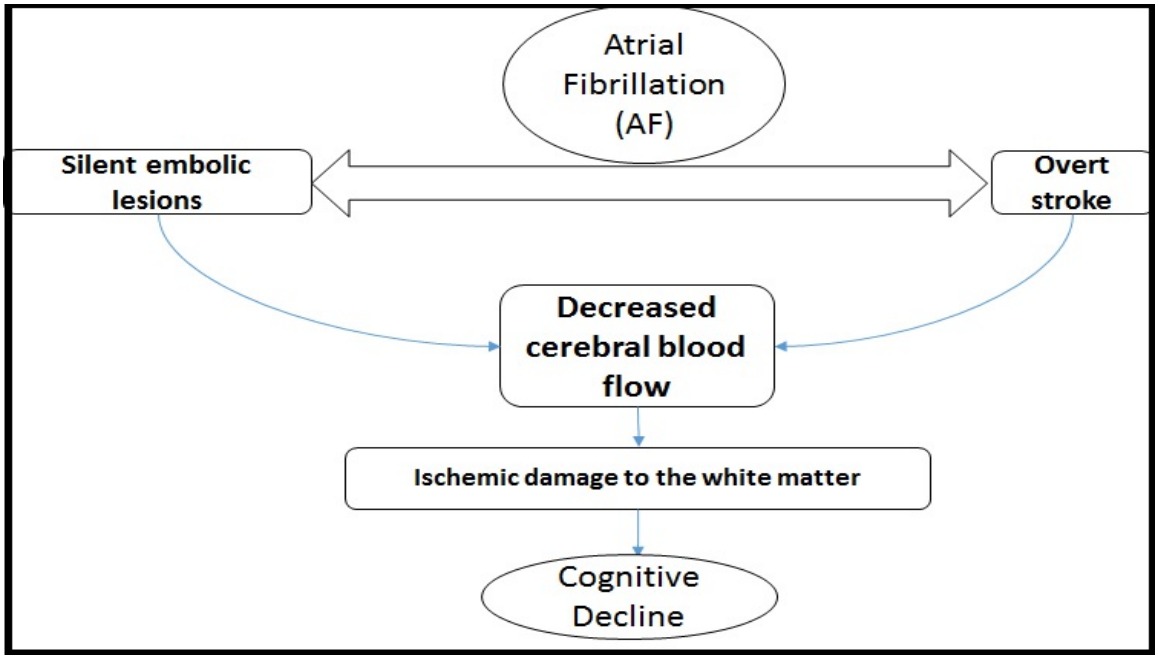
Abbreviation: CABG, Coronary Artery Bypass Grafting.

Patients with a history of MI were more likely to develop cognitive decline than their counterparts without a history of MI (Haring et al., 2013). It is worth mentioning that women with a history of myocardial infarction have five times the risk of developing dementia than those with no MI history (Aronson et al., 1990). The effects of acute coronary symptoms on cognition were found to be more than that of TIA, but slightly less than those caused by minor strokes. Cognitive domains affected by MI include both memory and language. Executive function has been shown to be affected to a lesser degree in person with MI (Volonghi et al., 2013). This distinguishes the cognitive effects from aging.

II. Atrial Fibrillation (AF):

AF may cause ischemic cerebrovascular damage through the following mechanisms: 1) higher risk of lacunar infarction, 2) silent embolic lesion of the cerebral circulation, 3) overt clinical stroke. All of these modes of injury can contribute to cerebral blood flow reduction and hypoperfusion which in turn lead to arteriolosclerotic WML and resultant cognitive decline (Kilander et al., 1998; Wolf, Dawber, Thomas, & Kannel, 1978) (Figure 1.7). The pathway to cognitive through WM injury is emphasized here but should not be taken as exclusive.

Figure 1.7. The mechanisms by which atrial fibrillation can cause cognitive decline through small vessel disease in WM.

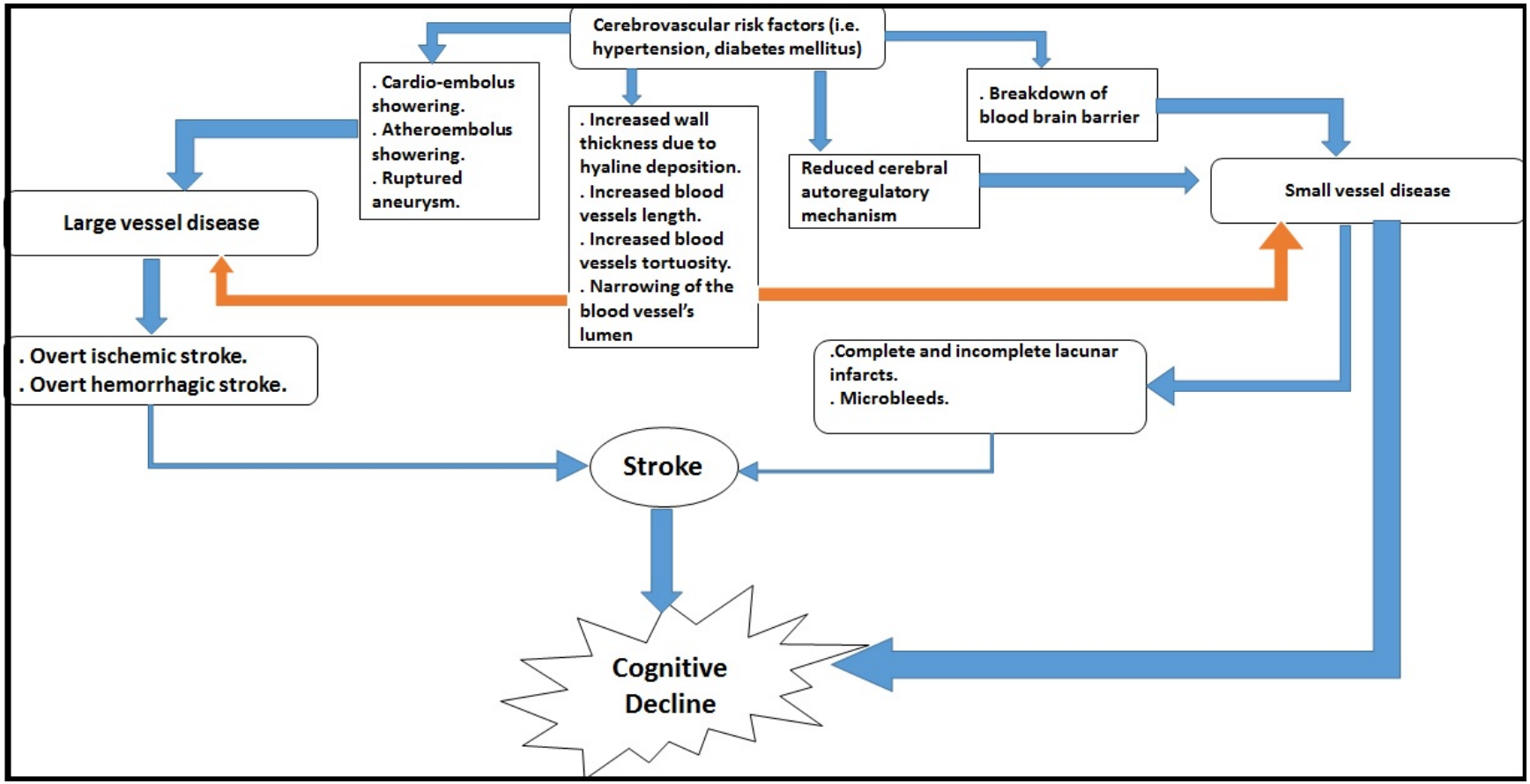


Atrial fibrillation was found to be strongly associated with cognitive decline and dementia especially mixed Alzheimer's – cerebrovascular dementia type (Ott et al., 1997). Poor performance in MMSE and the Trail Making Test A and B was found in men with atrial fibrillation compared to those without AF (Kilander et al., 1998).

1.2. F. Stroke:

Although both stroke and AS have many risk factors in common, it is important to note that they are distinct pathologic entities. Ischemic stroke is irreversible brain tissue injury due to deficient blood supply regardless of underlying cause. AS is one cause of deficient blood supply, and may be cause stroke when combined with other factors such as hypotension or blood clotting. It was found that persons with stroke are four times more likely to have arteriolar sclerotic changes than non-stroke patients (Inzitari et al., 1987). Arteriolosclerotic WML are strongly associated with lacunar infarcts and cerebral hemorrhage (Leys et al., 1999). Stroke patients have many risk factors that play central roles in AS formation such as HTN, DM, and HLD (Figure 1.8).

Figure 1.8. Show the contribution of CVD risk factors to small and large vessels disease.



Poor performance in the Trial Making Test B (TMT-B) can reflect poor function of the subcortico-frontal white matter (O'Donnell et al., 2012; Wiberg et al., 2010). Decline in TMT-B, orientation to place and time, and attention and delayed recall predict increase stroke risk in the elderly (Laukka, Jones, Fratiglioni, & Bäckman, 2004; O'Donnell et al., 2012). Cognitive decline due to stroke is a quite heterogenous, which lead to a wide varity of cognitive deficit. In contrast, cognitive deficits secondory to arteriolosclerotic changes in WM is relatively uniform in the absence of stroke and can overcome the confound of such heterogeneity.

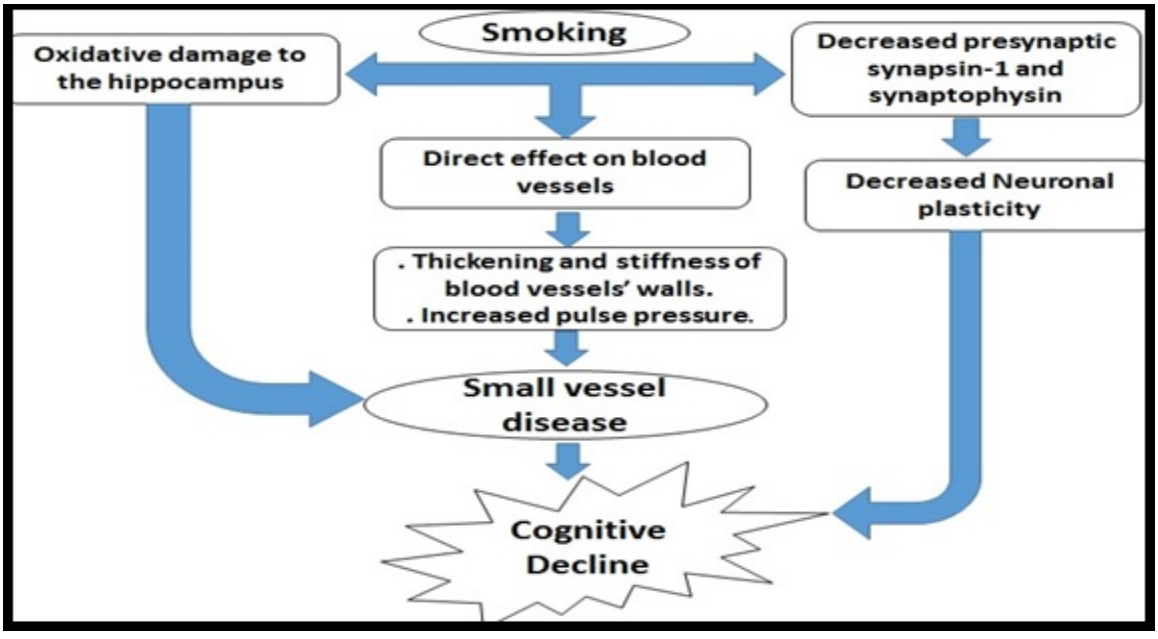
1.2. G. Smoking

Smoking causes oxidative stress in the hippocampus (Ho et al., 2012; Tuon et al., 2010) and can also affect neuronal plasticity by reducing presynaptic proteins (i.e. synapsin-1 and synaptophysin) levels in hippocampal cells (Ho et al., 2012) (Figure 1.9).

Smoking is found to increase pulse pressure and arterial stiffness in chronic smokers (Mahmud & Feely, 2003). Smokers were found to have higher pulse wave velocity regardless of whether they are current or ex-smokers. The duration of smoking cessation was found to improve pulse wave velocity (Jatoi, Jerrard-Dunne, Feely, & Mahmud, 2007). The risk of dementia in current smokers is 70% higher than in non-smokers (Etgen, Sander, Bickel, & Förstl, 2011).

Animal studies conducted over the previous two decades have measured the effects of nicotine agonists on cognition. These studies have demonstrated an association of nicotine administration with improved performance in the domains of attention and working memory (Levin, Christopher, Weaver, Moore, & Brucato, 1999; Stolerman, Mirza, Hahn, & Shoaib, 2000). Despite the negative impact of smoking on cerebrovascular health, these results have invigorated research using nicotinic agonists for the treatment of age-related cognitive decline and Alzheimer's disease.

Figure 1.9. The mechanisms by which smoking causes arteriolar sclerosis and cognitive decline.



1.2. H. Other risk factors:

Other risk factors including hyperhomocysteinemia, heart failure, chronic renal failure, and others have been shown to be important in the development of AS and resultant WMH burden. These will not be discussed individually in detail as unlike the prior risk factors these have not served as independent variables in the present thesis analysis.

1.3. Cognitive decline, stages, and tests used to measure it.

VaD can be divided into three stages: 1) the preclinical stage has been described by Hachinski V.C. et al. (Hachinski & Bowler, 1993), as the stage when there is a brain damage with lack of any cognitive impairment, 2) the mild cognitive impairment stage (MCI) is characterized by cognitive impairment with intact Activities of Daily Living (ADL), 3) the major cognitive impairment stage also recognized as the stage of dementia with decline in functional activities of daily living (Sachdev et al., 2014).

It is widely recognized that at the stage of advanced dementia, the brain has suffered significant irreversible injury. As such, the field has moved towards earlier detection of disease. Targeting, diagnosis and secondary prevention in the preclinical and MCI stages is reasonably believed to be the best way to impact the disease process, although specific risk factor interventions have not demonstrated benefits so far (Etgen et al., 2011). In addition, focusing on these early predementia stages of CVD allows planning for future needs for both the patient and potential caregiver (Patel & Holland, 2012). As such the focus of this thesis and the patient population studied include the preclinical and MCI stages of CVD.

1.3.1. Diagnosis of preclinical CVD:

Preclinical CVD is a term used to describe the early pathological changes of the cardiovascular system that will lead to clinical CVD, stroke, and cerebral small vessel disease if continued (Treiber et al., 2003). CVD risk factors influence the structure and function of blood vessel especially if they are poorly controlled over long period of time.

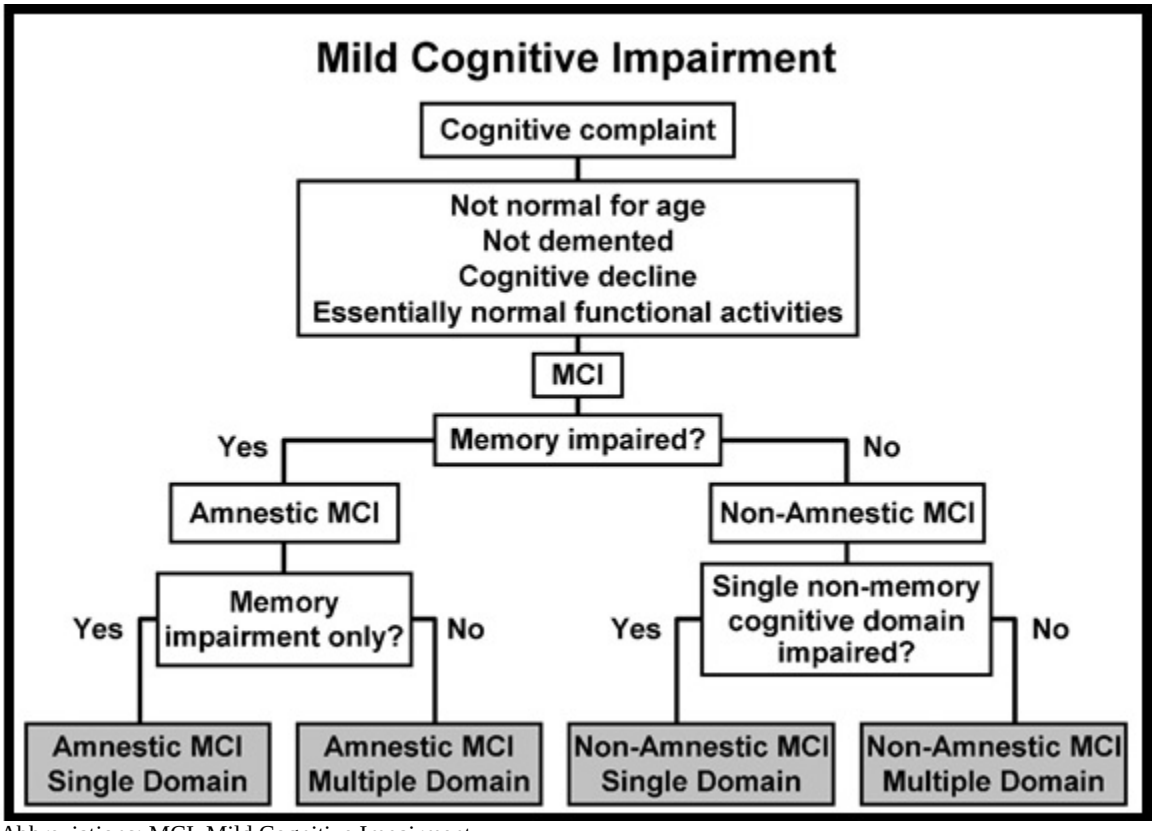
Currently Framingham Risk Score (FRS) is used as a primary preventive tool to predict risk of CVD in asymptomatic healthy persons. Traditional CVD risk factors are included in FRS are patient age, history of smoking and HTN, total serum cholesterol and HDL. Ten-year risk scores are expressed as a percentage. A percentage between 0-10% is considered low risk, the moderate risk falls between 11-20%, and a high risk occurs when the ten years risk is greater than 20% (R. B. D'Agostino, Sr. et al., 2008).

1.3.2. Definition of MCI-CVD:

Alzheimer's Disease Centers (ADCs) have adopted the criteria established by the second International Working Group on MCI (Winblad et al., 2004). Those criteria are as follows:
I. Global cognition should be preserved;
II. A cognitive deficit that is reported by self or caregiver with an evidence of such complaint; (typically set at > 1.5 s.d. below age and education adjusted means)
III. Not demented by DSM-IV criteria;
IV. No, or minimal functional impairment.

This schema includes diagnosis of MCI into four major subtypes based on presence vs. absence of memory involvement and further on the presence of involvement of a single vs. multiple cognitive domains as described below in figure (1. 10).

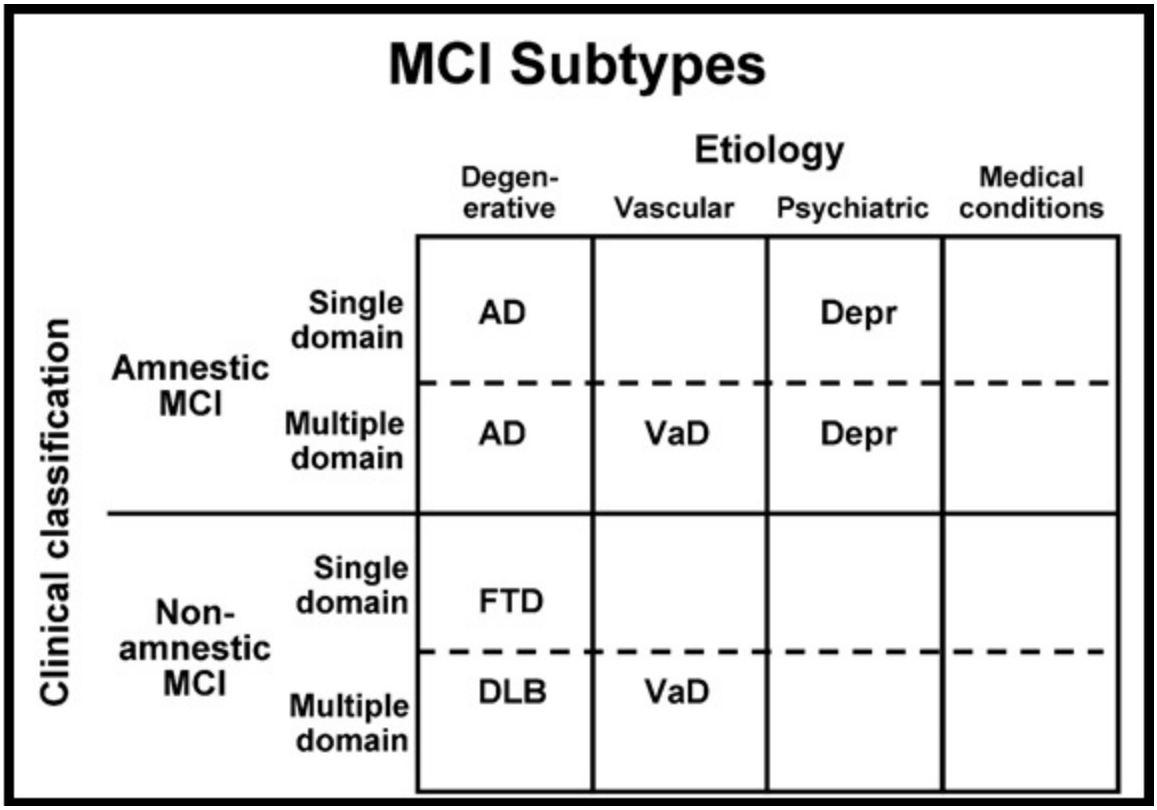
Figure 1.10. Diagnosis of Mild Cognitive Impairment.



Abbreviations: MCI, Mild Cognitive Impairment

This schema has been developed to allow clinical determination of the potential causes for the cognitive impairment noted. Practical application of the schema for predicting underlying cause of cognitive decline is illustrated below in figure (1.11). It should be noted that this diagnostic schema has not been fully validated and ongoing work similar to this thesis are needed to fully delineate the specific features of MCI due to specific underlying or mixed pathologies. This is a practical working clinical and conceptual model for the classification of mild cognitive impairment phenotypes that may be predictive of underlying etiology.

Figure 1.11. Mild Cognitive Impairment subtypes.



Abbreviations: AD, Alzheimer's Disease; VaD, Vascular Dementia; FTD, Fronto-Temporal Dementia; DLB, Lewy Body Dementia; Depr, Depression; MCI, Mild Cognitive Impairment.

1.3.3. Cognitive domains definitions and brief anatomical background:

To better understand how WML affect cognition, it is important to know the anatomy of brains' areas concerned with cognition and the importance of white matter fibers in connecting those different areas. Also, it is also important to know more about cognitive domains subdivisions and how to test these domains.

1.3.3. A. Memory:

The ability to store new information and recall previously stored information is what memory means. There are multiple memory systems including:

. Short-term memory (e.g. working memory – ability to hold information for short-term online use and is key for wide range of cognition). Short-term memory undergoes significant decline in cognitive aging and MCI (Grady, Furey, Pietrini, Horwitz, & Rapoport, 2001).

. Episodic memory: represents personal experience and life events that can be explicitly recalled (may be "short-term" or long term).

. Procedural memory: includes any motor or cognitive skill learning that is implicit and may not be recalled explicitly (i.e. using keys to open doors).

. Semantic memory: this includes facts and knowledge (i.e. the moon orbits the earth).

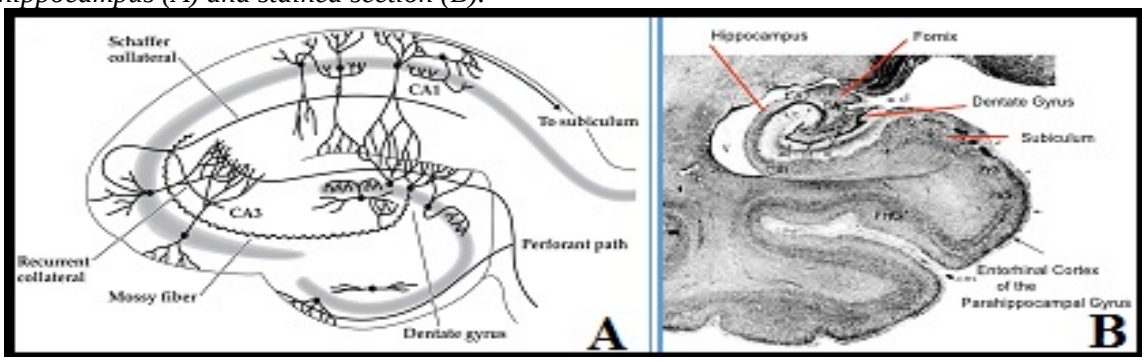
. Perceptual representation memory: this includes sensory memory (Halligan, Kischka, & Marshall, 2003).
. Prospective memory: ability to remember planned actions and intention at a later time. This memory is particularly important to older adults' ability to perform in daily life.

Many structures contribute to the process of memory formation, storage, and recall. Several sub-subcortical and cortical structures pertinent to the current study are illustrated. While different components of memory are widely distributed throughout neuroanatomic pathways are focus on the hippocampus and Perforant pathway is designed to show the importance of these areas and how WMH can preferentially affect them leading to memory impairment caused by underlying AS.

A. Hippocampal formation and the parahippocampal gyrus:

The hippocampal formation is located in the medial temporal lobe, and it looks like a hippocampus, which is Greek for "seahorse." It is divided into three parts, the dentate gyrus, the hippocampus, and the subiculum. The parahippocampal gyrus is formed by many cortical areas such as the entorhinal, perirhinal, prorhinal, piriform, parahippocampal, presubicular and parasubicular cortices. The entorhinal cortex represents the main receiver of hippocampal formation inputs, whereas the subiculum considered a vital part of output pathway from the hippocampal formation to the fornix (Blumenfeld, 2010). The intrinsic circuitry of the hippocampal formation consists of the perforant pathway, the Schaffer collaterals, and the alvear pathway. (Figure 1.12)

Figure 1.12 Coronal section of the medial temporal lobe showing the intrinsic circuit of the hippocampus (A) and stained section (B).



B. Thalamic Nuclei:

The thalamic nuclei that play an important role in memory formation are the anterior thalamic and dorsomedial thalamic nuclei in addition to mammillary bodies (Blumenfeld, 2010). The anterior thalamic is a part of the Papez circuit for memory. The dorsomedial nucleus is the relay for frontal function in the areas of attention and executive function. (Figure 1.14)

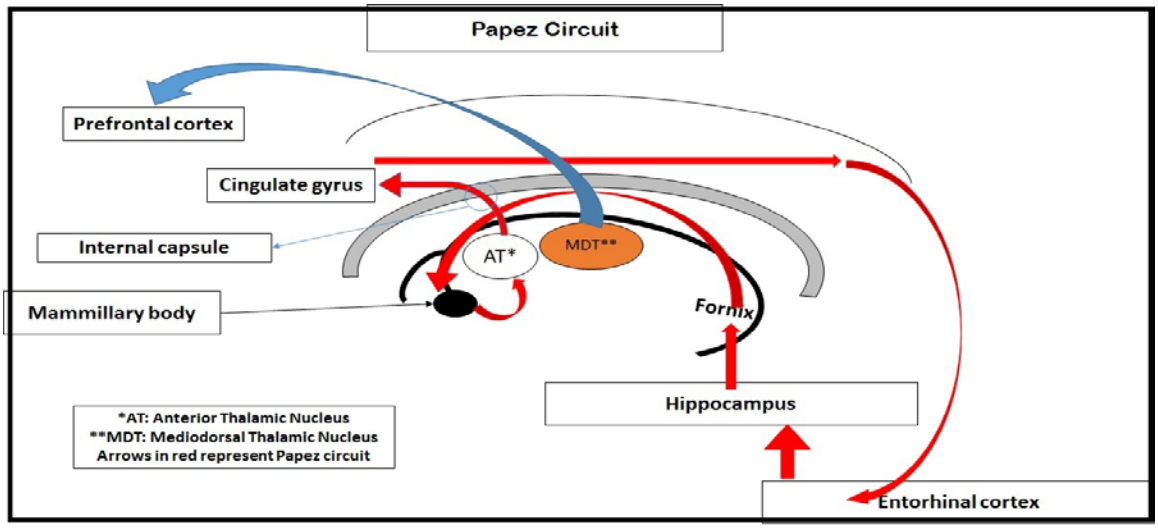
C. White matter connection between hippocampal formation and thalamic nuclei:

The white matter serves as the brain's subway network. One of the biggest white matter tracts is the fornix. *The fornix* is a C-shaped structure that follows the curvature of the lateral ventricles. This white matter structure connects the hippocampal formation with the thalamic nuclei and the septal areas. It can be subdivided into fimbria, crura, body, and columns of the fornix. In addition, there are fibers that serve as an inter-hippocampal connection called the hippocampal commissure. Furthermore, white matter tract that connects fornix with the mammillary bodies is the post-commissural fornix (Blumenfeld, 2010). Those post-commissural fornix fibers begin from subiculum and end at mammillary nuclei of the hypothalamus. Similarly, pre-commissural fornix fibers begin from the hippocampus and subiculum and end in the lateral septal nucleus (Blumenfeld, 2010). Finally, the fornix connects the hippocampus with the anterior thalamic nucleus. The uncinate fascicle provides a connection between the orbital cortex, the entorhinal cortex, and the hippocampal formation (Burgel et al., 2006). Injury to the genu of the corpus collasum of the right cerebral hemisphere results in memory loss. Injury to the genu in the left cerebral hemisphere, however, leads to losing of verbal memory (Schmahmann, Smith, Eichler, & Filley, 2008).

Papez circuit: this circuit connects the medial temporal lobe to the limbic system structures. Papez circuit begins with fibers that originate from the hippocampal formation. These fibers reach the fornix and make connections with the lateral and medial mammillary nuclei. The latter, connect to the anterior thalamic nucleus via the mammillothalamic tract. The anterior thalamic nucleus is then connected to the cingulate gyrus. The circuit is completed by connection back with entorhinal cortex via the cingulum (Blumenfeld, 2010).

Papez circuit is connected to the prefrontal cortex and frontal limbic structure including the nucleus basalis of Meynert, the caudate nucleus, and the amygdala. The nucleus basalis of Meynert is connected to the cingulate gyrus, whereas the amygdala and the caudate nucleus are connected to the anterior thalamic nucleus (Jicha & Carr, 2010) (Figure 1.13).

Figure 1.13 Papez Circuit.



Neuropsychological tests for memory:

There are many tests used to measure memory function. This include:

A. *The Wechsler Memory Scale* (WMS): widely used test for memory, it has six subsets. The WMS tests verbal and figural memory. The immediate and delayed recall is tested for each subset of the test.

Logical memory test is a subset of WMS. This test is done by telling the patient two short stories and asking the patient to immediately recall the story. Delayed recall of the story is tested 30 minutes after the immediate recall test (Wechsler D.: Wechsler Memory Scale. San Antonio, TX: Psychological Corporation, 2009).

B. *California Verbal Learning Test* (CVLT): This test is done by asking the patient to recall items from a list of things that were selected from semantic categories. This test is also known as a list learning task (SOWELL, DELIS, STILES, & JERNIGAN, 2001).

C. Other tests used to measure memory function are the Rey Auditory Verbal Learning Test (RAVLT), the Adult Memory and Information Processing Battery (AMIPB), Rivermead Behavioral Memory Test (RBMT), and RBMT Extended (RBMT-E) (Halligan et al., 2003).
Of note, all of these test have a strong language components that consider as a confounder when test for memory.

1.3.3. B. Language:

The language cognitive domain is concerned with speech production, language comprehension, and communication skills. Multiple brain areas take part in language expression, comprehension, and communication (Halligan et al., 2003). Also, language includes fluency, naming, and repetition. Language areas include the following:

A. *Broca's area* (Brodmann's area 44 and 45): this area is located in the inferior frontal gyrus of the dominant hemisphere (the left cerebral hemisphere is the dominant one in more than 95% of right-handed and 70% of left-handed people). Broca's area is responsible for speech expression; therefore, a lesion to this area may result in expressive aphasia.

B. *Wernicke's area* (Brodmann's area 22): this area is located in the posterior two-thirds of the superior temporal gyrus of the dominant hemisphere. This area is responsible for language comprehension and a lesion to this area results in Wernicke's aphasia.

C. *Transcortical motor* area: this area located in the frontal lobe and is essential for language formation. A lesion to the connections with frontal lobe areas lead to Broca's like aphasia that spare repetition function. ACA-MAC watershed stroke leads to such aphasia (Blumenfeld, 2002).

D. *Transcortical sensory*: Located in the parietal lobe. Disruption of connections with parietal lobe areas by MCA-PCA watershed stroke can result in transcortical sensory aphasia which resemble Wernicke's aphasia but spares repetition. The reason repetition remain intact is that the peri-Sylvian connections remain intact (Blumenfeld, 2002).

E. *Anterior temporal lobe*: the source of semantic information, injury to the dominant anterior temporal lobe results in impaired comprehension of words while injury to the non-dominant hemisphere results in visual agnosia for faces (Blumenfeld, 2002).

F. *Arcuate fasciculus*: this represents the subcortical white matter fibers, which connect Broca's and Wernicke's areas of the brain.

G. *Corpus callosum*: this is a bundle of white matter fibers connecting those language areas in the dominant hemisphere with the non-dominant hemisphere to assess in language processing (Blumenfeld, 2010).

H. *Superior longitudinal fascicle*: this white matter fibers connect the frontal lobe (Broca's area) with the temporal (Wernicke's area), parietal and occipital lobe (Burgel et al., 2006).

Many of these tracts are subcortical and located in the areas where cerebral white matter damage is found.

Neuropsychological tests for language:

A. Boston Naming Test: this is a picture naming test that requires the patient to have an intact store of semantic knowledge about visually presented objects. This test is sensitive to anomia (i.e. patients with damage to their anterior temporal lobe are unable to name objects and will have poor performance in this test) (Graves, Bezeau, Fogarty, & Blair, 2004; Halligan, Kischka, & Marshall, 2010).

B. Verbal Fluency Test (category animal and vegetable): This test asks the patient to start naming animals or vegetables start with letter A, and the B for example. The patient will have 1 minute per letter, and the score will be the number of correct words per letter (Halligan et al., 2003).

There are other language tests that are well validated and useful in the field, however, there are beyond the scope of this thesis as they were not included as variables in this study.

1.3.3. C. Attention and processing speed:

Attention is the process by which a person focuses on a certain task. Different tasks necessitate different levels of attention. Better information processing achieved by more intensive attention (Halligan et al., 2003).

Both hemispheres are involved in attention, but the non-dominant (mostly the right) hemisphere is the major hemisphere in attending to spatial and visual stimuli while the left hemisphere attending to language, math, and logic. Many structures are involved in the attention mechanism. Those include the thalamus (namely medial and interlaminar nucleus), the hypothalamus, the brain stem, and the forebrain. Furthermore, the cingulate gyrus, in addition to the lateral and medial fronto-parietal association cortex, is also part of the attention circuit (Blumenfeld, 2010). Processing speed was found to be associated with decrease white matter tracts integrity including the fronto-parietal and temporal portions of the SLF and the inferior fronto-occipital fasciculus (Kerchner et al., 2012). SLF connects the frontal lobe with the parietal and temporal lobes.

Neuropsychological tests for attention and processing speed:

A. *Digit Span Forward and Backward* in addition to *Digit Span Forward and Backward Length* (Wechsler Intelligence Scale for Children—Third Edition (WISC-III) The Psychological Corporation, San Antonio, TX (1991)).

B. *Trial Making Test part A* (TMT-A): Patient is asked to connect numbered circles from 1-25 written on paper. The score will be the amount of seconds needed to finish the test (Tombaugh, 2004). The goal of this test is to connect these numbered circles as fast as possible. Processing speed can be measured based on the time needed to complete the test (Kopp et al., 2015).

C. *Digit Symbols Substitution Test (DSST) from the Wechsler Adult Intelligence Scale* (WAIS-R): nine digit-symbol pairs and array of digits are given to the patient. The examiner asks the patient to write the corresponding symbol beneath each digit as fast as possible. The score is calculated as the number of correct symbol-digit pairs in 90 seconds (Dardiotis et al., 2012).

DSST is considered a valid way to measure processing speed, which is found to be responsible for more than 50% of variance in the test (Joy, Kaplan, & Fein, 2004). Since VaD greatly affects processing speed in addition to executive and visuospatial functions (Libon et al., 1998), researchers can use DSST to examine the cognitive consequences of CVD. To this end, performance on the DSST is found to be associated with VaD (van den Heuvel et al., 2006), HTN and microvascular disease (Hugenschmidt et al., 2013). All of these tests have visuospatial components which are confounders when we test for processing speed and attention.

1.3.3. D. Visuospatial function:

Visuospatial function is defined as the ability to recognize an object, together with its' location in space and relationship with other objects as well as to oneself. Objects and face recognition involve the ventral stream (inferior temporal and occipital lobes). The dorsal stream provides spatial information (dorsal parietal and occipital lobe; object location and movement). Lesions in areas that are involved in visuospatial processing may result in defective visuospatial processing (Halligan et al., 2003).

Cortical areas that participate in this system are the occipital (dorsal and ventral), the parietal, the temporal, and the prefrontal cortex. The parietal association cortex is responsible for the processing of movement and position of an object in space (Blumenfeld, 2010). The temporo-occipital pathways are responsible for object recognition. These pathways include 1) the U-fibers that connect the adjacent areas of the temporal and occipital lobe, 2) the inferior longitudinal fasciculus (Catani, Jones, Donato, & ffytche, 2003). These pathways are posterior and less involved in WMH development. Hence, lesser impact on these functions is expected.

1.3.3. E. Executive function:

Executive function is defined as the ability to plan for the future (making use of experience), react appropriately to an unexpected event, abstract thinking and decision making. A decline in executive function can have significant negative consequences in daily activity (Halligan et al., 2003).

Many areas are required for normal executive function. First, the dorsolateral frontal cortex is connected to the dorsolateral head of the caudate nucleus. This part is found to be associated with verbal fluency and abstract reasoning. Second, the orbitofrontal cortex is connected to the ventromedial nucleus of the caudate and is found to play a role in implementing appropriate behavior. Finally, the anterior cingulate is connected to the nucleus accumbens forming the ventromedial pathway, which involved in motivation (Alvarez & Emory, 2006). The dorsolateral frontal cortex is affected by aging process and CVD risk factors, this make it more vulnerable to WMH development resulting in poor executive function.

Other white matter tracts that connect frontal lobe with other brain areas include 1) the superior occipito-frontal fascicle which connects the prefrontal cortex with the limbic system, 2) the inferior occipito-frontal fascicle connects the frontobasal cortex to the parietal lobe. (Burgel et al., 2006). Disruption of these connecting tracts results in decreased executive function.

Neuropsychological tests for executive function:

A. *Trial Making Test part B* (TMT-B): Patient is asked to connect numbered and lettered circle (1-A-2-B-3-C) written on paper. The result will be the amount of seconds needed to finish the test (Tombaugh, 2004). This test also has motor performance, processing speed, and visuospatial components that can consider as a confounder when test for executive function.

B. Other tests like Stroop Test, Wisconsin Card Sorting Test, and Sex Element Test (SET).

1.4. Studies that have looked at T2 signal abnormalities:

According to the Rotterdam Scan Study, WML increases were strongly associated with the size of those lesions at the baseline scan, advanced age, female sex, higher blood pressure (especially diastolic BP) and current smoking status (van Dijk et al., 2008). The Cardiovascular Health Study showed that the aggregate effect of cerebrovascular risk factors was associated with increased WML progression (W. T. Longstreth et al., 2005). The Austrian Stroke Prevention Study found that WML progression was most dependent on high diastolic blood pressure and advanced age (R. Schmidt, Fazekas, Kapeller, Schmidt, & Hartung, 1999). These data suggest that different population may exhibit distinct and yet overlapping risk profiles for the development of WMH.

WML due to small vessel disease (AS) were found to be associated with cognitive decline that affects many domains, especially processing speed (van den Heuvel et al., 2006; van Dijk et al., 2008), demonstrated by poor performance on Digit-Symbol Substitution, and on the Mini-Mental State Exam (Reinhold Schmidt, Petrovic, Ropele, Enzinger, & Fazekas, 2007).

There remain many unanswered questions in this field. First, there is no current evidence for active intervention regarding small vessel disease risk factor modification (N. D. Prins & P. Scheltens, 2015). Therefore, it is essential to develop a more thorough understanding of risk associations and cognitive sequelae of WMH in order to better design interventional and therapeutic clinical trials designed to slow or halt the progression of cerebral small vessel disease-induced cognitive decline (Leonardo Pantoni, 2010). Second, improved understanding and clinical training in the use of both qualitative and quantitative measures of CVD is needed to move the field forward in both research and clinical practice (Sakurai, Tomimoto, & Pantoni, 2015).

Three experiments were developed as the core of this thesis to address these issues:

1. We conducted a preliminary study of the clinical features, including risk factors and cognitive sequelae in elderly MCI patients (n=88) categorized as either MCI-AD or MCI-CVD based on qualitative rating of WMH (surrogate marker for CVD) and medial temporal lobe atrophy (surrogate marker for AD).

2. The association of CVD risk factors with WMH volumes (semi-automated quantification) was examined in an independent sample of subjects with high and low CVD risks that were clinically diagnosed as either normal or MCI.

3. We further explored the relationship between WMH volume and cognitive test scores in the population described above.

Understanding the association CVD risk factors with arteriolar sclerotic change (WMH) and the resultant effect of these changes on cognitive domain performance profile outlined in this thesis will enable the design of interventions targeting key risk factors with appropriate outcome measures that will maximize success as we move closer to achieving our ultimate goal of primary and secondary prevention of cognitive decline associated with CVD.

1.5. CVD risk factors and AD:

It is important to note, that many of CVD risk factors discussed above have also been found to be associated with the development of AD (de Bruijn & Ikram, 2014) in addition to their role in CVD. Unfortunately we have not yet assessed AD changes in CSF biomarkers so are unable to control for this potential confound within this experiment. Given the widespread appreciation of the prevalence of comorbidity for AD and vascular pathology in association with these shared risk factors, some discussion of the relationship to AD changes with those risk factors is necessary.

CVD risk factors may play an independent role in AD changes through the following mechanisms:
1) In high insulin states such as those seen in Type 2 diabetes, both insulin and Aβ will compete for the insulin-degrading enzyme (IDE), resulting in accumulation of Aβ and exacerbation of AD pathology (Alafuzoff, Aho, Helisalmi, Mannermaa, & Soininen, 2009).
2) Uncontrolled HTN upregulates receptors for advanced glycation end products (RAGE) expression in cerebral blood vessels, which play a major role in Aβ transportation at the BBB. RAGE up-regulation results in increased Aβ accumulation (Carnevale et al., 2012; Shah et al., 2012).
3) In a HLD state, cholesterol upregulates the β/γ secretase activity on APP, which favors Aβ production (Di Paolo & Kim, 2011).

It is currently unclear if the associations postulated above are important in human's disease. Alternatively, it is possible that CVD and AD exist as comorbid diseases, and the association of CVD risks with AD pathology is an artifact. Further work is clearly needed to evaluate these possibilities.

2. Specific Aim 1: Comparison of the clinical features of mild cognitive impairment of the cerebrovascular type (MCI-CVD) vs. mild cognitive impairment of Alzheimer type (MCI-AD)

2.1. Introduction:

Mild cognitive impairment is a clinical term referring to the gray zone between a cognitively normal state and development of dementia of any type (Petersen et al., 2009). Until recently it was thought that Alzheimer disease (AD) was the most common cause of dementia, followed by cerebrovascular disease (CVD) (Korczyn, Vakhapova, & Grinberg, 2012), but currently, this is being challenged by the recognition of a stronger interlink between AD and CVD than previous thought (Grinberg & Heinsen, 2010; Korczyn & Vakhapova, 2007). This leads to a difficulty in assessing patients with mild cognitive impairment (MCI) when both pathologies may be present at mild levels, lying in a "gray zone" between normal for the patient's age and pathological (Snowdon et al., 1997).

For the reason mentioned above, we need to find the specific clinical features, laboratory and imaging biomarkers, unique for each type of MCI, which will enable us to distinguish between those two groups of patients in early stages. MCI-AD is characterized by the development of an amnestic problem (Petersen, 2007). This criterion enables us to identify people at risk of developing AD-type dementia. Current studies indicate that there are many medical interventions by which we can delay the symptomatic progression of AD if diagnosed in an early stage (Petersen et al., 2005). While the clinical phenotype of MCI-AD is elucidated, little is known about MCI caused by other brain pathology.

Another important cause of MCI is cerebrovascular disease (MCI-CVD), which refers to the clinical state prior to vascular dementia (VaD). There are limited studies comparing the clinical phenotype of MCI-AD to MCI-CVD. There is also an urgent need to develop detailed criteria for the diagnosis of MCI-CVD type in order to detect this phenotype at an early stage allowing appropriate intervention and clinical care options to be pursued. This is especially important in MCI-CVD as treatment options targeting CVD risks already exist and may provide an opportunity for secondary prevention of VaD.

2.2. Methods:

2.2.1. Subjects:

The study population is from University of Kentucky Alzheimer's disease center (UK-ADC): a total of 88 subjects with the clinical diagnosis of MCI (Winblad et al., 2004) (enrolled initially while cognitively intact) were identified and categorized into two groups, one with MCI-AD type (43 subjects) and the other with MCI-CVD (45 subjects) based on qualitative rating of WMH (surrogate marker for CVD) and medial temporal lobe atrophy (surrogate marker for AD). Exclusion criteria included any history of head trauma, history of substance abuse (including alcohol), epilepsy, psychiatric illness, chronic unstable medical conditions that may affect the central nervous system, history of meningitis or encephalitis and TIA or stroke at enrollment.

Clinical histories, cognitive, physical and neurological exams were performed annually as described below (Schmitt, Wetherby, Wekstein, Dearth, & Markesbery, 2001). Many of these subjects underwent MRI brain imaging as part of the research procedures or for other reasons during their research engagement. The study was approved by the UK IRB following international guidelines on Human Subjects Research Protections (Declaration of Helsinki).

2.2.2. Demographic, clinical, and genetic variables:

Demographic variables used include the following: age at scan, time between scan and AD assessment, education, age at onset of cognitive decline, and risk factors for cerebrovascular diseases, including (HTN, DM, hypercholesterolemia, body mass index, heart attack, stroke, and smoking). Clinical laboratory variables include APOE ε genotype.

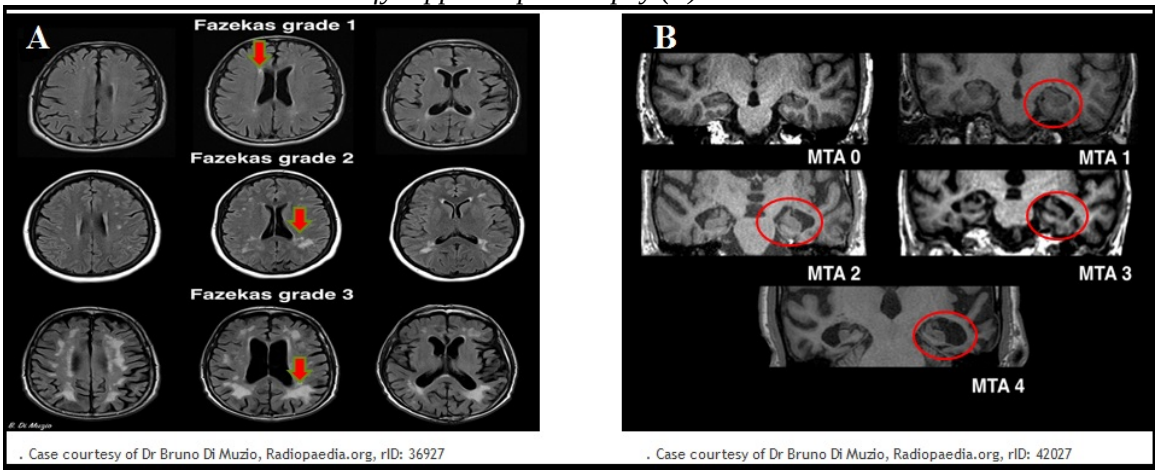
2.2.3. A. Cognitive and neurologic evaluation:

Cognitive and neuropsychiatric evaluations were performed at enrollment and then annually for all subjects. We used the following for the assessment of cognitive function: Mini Mental State Exam MMSE (Folstein, Folstein, & McHugh, 1975), Boston naming test (Graves et al., 2004), Wechsler-R Logical Memory Immediate and Delayed Recall Story A, Digit Span Forward and Backward Length, Trail Making Test A and Test B and Animal naming test. Clinical dementia rating including both global and the sum of boxes scores (J. C. Morris, 1993). CVD risks was assessed using the Hachiniski score (13 items) (L. Pantoni & Inzitari, 1993).

2.2.3. B. Imaging criteria that were used to classify subjects into low or high CVD risk:

Subjects without hippocampal atrophy on Scheltens scale (Scheltens, Launer, Barkhof, Weinstein, & Gool), but with Fazekas scale (Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987) 2 and 3 were classified as MCI-CVD, whereas, subjects with no vascular changes but with cognitive decline, and hippocampal atrophy were classified as MCI-AD. (Figure 2.1)

Figure 2.1. Imaging criteria that were used to subdivide subjects into low and high CVD burden. The Fazekas scale is used to identify those with low or high CVD changes (A), whereas the Scheltens scale is used to identify hippocampal atrophy (B).



2.2.4. Study Design:

A case-control study of Alzheimer's Disease Center cohort subjects with MCI that have either low (n=43) or high (n=45) CVD burden on brain imaging was conducted.

2.2.5. Statistical analysis:

Standard descriptive and comparative statistics were used to evaluate demographic, clinical, and genetic features of MCI-CVD.

2.3. Results:

Demographic, clinical and genetic characteristics of the study groups are provided in (Table 2.1) MCI-CVD subjects were older (83.1 ± 6.3) than MCI-AD subjects (74.8 ± 9.7) (p = < 0.001), had a higher prevalence of APOE 2/4 alleles (4.4 VS. 0.0), for all APOE 2 was (4.7 vs. 20.0), and for all APOE 4 was (30.2 vs. 35.5). The prevalence of depression in MCI-CVD was (40.0) higher than that for MCI-AD (30.2). These later findings were not significant.

Patients of MCI-CVD had a higher incidence of risk factors for cardiovascular diseases. HTN is more prevalent in MCI-CVD compared to MCI-AD patients (71.1 VS. 51.2 respectively). MCI-CVD patients had more history of heart attacks, atrial fibrillation, transient ischemic attack (TIA), and peripheral vascular disease PVD. Of significance is that MCI-CVD had more pack-years smoking rate than MCI-AD patients (Table 2.2). No significant differences were seen in cognitive test scores for MCI-CVD vs. MCI-AD subjects (Table 2.3). Physical and neurological exam findings also failed to distinguish MCI-CVD from MCI-AD subjects (Table 2.4).

Table 2.1. Demographics and genetic variables.

Characteristics	Low SVI changes (n=43)	High SVI changes (n=45)	p-value
Age at scan, y	74.8 ± 9.7	83.1 ± 6.3	< 0.001**
Time between scan and ADC assessment, y	0.4 ± 0.3	0.4 ± 0.3	1.00
Education, y	15.8 ± 3.6	15.6 ± 3.9	0.90
Age at onset of cognitive decline, y*	72.4 ± 10.0	80.4 ± 6.5	< 0.001**
APOE ε genotype (%)			
2/3	4.7	15.6	0.096
2/4	0.0	4.4	0.167
3/3	44.2	33.3	0.297
3/4	20.9	31.1	0.28
4/4	9.3	4.4	0.36
Missing	20.9	11.1	0.21

*data are missing for 5 in Low SVI, 6 in High SVI

***p-value ≤ 0.01

Abbreviation: SVI, Small Vessel Ischemic changes; APOE ε, Apolipoprotein E Epsilon ε allele;

Table 2.2. Cerebrovascular risk factors and small vessel ischemic changes

Characteristics	Low SVI changes (n=43)	High SVI changes (n=45)	p-value
Hachinski score (13 items)	2.1 ± 1.8	3.2 ± 2.1	0.01**
Body mass index §§	27.8 ± 7.4	24.7 ± 4.3	0.019
Systolic blood pressure	137.6 ± 24.6	139.4 ± 25.0	0.73
Diastolic blood pressure	77.6 ± 13.1	73.2 ± 10.0	0.08
Hypertension (%)	51.2	71.1	0.06
Taking anti-hypertensive (%)	80.9	87.1	0.43
Current smoker (%)	9.3	4.4	0.36
Ever smoker (%), includes current smokers	44.2	44.4	0.98
Pack-years, ever smokers	10.9 ± 15.3	30.2 ± 28.4	< 0.001**
Age quit smoking, y	39.3 ± 14.9	46.6 ± 12.1	0.01
Diabetes (%)	20.0	16.3	0.65
Taking anti-diabetic agent (%)	83.3	55.6	0.006**
Hypercholesterolemia (%)	46.5	42.2	0.69
Taking lipid lowering drug (%)	68.4	82.3	0.13
History of heart attack (%)	7.0	15.6	0.21
Atrial fibrillation (%)	7.0	24.4	0.03*
History of stroke (%)	4.7	17.8	0.06
History of transient ischemic attack (%)	2.3	17.8	0.02*
Taking anti-Alzheimer's drug (%)	27.9	20.0	0.39
Depression (%)	30.2	40.0	0.34
Taking anti-depressant (%)	46.2	55.6	
Geriatric Depression Scale score (15 items)	4.2 ± 3.0	3.9 ± 2.2	0.595
Peripheral Vascular Disease (%)	2.3	6.7	0.32

Abbreviation: SVI, Small Vessel Ischemic changes; §§ data are missing for 5 in Low SVI, 8 in High SVI
*p-value < 0.05
**p-value ≤ 0.01

*Table 2.3. Cognitive test battery**

Characteristic	Low SVI changes (n = 43)	High SVI changes (n = 45)	p-value
MMSE	26.9 ± 2.6	26.6 ± 2.6	0.59
Clinical Dementia Rating, Sum of Boxes	1.5 ± 1.2	1.8 ± 1.2	0.24
Wechsler-R Logical Memory Immediate Recall Story A	8.1 ± 4.2	9.4 ± 4.8	0.18
Wechsler-R Logical Memory Delayed Recall Story A	5.6 ± 5.0	7.3 ± 5.2	0.12
Boston Naming Test, 30-item	25.9 ± 4.2	24.2 ± 4.3	0.06
Animal Naming Test	15.4 ± 5.4	14.1 ± 4.5	0.22
Trail Making Test A (seconds, 150 max)	59.5 ± 34.6	60.2 ± 26.7	0.91
Trail Making Test B (seconds, 300 max)	162.5 ± 77.0	165.8 ± 79.2	0.84
Digit Span Forward Length	6.7 ± 1.0	6.7 ± 1.0	1.00
Digit Span Backward Length	4.3 ± 1.1	4.6 ± 1.3	0.24

Abbreviation: SVI, Small Vessel Ischemic changes;
*Not adjusted for age.

Table 2.4. Neurological examination findings

Characteristic	Low SVI changes (n = 43)	High SVI changes (n = 45)	p-value
Bruits (%)	0.0	2.2	0.33
Murmur (%)	7.1	9.1	0.73
Arrhythmia (%)	2.4	8.9	0.19
Congestive heart failure (%)	0.0	2.2	0.33
Cranial bruits (%)	19.1	11.4	0.31
Asymmetry on motor exam (%)	9.3	4.4	0.36
Asymmetry on tone exam (%)	7.0	2.2	0.28
Asymmetry on sensory exam (%)	4.7	2.2	0.52
Cranial nerves abnormality (%)	23.3	22.2	0.90
Frontal release signs noted on exam (maximum = 4)	0.9 ± 1.4	0.8 ± 1.0	0.70

Abbreviation: SVI, Small Vessel Ischemic changes;

2.4. Discussion:

These data demonstrate that the clinical profiles of MCI-CVD and MCI-AD are remarkably similar in regards to demographics, cognitive test profiles, and clinical exam findings. In contrast, age and specific CVD risks in the medical history are important clues to the underlying diagnosis and cause of MCI. This study shows that patients with MCI-CVD were older than their MCI-AD counterparts ($p < 0.001$). We defined CVD by rating MRI images and assigning a cutoff under the assumption that WMH are the result of AS, and therefore more WMH means more AS. This assumption may not be entirely correct. There may be other pathologies that contribute to WMH as discussed in the introduction.

Nonetheless the data demonstrate a higher rate of cardiovascular risk factors in patients with MCI-CVD defined by WMH when compared to those with MCI-AD type. MCI-CVD subjects were found to have a more frequent history of smoking, atrial fibrillation, HTN, heart attacks and transient ischemic attacks (TIA) than those with MCI-AD. This finding supports the findings from several other studies (Bellomo, Mancinella, Troisi, & Marigliano, 2009; Kerola, Kettunen, & Nieminen, 2011).

In this study, patients with MCI due to CVD or AD were found to have nearly equal results on the cognitive testing battery used, suggesting that it is problematic to distinguish between MCI etiologies based on cognitive testing.

The weaknesses of this study include a lack of neuropathological validation and AD biomarkers to distinguish groups on the basis of mixed pathology and validate the diagnosis of MCI-AD. There is also a subject selection bias in that pre-existing CVD (stroke and TIA) are exclusionary criteria for the UK-ADC normal control clinic at the time of enrollment, limiting the applicability of the findings in regards to the general population where such morbidities are prevalent in the age range for enrollment in the ADC. Our subjects are also largely Caucasian, with high education, potentially limiting generalizability for lesser educated as well as racially and ethnically diverse population.

The strengths of this study include the use of a longitudinally followed, well characterized community-based sample, with de novo CVD. The rigorous and standardized data collection protocol used allowed extensive comparison between groups.

Distinguishing between MCI-CVD and MCI-AD groups clinically can be problematic unless imaging and detailed CVD risk histories are pursued. It is possible, however, that a more detailed analysis using quantitative rather than subjective qualitative measures of CVD burden could reveal important associations that would expand our understanding of CVD risks and cognitive sequelae of CVD injury. More direct measures of CVD, such as vascular architecture, blood flow, and venular density would help to supplement WMH estimates. Further studies using more detailed quantitative measures of CVD burden are needed to move the field forward.

3. Specific Aim 2: Cerebrovascular Risk Factors and Arteriolar Sclerosis

3.1. Introduction:

Cerebrovascular risk factors play an important role in the pathogenesis of AS. Those biological changes can be indexed as a T-2 white matter hyperintense signal on magnetic resonance image MRI. For this reason, quantification of WMH volume may allow a better understanding of the relationship between vascular risk factors and AS and resultant effects on cognitive function.

Many studies have quantified WML volume on MRI and have analyzed the associations of cerebrovascular risk factors with these changes. The Alzheimer's Disease Neuroimaging Initiative ADNI study, examined longitudinal changes in white matter disease and cognition, reporting that even low cerebrovascular risk profile can greatly influence cognitive decline (Carmichael, Schwarz, Drucker, & et al., 2010). By definition, subjects enrolled in ADNI were suspected to have AD and not CVD as the cause of their cognitive impairment. The Framingham Heart Study has also played a pivotal role in our understanding of the associations of cerebrovascular risk factors with large WML (Jeerakathil et al., 2004). In this study the emphasis was on cardiovascular disease. HTN was found to be a major risk factor for MRI-evident CVD injury (Jeerakathil et al., 2004).

Similarly, the Leukoaraiosis and Disability in the Elderly Study (Reinhold Schmidt et al., 2010), Taylor et al. (Taylor et al., 2003), and Xiaohua Chen et al. (Chen, Wen, Anstey, & Sachdev, 2009) reported that patients with HTN were found to have more WML and lacunar infarcts. Other studies like Rotterdam Scan Study MRI-evident CVD injury was more prevalent in the current smoker and those with HTN (van Dijk et al., 2008).

A more recent study conducted by the Clinical Research Center for Dementia of South Korea (CREDOS) indicate that the severity of cerebral small vessel disease was found to be strongly associated with the aggregate of cerebrovascular risk factors (Noh et al., 2014). Finally, the 3-City Dijon Study and the Sunnybrook Dementia Study were used WMH quantification as a biomarker for cerebral small vessel disease secondary to cerebrovascular risk factors effect on the brain (Ramirez, McNeely, Scott, Masellis, & Black, 2016).

3.1.1. Aggregate CVD risk score:

A. Framingham Risk Score (FRS): FRS is a risk score use to predict the risk of cardiovascular disease in healthy and asymptomatic patients without prior stroke. The FRS variables are derived from patient history, physical examination, and lab values. Ten-year risk score represents the probability of developing heart attacks or dying from heart disease within ten years. Recent studies suggest this score is not valid after age 85 years (Sabayan, Gussekloo, de Ruijter, Westendorp, & de Craen, 2013). Ten-year risk scores are expressed as a percentage. A percentage between 0-10% is considered low risk, the moderate risk falls between 11-20%, and a high risk occurs when the ten years risk is greater than 20% (R. B. D'Agostino, Sr. et al., 2008).

B. Hachinski Ischemic Score (HIS): A risk score that used to identify vascular, degenerative, and mixed dementia. It was not primarily as a risk instrument. For the modified Hachinski Ischemic score (Rosen, Terry, Fuld, Katzman, & Peck, 1980), a total of 18 scores was given based on the

sum of each variable score. HIS variables are derived from the patient history and physical examination. A score greater than 7 was associated with a diagnosis of vascular dementia, scores of 5 and 6 were found to predict mixed dementia, and a score of less than 4 was associated with a diagnosis of AD (L. Pantoni & Inzitari, 1993).

Rosen et al. and Mölsä et al. reported that HIS failed to distinguish between VaD and mixed dementias (Mölsä, Paljärvi, Rinne, Rinne, & Säkö, 1985; Rosen et al., 1980). After using a modifiable HIS Rosen et al. found that the HIS score for mixed dementia was higher than that of VaD (Rosen et al., 1980). Inter-rater variability in measuring HIS might be due to lack of specific criteria to rate the information obtained from patients (L. Pantoni & Inzitari, 1993; Pantoni L., 1993).

In this study, we reported 3 Hachinski scores as a measurement of the aggregate risk score in this study. These include: 1) Hachinski Ischemic Score (HIS) short form, a 12 point scoring scale that obtained from patient's clinical history and physical examination finding. Eight variables are included in HIS short version, 2) the Other Hachinski Total Score (OHTS), which has six points scoring scale was used. This test includes five elements to check. OHTS is the dropped (less sensitive and specific) items, 3) the Hachinski Total Score (HIS long form), represents the sum of HIS short form and OHTS with a maximum of 18 points score was used in this study to assess for the aggregate CVD risk.

3.2. Methods:

3.2.1. Patients:

The study population was from University of Kentucky Alzheimer's disease center (UK-ADC) and affiliated clinical trials of aging (IRB#12-0837-F2L, IRB#13-0429-F2L, IRB#13-0603-F6A). All subjects were enrolled with a diagnosis of normal or mild cognitive impairment (MCI). A total of 114 subjects were divided into two groups, one with MCI (62 subjects), and a second normal group (52 subjects). These subjects represent a continuum of WMH volumes from essentially none to severe.

We used Clinical Dementia Rating (CDR) global scores to subdivide our cohort into normal (CDR=0) or mild cognitive impairment of Alzheimer's disease or vascular type (CDR=0.5). However, given that a global scale is heavily weighted toward an amnestic presentation that may or may not found in vascular dementia. We included two subjects in the MCI group that had CDR sum of boxes score of > 0. No subjects were enrolled in the study with a global CDR of more than 0.5, excluding all subjects with clinical diagnosis of dementia, with the exception of a single subject with CDR 1.0 (subjective interpretation) that had no functional decline precluding a diagnosis of dementia (objective criteria for MCI met).

All subjects provided consent (together with a caregiver or relative) under the University of Kentucky Medical Institutional Review Board approved procedures.

3.2.2. Clinical evaluation and cerebrovascular risk factors:

The clinical data used included a detailed history and examination (both medical and neurological) performed by neurologists. Subjects were examined at baseline and then annually. Clinical data collected included the history of HTN, DM, HLD, heart attack, atrial fibrillation, stroke, and smoking history (an individual with more than a 100 cigarettes/life included as a smoker). Furthermore, aggregate risk measures of CVD risk factors, such as FRS and Hachinski risk scores were recorded. Vital signs measured at baseline visit included systolic and diastolic blood pressure in mmHg. Laboratory testing included lipid profile (serum cholesterol, HDL, Total Cholesterol/HDL, LDL, and triglyceride), fasting blood glucose, HbA1c, and APOE ε4. Full neurologic and physical examinations were performed at annual visits.

3.2.3. Imaging data:

AS is a subtype of cerebral small vessel disease that leads to cerebral white matter damage, which can be visualized as hyperintense signal abnormalities (WMH) on 3-D FLAIR magnetic resonance images (MRI) (de Leeuw et al., 2001). Strong evidence of the association between WMH and cognitive decline exists (Au, Massaro, Wolf, Young, et al., 2006).

3.2.3. A. Image Acquisition:

A total of 114 subjects with normal cognition (n=52) or MCI (n=62) (clinically presumed to be due to either CVD or AD) were scanned at least once.

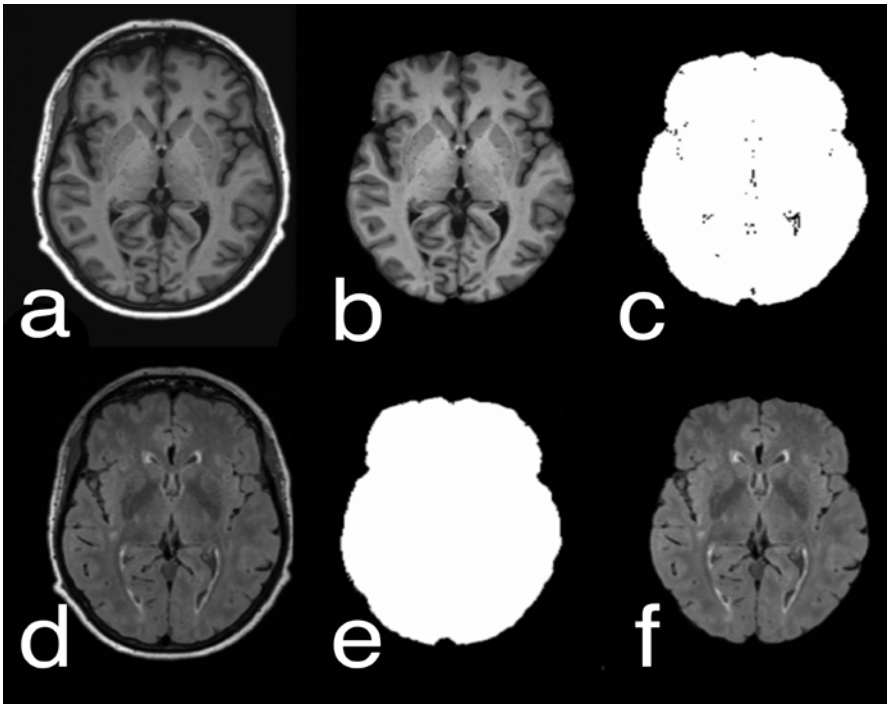
Data were collected on a Siemens 3 Tesla TIM TRIO scanner at the University of Kentucky Magnetic Resonance Imaging and Spectroscopy Center. A 32-channel imaging coil was used. Volumetric T1-weighted images were obtained with a magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence (TR 2530 ms, TI 1100 ms, TE 2.56 ms, Flip angle 7 degrees, 1 mm isotropic voxels). Volumetric fluid-attenuated inversion recovery (FLAIR) images were acquired with the same 1 mm^3 resolution (TR 6000 ms, TI 2200 ms, TE 388 ms).

3.2.3. B. Image processing:

Brain Image Extraction: MP-RAGE and FLAIR images were RF inhomogeneity-corrected using the N3 algorithm before registration (MIPAV; http://mipav.cit.nih.gov). The two MP-RAGE images were registered to each other and averaged to increase the signal to noise ratio (aveMPR). The FLAIR image was then registered to aveMPR.

Using FSL BET skull extraction (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BET) on the aveMPR image, the option of 'Robust brain center' was selected. Resulting images were edited manually to remove any remaining skull or eye tissue signal (MIPAV). The resulting image was converted to a binary mask by thresholding. Lacunae within the mask were filled morphologically. The FLAIR image was multiplied by the brain mask to obtain an extracted FLAIR brain image (Figure 3.1).

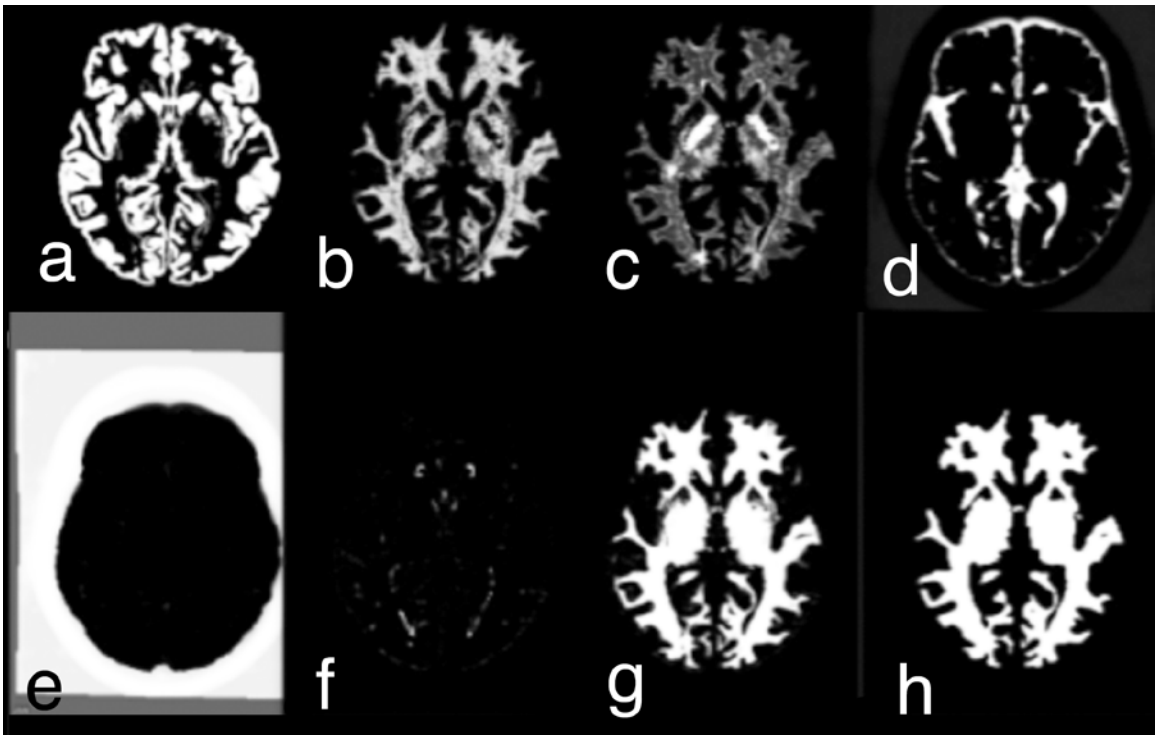
Figure 3.1. Processing steps to extract FLAIR brain image. a. aveMPR, b. Skull-stripped aveMPR, c. thresholded skull-stripped aveMPR, d. registered FLAIR image, e. brain mask (image c with holes filled), f. extracted FLAIR brain image.



Segmentation: Multimodal (aveMPR and FLAIR channels) segmentation was performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The brain was segmented into gray matter, white matter, and cerebral spinal fluid (CSF). Two images with different intensities (C2+C3) represent the combined white matter. White matter (WM) was modeled with two tissues to capture variability due to hyperintensities (WMH) (Smith et al., 2016). When extraneous tissue segments captured WMH, these segments were added to total WM, resulting in a total WM segment. This WM segment was converted to a binary mask by thresholding at probability 0.333 and dilated in 2.5 d. The last step of dilation is essential to minimize the partial volume effect (Smith et al., 2016) (Figure 3.2).

Total Intracranial Volume Calculation: Gray matter (C1), CSF (C4), and the white matter segments were added together, and the voxel volumes summed to estimate the total intracranial volume (TIV).

Figure 3.2. Segmentation steps to classify brain grey matter (GM), white matter (WM), and CSF. a. GM segment, b. first WM segment, c. second WM segment, d. CSF segment, e. extracranial tissue segment, f. extraneous tissue segment, g. total WM (C2+C3+C7). In most cases C2 and C3 capture all WM; in a few cases the extraneous tissue segment (C7) captured a small number of WMH. In these cases, C7 was combined with C2 and C3 segments as illustrated here, h. dilated mask from (g).



WMH volume Quantification:
Using MIPAV, the histogram of the white matter extracted from the FLAIR image was generated. The histogram was fit with a Gaussian model curve using Matlab 2015b. The mean and SD were used to calculate the thresholds for WMH (threshold = mean + 2.33 x SD). The image was then thresholded, and filtered by a 1x1x1 Gaussian kernel filter to remove noise. The resulting image was manually edited using slice by slice comparison with the FLAIR image windowed at level mean and window 10xSD to remove artifacts. WMH volume was defined as the summed volume (mm^3) of the remaining voxels (Smith et al., 2016) (Figure 3.3, 3.4).

Figure 3.3. Extraction of white matter (WM) hyperintensities for quantitation. a. Original FLAIR image, b. extracted FLAIR WM image, c. result of thresholding FLAIR WM image (b), d. Gaussian-smoothed extracted WM hyperintensities. WM hyperintensity volume is volume sum of voxels in d.

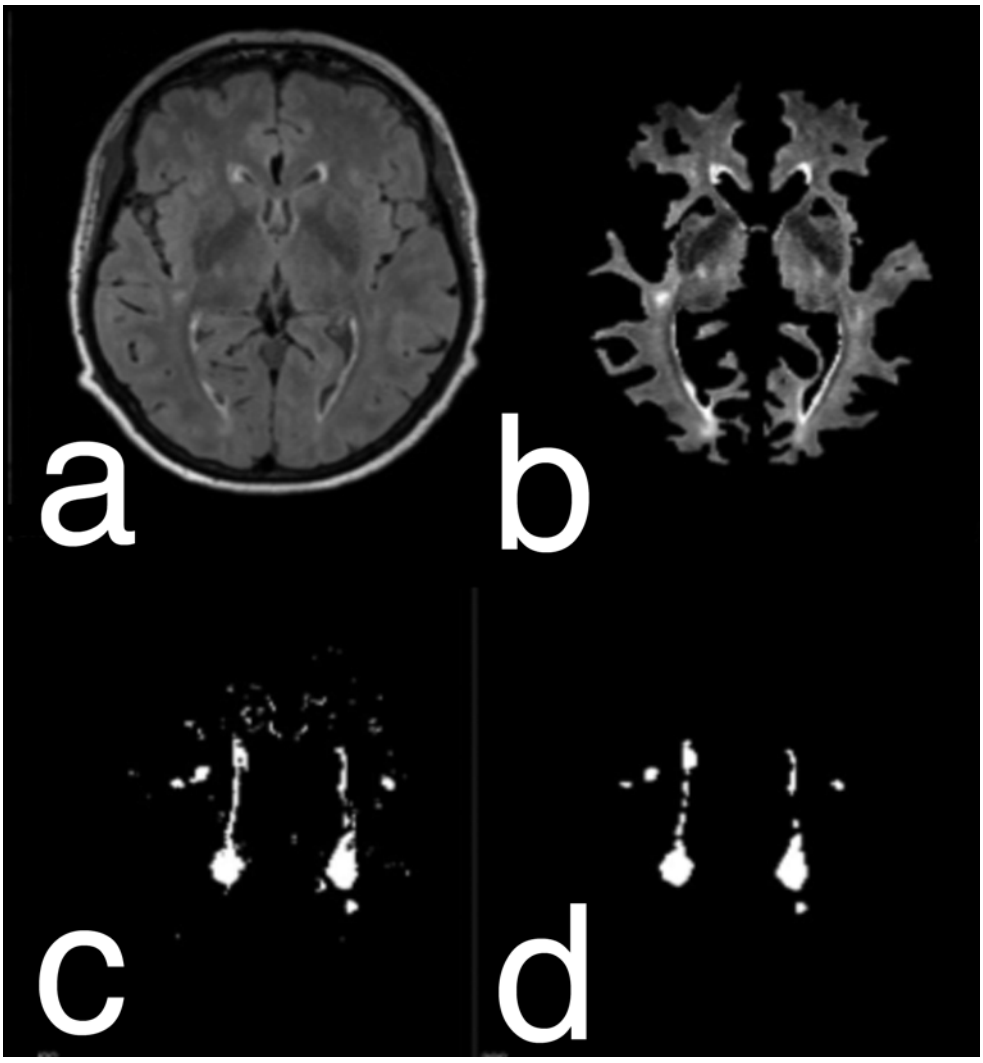
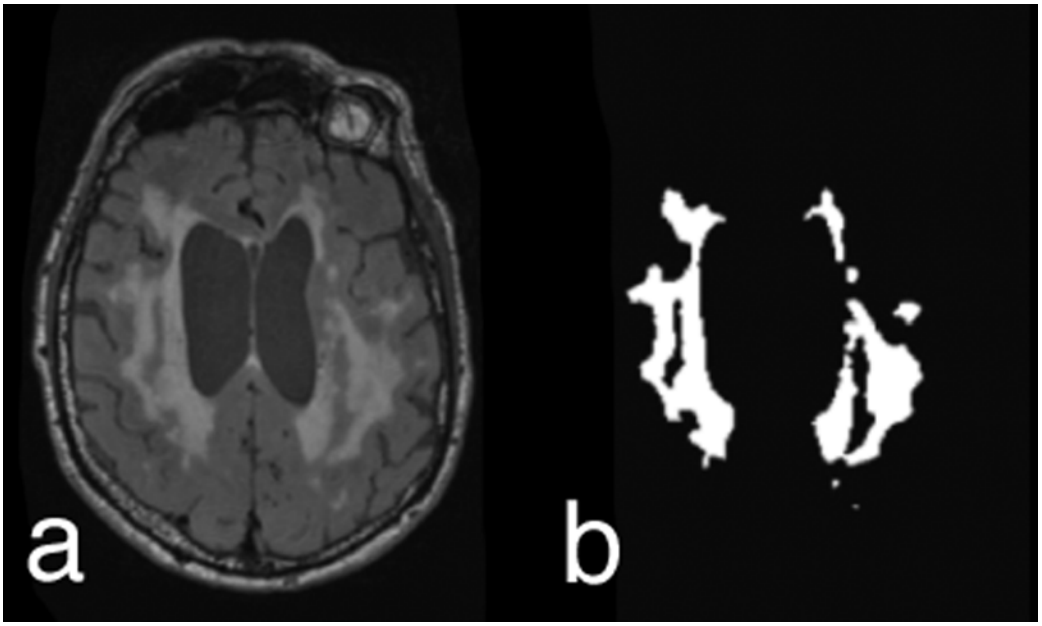


Figure 3.4. Final white matter hyperintensity images obtained from 3-D FLAIR image, compared on corresponding slices, illustrating capture quality of the method shown in Figure 3.3.



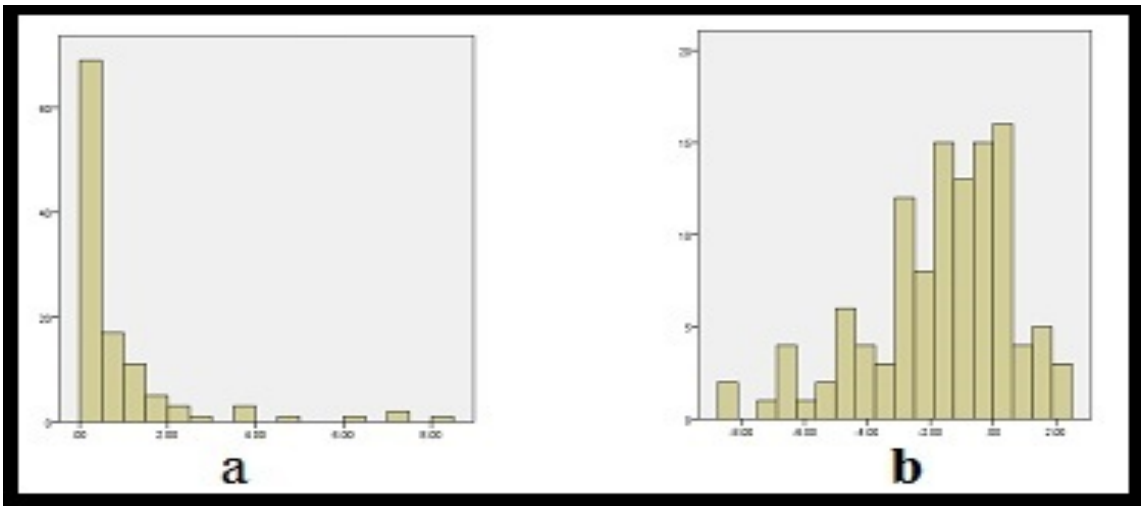
3.2.4. Cognitive Testing:

Cognitive testing included a Mini-Mental State Exam (MMSE) (Cockrell & Folstein, 1988; Diniz, Yassuda, Nunes, Radanovic, & Forlenza, 2007) and the Clinical Dementia Rating scale to evaluate global cognition (Hughes, Berg, Danziger, Coben, & Martin, 1982). Other cognitive tests were used in addition to the MMSE to determine cognitive domain involvement including: Wechsler Memory, Logical Memory (immediate and delayed recall), Verbal Fluency (Animals and vegetables categories), California Verbal Learning Test, Trail Making Tests A and B, and Boston Naming Test (Mohs, Rosen, & Davis, 1983) (Schmitt et al., 2012). All test were administered according to the National Alzheimer's Coordinating Center Uniform Data Set (UDS) instructions (John C. Morris et al., 2006). All test were scored by neurologists and trained personnel, and interpreted by a staff neuropsychologist.

3.2.5. Statistical analysis:

Standard descriptive statistics was used to characterize the cohort demographic and clinical variables (means, standard deviation, proportion, and p-value). First, the WMH was divided by the total intracranial volume (TIV) and then multiplied by 100 to obtain normalized WMH volume. WMH volume data was transformed using the natural logarithm of original normalized values to approximate a normal distribution amenable to analysis. Histogram plots of the normalized data are presented in Figure 3.5.

Figure 3.5. White matter hyperintensity volumes adjusted to total intracranial volume histograms a. before natural logarithm transformation b. after natural logarithm transformation.



Non-adjusted linear regression of the transformed white matter hyperintensity (T-WMH) volumes versus age, gender, and education was performed to determine confounders that are not amenable to intervention. These variables were carried forward as covariates in the analyses of CVD risk factor associations with WMH volumes.

Adjusted linear regression modeling was then performed to examine the relation between T-WMH versus the Framingham Risk Score, Hachinski Ischemic Score short form, Hachinski total scores (long form, and discrete cerebrovascular risk factors. The purpose of this regression was to explore the relationship between global cerebrovascular risk scores as well as individual CVD risk score in association with WMH volume burden.

3.3. Results:

A total of 114 subjects, representing a continuum of WMH volumes, were divided into two groups, one with MCI (62 subjects), and a second normal group (52 subjects). Mean age was lower for the MCI vs. control population. Men were overrepresented in the MCI group which was expected given the male predominant gender distributions of CVD risk factors and the established male predominant gender prevalence of MCI in the general population. There was no significant difference between the normal and MCI groups regarding the years of formal education or APOE genotype. (Table 3.1. A. Demographic and genetic variables)

Table 3.1. A. Demographic and genetic variables by cognitive diagnosis in the study cohort

Demographic and genetic variable	Normal (CDR= 0)	MCI (CDR= 0.5)	Total	P-value
Age (mean ± standard deviation)	76.86 ± 6.62	73.30 ± 8.91	74.93 ± 8.12	0.019** §
Gender (men/women)%	23.1 % (12)	48.4 % (30)	36.8 % (42)	0.004 #
Education (mean ± standard deviation)	16.65 ± 2.23	16.24 ± 3.46	16.43 ± 2.96	0.463 §
APOE ε4* % (n)	33.3 % (12)	28.6 % (2)	32.6 % (14)	0.590 #

Abbreviation: APOE ε4, Apolipoprotein E ε4 allele; CDR, Clinical Dementia Rating;
* APOE ε4 is only available in (n=43) subjects. We report the result for subjects with one or more APOE ε4 alleles.
§P value: t-test (2-tailed).
#P value: Fischer Exact (one-sided).

Mean FRS was higher in the MCI group compared to the normal group (17.14 ± 3.38, 15.44 ± 4.73). There was a statistically significant difference in FRS between the normal and the MCI group (p = 0.028). Moreover, the ten years risk of heart attacks for total subjects was 15.50 ± 10.28, which is in between that for the normal group 15.17 ± 11.83 and the MCI group 15.77 ± 8.88. There was no statistical difference in ten years risk between the normal and the MCI group (p = 0.758). (Table 3.1. B)

Mean HIS short form was higher in the MCI group when compared to the normal group (2.25 ± 2.64, 0.69 ± 1.09; difference p = < 0.001). Similarly, the mean for OHTS in the total population was (1.66 ± 0.89), and it was higher in the MCI group than the normal group (2.05 ± 0.99, 1.17 ± 0.38; difference p = < 0.001). The mean for the Hachinski total scores (long form) for the total population was (3.32 ± 2.85). Again, the mean in the MCI group was higher (4.42 ± 3.24, 1.93 ± 1.34; p = < 0.001). (Table 3.1. B)

Regarding discrete CVD risk factors, the mean systolic blood pressure was higher in the normal group 148.75 ± 105.40 compared to the MCI group 138.27 ± 15.93. Similarly, the mean diastolic blood pressure was higher in the normal group when compared their MCI counterpart (90 ± 113.31 and 81.53 ± 77.02), respectively. No significant difference was found between the MCI and normal group regarding the systolic and diastolic blood pressure (p = 0.441, and 0.284). (Table 3.1. B)

In the normal group (n=52), 38.5% (20) subjects reported a history of HTN and 23.1% (12) indicated having a history of DM. Also, our results showed that 38.5% (20) subjects disclosed a positive history of HLD, no one had a history of heart attacks, 3.8% (2) subjects have a history of atrial fibrillation and 1.9% (1) with a history of stroke. Finally, 44.2% (23) subjects were found to be smokers. (Table 3.1. B)

On the other hand, in those within the MCI group (n=62), 77.4% (48) subjects were diagnosed with HTN, 35.5% (22) subjects were found to have a positive history of DM and 81.7% (49) subjects with a history of HLD. Furthermore, 14.5% (9), 12.9% (8), and 17.7% (11) subjects had histories of heart attacks, atrial fibrillation, and strokes, respectively. Finally, 41.9% (26) were smokers (Table 3.1. B).

A significant difference between the normal and MCI groups was found in the history of HTN and history of HLD ($p = <0.001$ each). Also, there was a significant difference between the two groups regarding the history of heart attacks ($p = 0.004$), and history of stroke ($p = 0.006$). However, no significant difference was found between the two groups regarding the history of DM ($p = 0.158$), history of atrial fibrillation ($p = 0.107$), or history of smoking ($p = 0.851$). (Table 3.1. B)

Unadjusted linear regression analysis of the effect of age, gender, and education on WMH (normalized and transformed) revealed that age is a major confounder in our cohort (p-value < 0.001). Similarly, education is a major confounder as well (p-value = 0.003). Sex did not appear to be a major confounder (p-value = 0.778). Even though gender was not a significant confounder in our cohort, we included it as an adjustment given that other studies have raised the possibility of a gender confound in regards to CVD risks for cognitive decline (Table 3.2).

Many recent studies rely on FRS and HIS to weight cerebrovascular disease risks. In our cohort, we found a better relationship Hachinski total scores (long version) (the sum of HIS short version and Other Hachinski Total Score) (p-value = 0.044) with the increased WMH volume in a linear regression model. FRS and HIS short version were not found to have a significant relationship with the increased WMH volume in our study (p-value = 0.333 and 0.164 respectively) (Table 3.3).

Table 3.1. B. Cerebrovascular risk factors by cognitive diagnosis in the study cohort

CVD risk factors	Normal (CDR= 0)	MCI (CDR= 0.5)	Total	P-value
Framingham Risk Score (mean ± standard deviation)	15.44 ± 4.73	17.14 ± 3.38	17.23 ± 3.18	0.028* §
Ten years risk of heart attack % (mean ± standard deviation)	15.17 ± 11.83	15.77 ± 8.88	15.50 ± 10.28	0.758 §
HIS (short form)(mean ± standard deviation)	0.69 ± 1.09	2.25 ± 2.64	1.54 ± 2.22	< 0.001** §
OHTS (mean ± standard deviation)	1.17 ± 0.38	2.05 ± 0.99	1.66 ± 0.89	< 0.001** §
Hachinski Total Score (long form) (mean ± standard deviation)	1.93 ± 1.34	4.42 ± 3.24	3.32 ± 2.85	< 0.001** §
Systolic blood pressure mmHg (mean ± standard deviation)	148.75 ± 105.40	138.27 ± 15.93	143.05 ± 71.965	0.441 §
Diastolic blood pressure mmHg (mean ± standard deviation)	90 ± 113.31	74.42 ± 11.99	81.53 ± 77.02	0.284 §
History of hypertension % (n)	38.5% (20)	77.4 % (48)	59.6 % (68)	< 0.001** #
History of diabetes Mellitus % (n)	23.1% (12)	35.5 % (22)	29.8 % (34)	0.158 #
History of hyperlipidemia % (n)	38.5 % (20)	81.7 % (49)	61.6 % (69)	< 0.001** #
History of heart attack % (n)	0 % (0)	14.5 % (9)	7.9 % (9)	0.004 ** #
History of atrial fibrillation % (n)	3.8 % (2)	12.9 % (8)	8.8 % (10)	0.107 #
History of stroke % (n)	1.9 % (1)	17.7 % (11)	10.5 % (12)	0.006** #
History of smoking % (n)	44.2 % (23)	41.9 % (26)	43 % (49)	0.851 #

Abbreviation: CVD, Cerebrovascular Disease; CDR, Clinical Dementia Rating; HIS, Hachinski Ischemic Score short form; OHTS, Other Hachinski Total Score.

§P value: t-test (2-tailed).

#P value: Fischer Exact (2-sided).

Table 3.2. Unadjusted linear regression model for the effect of age, gender, and education on white matter hyperintensity volume adjusted for total intracranial volume

Model	R	R-squared	Unstandardized coefficient		Standardized coefficient	t	Significance
			B	Standard error	Beta		
Age	0.472	0.223	0.131	0.023	0.472	5.664	< 0.001**
Gender	0.027	0.001	-0.124	0.440	-0.027	-0.283	0.778
Education	0.276	0.076	0.210	0.069	0.276	3.041	0.003**

Dependent variable: Log-Transformed White Matter Hyperintensity Volume
Independent variables: Age, gender, and education

Table 3.3. Linear regression model examining the relationship between global vascular risk scores and white matter hyperintensity volume adjusted for total intracranial volume. Model adjusted for age, education and gender.

Model	R	R squared	Unstandardized coefficient		Standardized coefficient	t	Significance
			B	Standard error	Beta		
FRS	0.501	0.251	-0.049	0.050	- 0.090	-0.972	0.333
HIS (short form)	0.489	0.239	0.124	0.088	0.123	1.402	0.164
OHTS	0.539	0.290	0.683	0.223	0.267	3.058	0.003**
HIS (long form)	0.505	0.255	0.143	0.070	0.179	2.043	0.044*

Abbreviation: FRS, Framingham Risk Score; HIS, Hachinski Ischemic Score short version; OHTS, Other Hachinski Total Score.
*p < 0.05
**p < 0.01
Dependent variable: Log-Transformed White Matter Hyperintensity Volume
Independent variables: FRS, Framingham Risk Score; HIS, Hachinski Ischemic Score; OHTS, Other Hachinski Total Score.

Linear regression models demonstrated that a history of chronic HTN was strongly associated with the increase in WMH volume (p-value = 0.012). Similarly, a positive history of HLD was also found to be strongly associated with increased WMH (P-value = 0.008).

Unexpectedly, a history of DM was not found to be associated with increased WMH volume (p-value = 0.205). Likewise, we were unable to find a significant relationship between a positive history smoking and increased WMH volume in our cohort (p-value =0.324). Finally, a history of heart attacks, AF, and strokes was not associated with the increase in WMH volume in our cohort (p-value = 0.094, 0.459, and 0.555 respectively) (see Table 3.4)

Table 3.4. Linear regression model examining the relationship between reported individual cerebrovascular risk and white matter hyperintensity volume adjusted for total intracranial volume. Model adjusted for age, education and gender.

Model	R	R squared	Unstandardized coefficient		Standardized coefficient	t	Significance
			B	Standard error	Beta		
Hypertension	0.536	0.287	0.956	0.372	0.209	2.566	0.012**
DM	0.506	0.256	-0.529	0.414	-0.108	-1.276	0.205
HLD	0.543	0.295	1.048	0.388	0.225	2.698	0.008**
Smoking	0.501	0.251	0.374	0.378	0.082	0.991	0.324
Heart attacks	0.513	0.264	1.204	0.714	0.144	1.687	0.094
AF	0.498	0.248	0.513	0.691	0.065	0.743	0.459
Stroke	0.497	0.247	0.367	0.619	0.050	0.593	0.555

Abbreviation: DM, Diabetes Mellitus; HLD, Hyperlipidemia; AF, Atrial Fibrillation
Dependent variable: Log-Transformed White Matter Hyperintensity Volume
Independent variables: Hypertension, diabetes mellitus, hyperlipidemia, smoking, heart attacks, atrial fibrillation, and strokes.

Current control of CVD risk factors appeared irrelevant to increased WMH volume in our cohort, which means that a chronic history of HTN, DM, and HLD will lead to an increase in the WMH volumes not the current control of CVD risk factors (Table 3.5).

Table 3.5. Linear regression model examining the relationship between reported individual cerebrovascular risk and white matter hyperintensity volume adjusted for total intracranial volume. Model adjusted for age, education and gender.

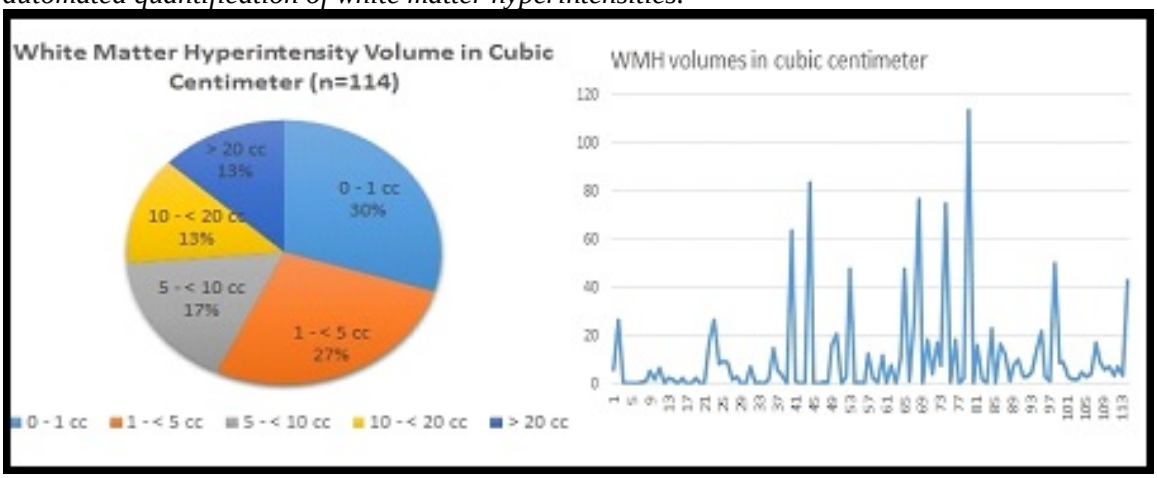
Model	R	R squared	Unstandardized coefficient		Standardized coefficient	t	Significance
			B	Standard error	Beta		
Sys. BP	0.495	0.245	0.000	0.003	- 0.015	- 0.180	0.857
Dias. BP	0.494	0.244	0.000	0.002	0.006	0.067	0.947
Blood glucose	0.506	0.256	- 0.008	0.005	- 0.137	- 1.403	0.164
HbA1c	0.507	0.257	- 0.291	0.220	- 0.133	- 1.324	0.189
S. Cholesterol	0.513	0.263	- 0.010	0.006	- 0.163	- 1.667	0.099

Abbreviation: Sys. BP, Systolic Blood Pressure; Dias. BP, Diastolic Blood Pressure; HbA1c, Hemoglobin A 1c; S. Cholesterol, Serum Cholesterol.
Dependent variable: Log-Transformed White Matter Hyperintensity Volume
Independent variables: Systolic blood pressure, diastolic blood pressure, blood glucose level, hemoglobin A 1c, and serum cholesterol level.

White matter hyperintensity (WMH) volume:

Our data reveal a wide distribution of WMH volumes similar to those from the Sunnybrook Dementia Study (SDS) but distinctly different from that reported by Alzheimer's Disease Neuroimaging Initiative (ADNI-1) (Ramirez et al., 2016). (Figure 3.6)

Figure 3.6. White matter hyperintensity volume in cubic centimeter obtained from the semi-automated quantification of white matter hyperintensities.



3.4. Discussion:

There were two main findings in this study. First, HTN and HLD were significantly associated with increased WMH volume after adjustment for age, gender, and education. This result supports current growing literature in regard to HTN (Chen et al., 2009; Jeerakathil et al., 2004; W. T. Longstreth et al., 2005; Reinhold Schmidt et al., 2010; Taylor et al., 2003; van Dijk et al., 2008; Verhaaren et al., 2013) and HLD (Park et al., 2007) .

Second, Hachinski total scores (long form) were significantly associated with increased WMH volume but the currently used HIS short form was not. FRS was not found to be associated with significant change in WMH volume in our cohort. Future studies in cohorts resembling ours may wish to use the Hachinski long form to measure CVD risk effects rather than relying on the short form or FRS for CVD risk assessment in regards to prediction of WMH volumes (Jeerakathil et al., 2004).

In our cohort, we found that DM was associated with decrease WMH volumes (B= - 0.529). This could be due to a small number of diabetic patients in our study (n=34). It is also possible that our subjects represented a population with well-controlled blood sugar over a long time preventing WMH caused by DM. While the Cardiovascular Health Study (W. T. Longstreth, Jr. et al., 1996) and Ylikoski et al. both have reported increased risk of WMH with DM, the later study found the association between DM and WMH to exist in the young-old group only (Ylikoski et al., 1995).

Similarly, we failed to find a significant relationship between smoking and the increased WMH volume in our study. This may be in part due to the operational criteria for smoking in our study (a history of smoking, at least, a 100 cigarettes/ life). This means that an individual who has a history

of only 100 cigarettes over the span of his life will be considered as a chronic smoker where in fact this is not always true. Our result regarding smoking is not in line with the results from the Rotterdam Study. In the Rotterdam Study, they used different criteria (never, former, and current) to define “smoking” and this is why the results were different (van Dijk et al., 2008). In that study current smoking was most strongly associated with increased WMH.

WMH volume was found to increase with higher years of formal education in our cohort. This is because higher education in our cohort is associated with longevity and advanced age that is the major risk factor for WMH. The other explanation is that our educated cohort might be exposed to the effect of chronic CVD risk factors for a longer time.

One limitation of this study is selection bias. Our population included only highly educated subjects with a small sample of patients with DM, smoking, heart attacks, AF, and strokes. This bias may have resulted in an underestimation of the relationship between DM, smoking, and heart disease with the WMH volume that could be seen in the larger general population. We do note however that the association of all CVD risks factors with increased WMH volume were observed, although the analyses were not significant.

These limitations are; however, overcome by major strengths of our study, which include the use of quantitative measures of the WMH that objectively quantify WMH volumes. Detailed, uniform application of global CVD risk scores and individual risk factors were used in our cohort which enables us to explore many aspects of the CVD risk-WMH volume relationship that have not been universally included in studies of other cohorts.

While these results clearly delineate HTN and HLD as the major modifiable risk factors for CVD in our cohort, it remains to be determined what the cognitive consequences of such CVD insults may be.

4. Specific Aim 3: Arteriolar Sclerosis and Cognitive Decline

4. 1. Introduction:

Subcortical white matter is preferentially affected by small vessel disease (AS). WML from such an effect can be identified as WMH signals in a T2- weighted MRI. Those signals represent a potential biomarker for cerebral SVD. Quantification of these signals may help us better understand the relationship between WMH and their consequences on brain functions such as cognition.

Many large longitudinal, as well as cross-sectional studies, have reported a strong association between WMH volumes and cognitive decline (Carmichael et al., 2010; W. T. Longstreth, Jr. et al., 1996; Niels D. Prins & Philip Scheltens, 2015). WMH volumes was found to be associated with increased conversion rate to both vascular and mixed dementia. The importance of identifying SVD in the clinical state of MCI-CVD rather than VaD cannot be understated in regards to secondary prevention of dementia (Bombois et al., 2008).

WMH-associated neuronal dysfunction does not affect cognitive domains to the same extent. According to Schmidt et al., WMH volume was found to decrease performance in global cognition, memory, executive function, and processing speed. Language and orientation, however, were found to be unaffected by WMH volume in this study (Reinhold Schmidt et al., 2010). Similarly, the Rotterdam Scan and Cardiovascular health studies demonstrated decreased processing speed, executive function and global cognition in association with increased WMH volumes (de Groot et al., 2000; W. T. Longstreth et al., 2005; Prins et al., 2005). Yet, other studies have reported declines in executive function and a decrease in episodic memory function in MCI patients (Nordahl et al., 2005) and in non-demented patients (Tullberg et al., 2004).

On the other hand, the Austrian Stroke Prevention Study reported that WMH and brain atrophy can lead to a decline in memory and visuospatial function but not in executive function (Reinhold Schmidt et al., 2005). Moreover, The Framingham Study also reported a strong association between WMH and decreased visuospatial function, attention, and executive function (Au, Massaro, Wolf, & et al., 2006). Finally, Mungas D. reported that WMH was not related to the executive function or memory if considered alone apart from other brain features such as brain and hippocampal atrophy (Mungas et al., 2005).

There are many reasons why WML lead to cognitive decline. One reason may be due to damaging of neuronal fibers in the subcortical white matter, which results in poor processing speed and executive functioning (Stéphanie Debette & H S Markus, 2010). People with stroke have variable presentation in regards to cognitive decline that reflects the variability of anatomic targets in stroke. The heterogeneous cognitive deficits of stroke confound arteriolosclerotic cognitive deficits. For this reason, it is important to find a common features of cognitive decline in MCI-CVD rather than overt stroke.

4.2. Methods:

4.2.1. Patients:

The study population was from University of Kentucky Alzheimer's disease center (UK-ADC) and affiliated clinical trials of aging. A total of 114 subjects divided into normal and MCI groups (for details see Chapter 2 Methods section). Grouping of MCI vs. normal was for descriptive purposes only and the regression modeling was done on a complete (ungrouped) sample.

4.2.2: Imaging data:

See chapter 2 for details.

4.2.3. Cognitive testing:

Neuropsychiatric and cognitive evaluation were performed by a neurologist or trained psychometrist at the beginning of the study and then annually for all subjects from UK-ADC. We used the: Mini-Mental State Exam (MMSE) for the assessment of cognitive function (Folstein et al., 1975). The MMSE data was missed for only one subject. We obtained the MMSE for that subject by converting his MoCA score using the conversion table from Monsell S.E. et al. (Monsell et al., 2015). The MoCA for that subject was 28 and converted to 30.

Cognitive tests of each domain were performed. For memory, we used immediate and delayed recall of the logical memory test (Wechsler D.: Wechsler Memory Scale. San Antonio, TX: Psychological Corporation, 2009), Late Delay Free Recall Correct (LDFRC) of the California Verbal Leaning Test (CVLT) was used to test memory as well (Delis DC, 2000; Woods, Delis, Scott, Kramer, & Holdnack, 2006). The Boston Naming Test and Verbal Fluency (category animal and vegetable) were used to test language function (Graves et al., 2004). Attention and processing speed domains were assessed with Digit Span Forward and Backward (The Wechsler Intelligence Scale for Children—Third Edition (WISC-III) The Psychological Corporation, San Antonio, TX (1991), Trail Making Test part A (TMT-A) (Tombaugh, 2004), and Digit Symbols from Wechsler Adult Intelligence Scale (WAIS-R) (Kaplan, E., Fein, D., Morris, R. et al, WAIS-R as a Neuropsychological Instrument. Psychological Corporation, San Antonio; 1991). Trial Making Test part B (TMT-B) was used to measure executive function in our cohort (Tombaugh, 2004).

4.2.4. Statistical Analysis:

WMH volume normalization and transformation was discussed in details in specific aim 2). The same values were used in the present analysis.

Z-Scores adjusted for age; gender and education for all cognitive test measures with the exception of the CVLT were obtained using the Normative Calculator for the Uniform Data Set (UDS) (Shirk et al., 2011). Linear regression modeling of T-WMH adjusted for age, gender, and education was performed to explore the relationship of T-WMH with each cognitive test z-score (adjusted for age, gender, and education).

For the LDFRC of the CVLT-II, we use z-scores that were adjusted for age and gender only. We calculate these scores based on CVLT-II normative values (Woods et al., 2006). Linear regression modeling of T-WMH adjusted for age and gender was performed to measure the relationship between the T-WMH and the CVLT z-score, accounting for all confounding demographic variables.

4.3. Results:

Our results revealed that WMH volume was not associated with the performance in the MMSE test ($p = 0.078$), immediate logical memory test ($p = 0.111$), digit forward score or digit forward length tests in our cohort ($p = 0.179$ and 0.087, respectively), Digit backward score and digit backward length ($p = 0.352$ and 0.053, respectively), verbal fluency tests including both category animal and vegetable ($p = 0.131$ and 0.685, respectively), WAIS digit symbol substitution, or Boston Naming Test ($p = 0.059$ and 0.452, respectively) (Table 4.1).

In contrast, there was a significant relationship seen between adjusted WMH volume and the Trail Making Test part A ($p = 0.001$), Trail Making Test part B ($p = 0.008$), and Long Delayed Free Recall Correct scores on the CVLT ($p = 0.009$) (Table 4.1).

A trend was seen, however, for increased WMH volume and decreased performance on all cognitive test scores although this was significant only in the tests detailed above.

In our cohort, each 1-SD increase in WMH volume was associated with 0.172-SD decrease in MMSE, 0.100-SD decrease in Logical memory (immediate recall), 0.073-SD decrease in Digit Span Forward Test, a 0.104-SD decrease in Digit Forward Length, a 0.047-SD decrease in Digit Span Backward Test, a 0.097-SD decrease in Digit Backward Length, 0.078-SD decrease in Verbal Fluency (category animal), a 0.18-SD decrease in Verbal Fluency (category vegetable), a 0.332-SD decrease in TMT-A and a 0.404-SD decrease in TMT-B and accounted for 0.126-SD, 0.042-SD, and 0.292-SD decrease in WAIS, Boston Naming Test, and LDFRC, respectively (Table 4.1).

Table 4.1. Linear regression model examining the relationship between the transformed white matter hyperintensity volumes adjusted for total intracranial volume and neuropsychological tests

Model	Dependent variables §	Independent variables §§	R	R-squared	Unstandardized coefficient		Standardized coefficient	t	Significance
					B	Standard error	Beta		
1	MMSE	T-WMH volume	0.283	0.080	- 0.172	0.097	- 0.188	- 1.778	0.078
2	Log - Im	T-WMH volume	0.449	0.202	- 0.100	0.062	- 0.176	- 1.609	0.111
3	DF	T-WMH volume	0.201	0.040	- 0.073	0.054	- 0.150	- 1.353	0.179
4	DFL	T-WMH volume	0.231	0.054	- 0.104	0.060	- 0.190	- 1.730	0.087
5	DB	T-WMH volume	0.366	0.134	- 0.047	0.050	- 0.099	- 0.935	0.352
6	DBL	T-WMH volume	0.386	0.149	- 0.097	0.049	- 0.205	- 1.961	0.053
7	VF (animal)	T-WMH volume	0.222	0.049	- 0.078	0.051	- 0.168	- 1.521	0.131
8	VF (vegetable)	T-WMH volume	0.629	0.396	- 0.018	0.045	- 0.036	- 0.407	0.685
9	TMT- A	T-WMH volume	0.331	0.109	- 0.332	0.094	- 0.376	- 3.524	0.001**
10	TMT- B	T-WMH volume	0.304	0.092	- 0.404	0.148	- 0.293	- 2.722	0.008**
11	WAIS	T-WMH volume	0.363	0.132	- 0.126	0.066	- 0.218	- 1.909	0.059
12	Boston Naming Test	T-WMH volume	0.303	0.092	- 0.042	0.055	- 0.088	- 0.756	0.452
13	LDFRC	T-WMH volume	0.519	0.269	-0.292	0.110	- 0.247	- 2.653	0.009**

Abbreviation: MMSE, Mini Mental State Exam; Log – Im, Logical Memory Immediate Recall; DF, Digit Span Forward; DFL, Digit Span Forward Length; DB, Digit Backward; DBL, Digit Span Backward Length; VF (animal), Verbal Fluency Category Animal; VF (vegetable), Verbal Fluency Category Vegetable; TMT-A, Trial Making Test part A; TMT-B, Trial Making Test part B; WAIS, Wechsler Adult Intelligence Scale; LDFRC, Long-Delay Free Recall Correct (Part of California Verbal Learning Test CVLT). T- WMH volume, Transformed White Matter Hyperintensity Volume.

§ Dependent variables were adjusted for age, gender, and education in model 1-12 but only for age and gender in model 13.

§§ WMH, White Matter Hyperintensity volumes were adjusted for age, gender, and education in model 1-12 but only for age and gender in model 13.

**P-value < 0.01

4.4. Discussion:

This study revealed two main results. First, it revealed that the WMH volume adjusted for age, gender, and education was strongly associated with worsening of processing speed and possibly executive function. This result is consistent with the growing body of literature including the results from Rotterdam Scan and Cardiovascular health studies in addition to many other studies (de Groot et al., 2000; Epelbaum et al., 2011; W. T. Longstreth et al., 2005; Prins et al., 2005; Reinhold Schmidt et al., 2010) that have implicated processing speed and executive function decline as primary clinical sequelae of CVD. These data also support the findings of other studies reporting poor executive function such as Nordahl et al., Tullberg et al., and the Framingham Study (Au, Massaro, Wolf, Young, et al., 2006; Nordahl et al., 2005; Tullberg et al., 2004). In contrast, our results were not in line with the results from the Austrian Stroke Prevention Study, which reported no decline in executive function (Reinhold Schmidt et al., 2005). This can be attributed to the fact that a different battery of neuropsychological tests, as well as a different approach to WMH volume quantification, were used in each of the studies. Further standardization of cognitive test batteries and biomarker measures of CVD are needed in the field.

Second, our results showed that age and gender adjusted WMH volume was strongly associated with poor short-term memory function exhibited as delayed free recall deficit. This result supports those reported by other studies (Capizzano et al., 2004; Epelbaum et al., 2011), but contrasts again with other studies that have reported no relation between executive function, memory and WMH (Mungas et al., 2005).

This study has some limitations. First, the data is amenable to evaluation of association only; it cannot predict causality. Second, study's subjects are highly educated. This bias may have resulted in an underestimation of the relationship WMH volumes and cognitive decline that could be seen in the larger general population.

We also included global WMH volume without regard to the specific white matter tracts involved, WMH demonstrate different patterns of WM affected in deep and periventricular regions, with patchy random areas of WMH often seen in the latter. The variable nature of WM tracts that lie within individual WMH may produce variability in the specific cognitive domains affected. Global aspect of cognition such as processing speed emerge strongly, but specific and variable deficits could occur only in a minority of subjects and thus may fall below the level of detection by group statistics. In addition, cerebrovascular disease may affect cognition through mechanisms other than AS in small WM vessels. Finally, WMH on MRI imaging may include changes other than injurious WM damage due to ischemia and inflammation.

Strengths of our study include the use of the uniform and comprehensive neuropsychological battery and the quantitative measurement of WMH volume.

In conclusion, our study showed that CVD risk factors and AS were strongly associated with cognitive decline, which affects mainly processing speed and short-term memory, and also suggests a possible decline in executive function as reflected by poor performance in TMT-B. Future clinical trial outcome measures should include the TMT-A, TMT-B, and LDFRC as a predictor of vascular cognitive decline in the setting of progressive WMH volume modification.

5. Conclusion:

5.1. Vascular Contribution to the Arteriolar Sclerosis:

HTN and HLD are the two most prominent risk factors that contribute to the formation and progression of AS in our data set. According to the Framingham Study, HTN and HLD often coexist (Castelli & Anderson, 1986). The prevalence of HTN and HLD combined was 18% (Wong, Lopez, Tang, & Williams, 2006). The risk of cardiovascular disease increased when both HTN and HLD exist together (Thomas et al., 2002).

Thus, targeting both risk factors together will result in optimal results that will help us stop the progression of AS and provide more protection against cognitive decline (Figure 5.1).

5.2. Neuroanatomical Consideration:

Our study showed poor performance in the TMT-A, TMT-B, and the LDFRC part of the CVLT. The most affected domain based on the latter findings are processing speed and memory. The fact that TMT-B scores were positive could suggest poor executive function as well.
The area of the brain involved in memory (short-term) is the medial temporal lobe. Disruption of white matter tracts such as the fornix, the post-commissural fornix, hippocampal connections, and the uncinate fasciculus could affect memory. The latter provide connection among the orbital, entorhinal, and the hippocampus.

Furthermore, the subcortical white matter of the frontal lobe and the superior parietal lobe is the areas that are critical for optimal processing speed. Lesions that disrupts white matter fibers such as ILF, the fronto-parietal and temporal parts of the SLF can result in poor processing speed performance.

Dorsolateral prefrontal cortex (superior and middle frontal gyri), is critical for executive function. Injury of white matter fibers including superior occipito-frontal fascicle which connects the prefrontal cortex with the limbic system and the inferior occipito-frontal fascicle that connects the frontobasal cortex to the parietal lobe can result in decreased executive functions.
These brain areas all are located in watershed zones of the brain where arteriolar sclerotic injury is maximum. Dorsolateral prefrontal cortex, subcortical frontal white matter, and superior parietal are located at the anterior cerebral-middle cerebral border zone while the medial temporal lobe is located at the middle cerebral-posterior cerebral border zone (Figure 5.2).

Damage to the subcortical connecting fibers in the brain lead to impaired processing speed (S. Debette & H. S. Markus, 2010). Executive function impairment can be explained by the severed connection between the dorsolateral frontal lobe with its target (Nordahl et al., 2005).

One important consideration that need to be recognized and acknowledged in the field involves the heterogeneous nature of VaD due to the inclusion of persons with large vessel and lacunar strokes, in cohort studied. The core features of vascular cognitive impairment are uniform across all in small vessel AS.

In conclusion, our study findings showed that AS associated with a consistent pattern of CVD risk factors that are contributing to VaD across the early preclinical and MCI spectrum of disease and that we should focus on (AS) as a defined disease that we can target and understand.

This study has some limitations worth mentioning. First, the study's subjects are highly educated and Caucasian. This selection bias may have resulted in an underestimation of the relationship between CVD risk factors, WMH volumes and cognitive decline that might be seen in the larger general population. Second, as the analysis is purely cross-sectional at this point, the findings cannot predict causality, only association. Longitudinal studies can assess changes in WMH overtime, so that processes causing accumulations may be separated from previous, possibly static, WM injuries. Finally, our imaging analysis was restricted to T2 structural changes only, although there are other important ways to investigate these vascular changes such as through Diffusion Tensor Imaging (DTI), Arterial Spin Labeling (ASL), and MR spectroscopy.

These limitations, however, are offset by the many strengths of the current study: first, this study has a uniform and well-characterized cohort with extensive clinical data and characterization. Second, patients were recruited from multiple cross-sectional studies that used uniform clinical and imaging procedures to provide a large number of subjects with a wide range of WMH burden and CVD risks. Finally, we used highly quantitative measures of T2 volumetric abnormalities that provided state-of-the-art total WMH volumes.

Future research should work to develop a longitudinal study design to further examine elements of causality and to track WMH volume and cognitive function changes over time. Furthermore, AD pathology should be taken into account in any further analyses, and the inter-relationship between AD and AS should be studied. Finally, the use of other imaging modalities such as DTI, ASL, and MR spectroscopy may provide us with a more detailed picture of small vessel disease and WMH.

Based on these results, future clinical trials must be designed to abrogate the insults of HTN and HLD in mid-life to decrease arteriolar sclerotic changes of the brain and ultimately halt the progression of cognitive decline secondary to CVD. In addition, TMT-A, TMT-B as well as the LDFRC of the CVLT may prove to be the neuropsychological tests of choice in predicting improved outcome in CVD.

5.3. Future planned studies

Ongoing studies in this cohort include an assessment of AD pathology (CSF amyloid & tau), inflammatory and angiogenic mediators, and genetic influences on arteriosclerosis (ABCC9), and intend to incorporate these variables into the analysis when data collection is complete for a fuller understanding of the interplay between CVD, AD, and systemic modulators of cognitive decline in mixed pathological disease states. I am currently applying to graduate school at UK to hopefully complete this work necessary to advance our understanding of arteriolar sclerosis in aging and cognitive decline.

Figure 5.1. Interlink between hypertension and hyperlipidemia and how they both contribute to arteriolar sclerotic changes.

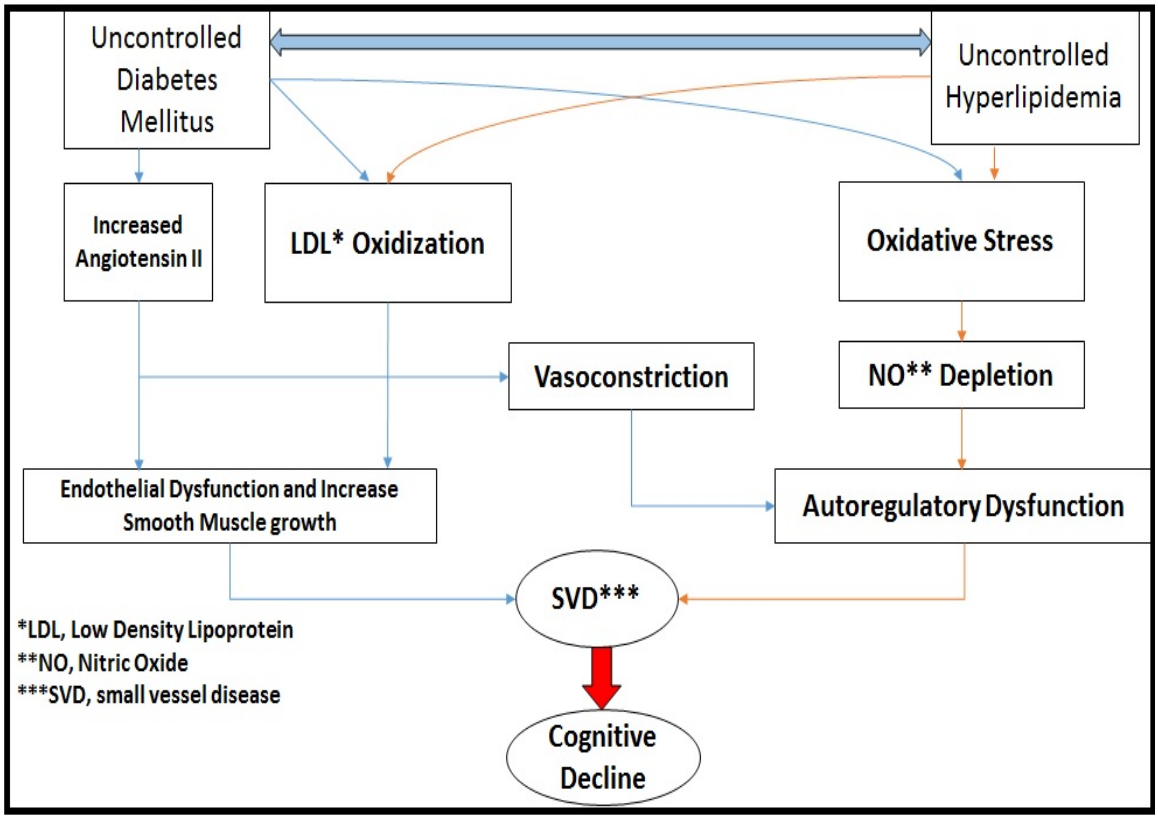
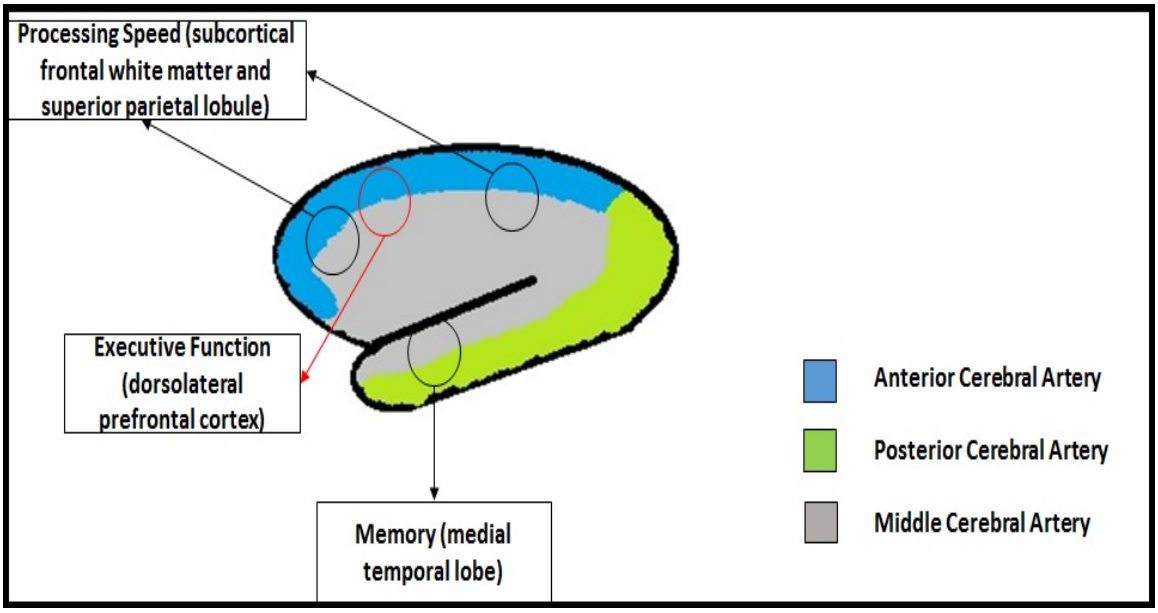


Figure 5.2. Lateral view of the left cerebral hemisphere showing the relationship between brain areas involved in processing speed, executive function, and memory regarding watershed zones of the brain.



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Vita

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Academic Honors:
. Academic Scholarship:

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. Academic Honor:

- Received shield of top ranked Iraqi valedictorian for a distinguished performance in medicine. Office of Iraqi Vice President 09/2009.
- Ranked as the second student in my class at Tikrit University College of Medicine 07/2009.