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Manju Ramakrishnan Date

Association Between Vascular Measures and MRI Biomarkers in Individuals with Mild Cognitive Impairment: The VASCULAR Study

By

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Master of Public Health

Epidemiology

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By

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Bachelor of Medicine, Bachelor of Surgery (MBBS)

SRM Medical College Hospital and Research Centre, 2015

Faculty Thesis Advisor: Ambar Kulshreshtha, MD, PhD

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Abstract

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Background:
Vascular dysfunction is increasingly implicated in the early development of Alzheimer's disease (AD) and related dementias. Mild cognitive impairment (MCI), often preceding AD, provides a critical window to examine vascular contributions to early neurodegeneration. This study explores the associations between noninvasive vascular measures and MRI-derived brain biomarkers in older adults with and without MCI.

Methods:
Data were drawn from the VASCULAR study, a prospective observational cohort of adults aged ≥50. Vascular health was assessed using the reactive hyperemia index (RHI) and carotid intima-media thickness (CIMT). Brain structure was evaluated using MRI-derived hippocampal volumes and white matter hypointensities. Analyses included group comparisons and linear models stratified by cognitive status.

Results:
Among 127 participants (mean age of 63.9 years; 66% female), 39 had MCI and 88 had normal cognition. The MCI group had lower educational attainment and higher obesity prevalence. Compared to those with normal cognition, individuals with MCI had lower RHI (median: 1.80 vs. 2.17; $p = 0.007$) and higher right CIMT (0.76 mm vs. 0.71 mm; $p = 0.032$), indicating worse endothelial function and more subclinical atherosclerosis. They also exhibited smaller bilateral hippocampal volumes (Left: 3,525 mm^3 vs. 3,740 mm^3; Right: 3,528 mm^3 vs. 3,867 mm^3). Left CIMT was positively associated with white matter hypointensities ($\beta = 0.98$, 95% CI: 0.05 to 1.90, $p = 0.04$).

Conclusion:
Vascular dysfunction is linked to structural brain changes in MCI, underscoring its potential role in early cognitive decline. Noninvasive vascular assessments may aid in identifying individuals at heightened risk and inform midlife public health interventions.

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Table of Contents

Abstract

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Results

Among 127 participants (mean age 63.9 years; 66% female; 60 % African Americans), 39 had MCI and 88 had normal cognition. The MCI group had lower educational attainment and higher obesity prevalence. Compared to those with normal cognition, individuals with MCI had lower RHI (median: 1.80 vs. 2.17; $p = 0.007$) and higher right CIMT (0.76 mm vs. 0.71 mm; $p = 0.032$), indicating worse endothelial function and more subclinical atherosclerosis. They also exhibited smaller bilateral hippocampal volumes (Left: 3,525 mm^3 vs. 3,740 mm^3; Right: 3,528 mm^3 vs.

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Conclusion:

Vascular dysfunction is linked to structural brain changes in MCI, underscoring its potential role in early cognitive decline. Noninvasive vascular assessments may aid in identifying individuals at heightened risk and inform midlife public health interventions.

Introduction

As the life expectancy of people continues to increase, age-related changes like Alzheimer's disease (AD) and other types of dementia are becoming increasingly prevalent. Dementia is a progressive neurodegenerative disorder that affects more than 6 million people and contributes to the death of approximately 100,000 people annually.[1,2] It is the seventh leading cause of death across the globe and is marked by a gradual decline in cognition.[2] It commonly presents with memory loss, impaired judgment, difficulty thinking, reasoning, and behavioral changes that interfere with an individual's daily life.[3]

AD is the most prevalent type of dementia and accounts for approximately 60-70% of cases. [4,5] It is characterized by widespread changes across the brain. The accumulation of protein structures like beta-amyloid and tau protein partially drives these extensive changes. Other pathological processes like neuroinflammation, synaptic disruption, and vascular injury further contribute to the brain's neuronal damage, leading to AD. [6] These pathophysiological changes begin years before the clinical symptoms are noticeable. Mild cognitive impairment (MCI) is a measurable cognitive deficit and is often one of the earliest clinical manifestations of this disease. The presence

of comorbid conditions may further influence the progression from MCI to more severe forms of cognitive dysfunctions and neurodegenerative effects. [6]

Despite several advances in understanding the neuropathology of AD, the triggers for the early changes are still under investigation. The brain has a high metabolic demand, which makes vascular health one of the most essential components in assessing brain aging. Vascular dysfunctions have been recognized as a key contributor to the pathogenesis of AD. In recent research, circulating beta-amyloid has been linked to subclinical atherosclerosis, arterial stiffness, endothelial dysfunction, and increased risk of cardiovascular disease-associated mortality.[7–9] Their accumulation weakens the blood-brain barrier, thus promoting the development of vascular lesions like microinfarcts and small vessel disease. These lesions can further interact with the effects of the amyloid deposits, causing accelerated cognitive decline and damage to the brain.[10,11] AD and Cardiovascular diseases (CVD) share several risk factors, with diseases like hypertension, diabetes, obesity, and dyslipidemia precipitating vascular dysfunction, leading to chronic hypoperfusion of the brain and thus damaging the neurovascular units, causing characteristic neurodegeneration observed in AD.[12,13] These findings highlight the importance of early strategies in targeting vascular health to mitigate dementia risk.

Several noninvasive vascular measures provide insights into evaluating vascular dysfunction. Carotid intima-media thickness (CIMT) and reactive hyperemia index (RHI) can serve as early proxies in identifying vascular pathologies and are widely used in assessing arterial stiffness, endothelial function, and arterial remodeling. [14–16]

CIMT, measured by an ultrasound, has been used as a marker for arterial wall thickening and subclinical atherosclerosis. An elevated CIMT has been associated with increased risk of stroke,

MI, and cognitive decline.[17] Studies have determined that a higher CIMT is associated with smaller hippocampal volume and poor cognitive function.[18] The hippocampus is a structure vulnerable to ischemia and cerebral hypoperfusion and is a key marker for early Alzheimer's disease pathology.[18] Therefore, CIMT can be useful for evaluating the vascular contribution towards early neurodegenerative changes.

RHI is a vascular measure derived from peripheral arterial tonometry. It assesses the vascular response to transient ischemia and is useful for quantifying endothelial function.[14,20] Low RHI is also indicative of early peripheral vascular dysfunction, which is associated with poor cognitive function and white matter injuries.[14,20] It is also prudent to note that endothelial dysfunction is more likely to precede brain changes on imaging, making RHI a useful vascular marker.

The hippocampus is a key region of the brain that is central to memory and learning. It is especially sensitive to any vascular insufficiency, making it an important area to evaluate vascular contributions to the development of early cognitive decline. Hippocampal atrophy, measured as reduced volume and cortical thickness, is one of the earliest signs observed in AD and MCI.[18,21] Additionally, white matter injury observed on MRI can reflect chronic ischemia, small vessel damage, and is associated with slowing of cognitive processing and increased dementia risk. MRI markers have increasingly been used to assess systemic vascular health. For example, an increase in carotid arterial stiffness and CIMT levels is tied to reduced hippocampal volume and increased white matter lesion volume. Similarly, endothelial dysfunction measured by RHI is associated with higher white matter lesion burden, suggesting impaired perfusion and vascular reactivity.

Despite the advances, few studies have utilized multiple vascular measures simultaneously to examine the associations with brain structural outcomes across cognition status. There remains a

need to understand how detectable early changes through noninvasive measures are linked to brain health markers like hippocampal morphology and white matter integrity, especially in the prodromal AD stages, like the MCI.

The primary objective of this study is to determine whether vascular function, including RHI and CIMT, is associated with the MRI markers of brain integrity, specifically hippocampal volume, and white matter hypointensities (T1-weighted).

Methods

Study Design and Participants

The data was obtained from the VAScular ContribUtors to prodromaL AlzheimeR's disease (VASCULAR) study. It is a prospective, single-center, observational study conducted at Emory University in Atlanta, GA. 340 participants aged 50 or older were recruited in the study, with 150 individuals diagnosed with MCI and 190 individuals with normal cognition (NC). Participants were matched based on age, sex, race, and education status to minimize the confounding effects of these variables. The exclusion criteria included a history of stroke within the past 3 years, diagnosis of any dementia, neurological or psychiatric conditions that might affect cognition (including Parkinson's disease and related movement disorders, multiple sclerosis, epilepsy, schizophrenia, and other psychotic disorders).

Covariates and Exposures of interest

The sociodemographic characteristics that were assessed include age (which was recorded in years and treated as a continuous variable), sex (male/female), marital status (married, divorced or

separated, widowed, or single/never married), educational attainment (measured as the total number of years of formal education completed), employment status (indicating whether participants were currently employed or not), annual household income (<$25,000, $25,001 to $50,000, $50,001 to $80,000, and > $80,000), body mass index (BMI) categorized according to the WHO criteria (underweight (<18.5 kg/m²), healthy weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), or obese (≥30.0 kg/m²)), race (African American, White). Medical history, including diabetes, hyperlipidemia, and heart disease, was obtained through self-report.

Reactive Hyperemia Index (RHI): Endothelial function was assessed using Peripheral Arterial Tonometry (PAT) to measure pulse volume amplitude in the index fingertip. Reactive hyperemia was obtained by releasing an upper arm blood pressure cuff inflated to suprasystolic pressure for 5 minutes. The ratio of the post-to-pre-occlusion pulse volume in the tested arm divided by the post-to-pre-occlusion ratio of the control arm was used to calculate the reactive hyperemia index (RHI).

Carotid Intima-Media Thickness (CIMT): Subclinical atherosclerosis was assessed using high-resolution B-mode ultrasound of the common carotid artery with a 7.5-MHz linear-array transducer. CIMT measurements were taken according to standardized protocols.

Outcomes

Hippocampal Volumes (bilateral), White Matter Hypointensities: High-resolution T1-weighted structural MRI images were acquired using a 3D MPRAGE sequence (acquisition time: 8:37 minutes; voxel size: 1.0 × 1.0 × 1.0 mm; parallel acquisition: off; relative signal-to-noise ratio: 1.00) on a Siemens scanner. Images were processed using FreeSurfer to derive cortical thickness

and subcortical volume estimates, including hippocampal volume. Standard surface reconstruction, segmentation, and anatomical labeling pipelines were applied, as previously described (Fischl et al., 1999; Dale et al., 1998). White matter hypointensities were also quantified using FreeSurfer, based on signal intensity differences within white matter regions on T1-weighted images.

Statistical Analysis

Data Cleaning and Preparation: Data cleaning included variable renaming for clarity, recoding categorical variables, and exclusion of biologically implausible or extreme outlier values based on clinical thresholds. Categorical variables such as sex, race, marital status, BMI, employment, and medical history were recoded into labeled factor variables. Normality of continuous variables was assessed through histograms, density plots, and skewness coefficients. Log transformation was applied to highly skewed variables, including right hippocampal thickness and white matter hypointensities, to improve distributional symmetry for regression analyses.

Demographic and Clinical Characteristics Assessment: Participants' characteristics were compared between those with normal cognition (NC) and those with mild cognitive impairment (MCI). Continuous variables were summarized using medians and interquartile ranges and compared using the Wilcoxon rank-sum test due to non-normal distributions. Categorical variables were summarized as counts and percentages and compared using Pearson's chi-squared or Fisher's exact test (cell size < 5), as appropriate based on cell size. A two-sided p-value of <0.05 was considered statistically significant.

Correlation and Bivariate Associations: Spearman's rank correlation coefficients were calculated to assess bivariate associations between all continuous variables. A correlation matrix and significance heatmap were constructed using the corrplot package. Statistically significant correlations ($p < 0.05$) were visualized, with non-significant values masked to improve interpretability.

Regression Modeling of Vascular and MRI Measures: Univariate and multivariate linear regression models were used to evaluate associations between vascular predictors (RHI, central blood pressures, and CIMT) and MRI outcomes (hippocampal volume, hippocampal thickness, and white matter hypointensities). Analyses were stratified by cognitive status (NC vs. MCI) to assess differential associations across groups. Both unadjusted and adjusted models were conducted, with covariates including age, sex, race, education, BMI category, and history of hypertension, diabetes, and hyperlipidemia. Models followed the general form:

$$\textit{MRI Outcome Measure} = \beta_0 + \beta_1\,(\textit{Vascular Predictors}) + \beta_2\,(\textit{Age}) + \beta_3\,(\textit{Sex}) + \beta_4\,(\textit{Education}) + \beta_5\,(\textit{BMI category})) + \beta_6\,(\textit{Hx of HTN}) + \beta_7\,(\textit{Hx of Diabetes}) + \beta_8\,(\textit{Hx of Hyperlipidemia}) + \varepsilon$$

Log-transformed outcomes were used in models where variables exhibited non-normal distribution. Model diagnostics included variance inflation factors (VIF) to assess multicollinearity, and the Breusch–Pagan test to evaluate heteroscedasticity was performed. All VIFs were less than 5, consistent with accepted thresholds, indicating the absence of multicollinearity among covariates. All analyses were performed using R version 4.4.0.

Results

Demographic and Clinical characteristics of participants

A total of 127 participants were included in the analysis; 88 were classified as having normal cognition, and 39 had mild cognitive impairment (MCI). The mean age was 63.9 years (IQR: 58–69), with 66% female and 60% African American, with no significant age or sex differences observed between cognitive groups. Racial distribution differed significantly, with a higher proportion of African American participants in the normal cognition group (69%) and a greater proportion of White participants in the MCI group (62%) ($p = 0.001$). Compared to those with normal cognition, individuals with MCI had significantly lower years of education and a higher prevalence of obesity (49% vs. 23%, $p = 0.018$). No significant differences were observed between groups in the prevalence of hypertension, diabetes, hyperlipidemia, myocardial infarction, stroke, or kidney disease. MoCA scores were significantly lower in the MCI group (median: 23) compared to the normal cognition group (median: 27, $p < 0.001$), consistent with diagnostic classification (**Table 1**).

Vascular and MRI measures in participants

Participants with mild cognitive impairment (MCI) had significantly lower RHI values than those with normal cognitive status (median: 1.80 vs. 2.17; p = **0.007**). Individuals with MCI also demonstrate greater right CIMT than the normal cognition group (median: 0.76 mm vs. 0.71 mm; p = **0.032**), indicating a higher burden of subclinical atherosclerosis. Further, Participants with mild cognitive impairment (MCI) exhibited significantly smaller hippocampal volumes than those with normal cognition. The median right hippocampal volume was 3,528 mm^3 in the MCI group

versus 3,867 mm^3 in the normal cognition group (p = **0.013**), and the left hippocampal volume was 3,525 mm^3 compared to 3,740 mm^3, respectively (p = **0.012**). In contrast, although white matter hypointensity volume was higher among those with MCI than the NC group, the differences did not reach statistical significance **(Table 2).**

Association of Vascular and MRI Measures

Associations between vascular health markers and structural brain outcomes were examined using linear regression models stratified by cognitive status, MCI, and NC.

In the normal cognition group, higher left CIMT was associated with reduced right hippocampal volume in unadjusted models (β = –585.1 mm^3, 95% CI: –1166 to –4.42, p = **0.05**). However, this effect was attenuated after covariate adjustment **(Table 5)**. Additionally, among individuals with MCI, each 1 mm increase in left CIMT was associated with a 0.98-unit increase in log-transformed white matter hypointensity volume (β = 0.98, 95% CI: 0.05 to 1.90, p = **0.04**) (**Table 5**). Due to skewed distribution, white matter hypointensity was natural log-transformed before analysis.

Discussion

This study examined the relationship between vascular function and brain structural changes in a cohort of older adults with and without mild cognitive impairment (MCI). Overall, participants with MCI exhibited lower endothelial function (as measured by RHI), greater carotid intima-media thickness (CIMT), and smaller hippocampal volumes than cognitively normal individuals. When exploring associations between vascular markers and neuroimaging outcomes, poorer vascular health, particularly reduced RHI and elevated CIMT, was linked to smaller hippocampal structures and greater white matter lesion burden among MCI participants, suggesting that vascular

dysfunction may have a more substantial impact on brain integrity during the early stages of cognitive decline. Our findings contribute to the growing body of literature demonstrating a link between vascular dysfunction and neurodegeneration, particularly during the early prodromal stage of cognitive decline.[22,23]

The demographic and clinical characteristics observed in this study reflect several established risk patterns for cognitive decline. Of note is that the MCI group showed a higher prevalence of obesity and fewer years of formal education. These findings are consistent with prior research suggesting that lower educational attainment, a widely recognized proxy for reduced cognitive reserve, may accelerate the clinical determination of cognitive impairment in the presence of underlying neuropathology. Individuals with higher educational attainment appear to cope better and only demonstrate dementia symptoms when they experience a higher pathological burden.[24,25] Obesity may contribute to cognitive impairment through pathways involving chronic inflammation, insulin resistance, and vascular dysfunction, all of which can negatively impact brain health and accelerate neurodegenerative processes.[26,27] Large cohort studies such as the Framingham Offspring Study have similarly shown that midlife obesity and lower educational levels are independently associated with higher risk of late-life cognitive decline and dementia.[28] Interestingly, while many prior studies have reported higher rates of vascular comorbidities such as hypertension and diabetes in cognitively impaired populations, our study did not find significant between-group differences in these conditions. This may be attributed to the relatively small sample size or the early stage of cognitive impairment represented by our MCI cohort. Nonetheless, the pronounced difference in MoCA scores between groups reinforces the validity of our cognitive classification and reflects the subtle yet clinically relevant changes seen in early cognitive decline.

While the median RHI in the MCI was not lower than the cut-off of 1.67 to be considered abnormal, they were lower compared to individuals with NC. Additionally, our findings showed an unexpected inverse association between RHI and hippocampal volume, where higher RHI values were linked to smaller hippocampal volumes. These results contradict the existing literature that better endothelial function protects against neurodegeneration. Endothelial dysfunction can lead to reduced cerebral perfusion and increased oxidative stress and blood-brain barrier dysfunction, all of which have been associated with hippocampal atrophy and cognitive decline.[29–31] The hippocampus is supplied by small-caliber arterioles from the posterior cerebral circulation and has limited collateral flow.[32,33] Any perfusion or arteriolar dysfunction changes make it a critical target for vascular compromise.[32] These changes can contribute to progressive structural and memory dysfunction observed in cognitive decline. Several factors may explain our contradictory observation, including residual confounding, measurement variability in RHI, or reverse causation, where hippocampal atrophy may be associated with systemic physiological changes that secondarily influence vascular tone. Alternatively, this association may reflect the small sample size within the MCI subgroup, which may reduce statistical power and inflate anomalous associations.

Beyond the peripheral microvascular and endothelial dysfunction effect, our study also determined that individuals with MCI exhibited increased CIMT, potentially pointing towards a greater burden of subclinical atherosclerosis. An increase in right CIMT was associated with a reduction in hippocampal. A longitudinal study conducted by Ferreira et al. determined that high CIMT is associated with greater verbal, memory, and global cognitive decline.[34] Additionally, our study also echoes earlier reports that an increase in thickening of the carotid arteries is associated with a

greater burden of white matter hyperintensities and microvascular damage, which is characteristic of small vessel disease.[17]

Building on these findings, the link between left CIMT and increased white matter lesion burden in MCI suggests that vascular changes may extend beyond the hippocampus to affect broader white matter networks.[35,36] This damage is thought to impair communication between cortical and subcortical regions, contributing to broader functional network disturbances rather than isolated structural loss.[37] Hypointense white matter lesions on T1-weighted imaging often indicate more advanced small vessel pathology, including demyelination and axonal degeneration.[37] These network-level disruptions may underlie the widespread cognitive difficulties frequently seen in vascular cognitive impairment and mixed dementia, where disconnection across brain regions plays a central role in functional decline.[37]

Vascular dysfunction may contribute to neurodegeneration through several mechanisms. Chronic hypoperfusion, arterial stiffening, and endothelial injury reduce oxygen and nutrient delivery to especially high-demand regions like the hippocampus.[23,38] Endothelial injury can trigger neuroinflammation and interfere with the brain's ability to clear harmful proteins like amyloid-beta, thereby accelerating the pathological processes associated with AD.[39–41] Loss of nitric oxide signaling due to vessel damage plays a significant role in promoting amyloid and tau protein deposits, two hallmark features of neurodegenerative pathology.[39,42]

Limitations

While this study provides a comprehensive insight into the vascular and MRI markers of MCI, it has several limitations. The study's cross-sectional design does not prove a causal and temporal

relationship. Therefore, it is unclear whether vascular dysfunction drives neurodegeneration or reflects underlying pathology. Additionally, the relatively small size, especially in the MCI group, may have limited our ability to detect more nuanced associations. Though we adjusted for major demographic and clinical factors, unmeasured confounders like physical activity, diet, sleep, and inflammation may have influenced the results. The sample came from a single cohort and lacked broad racial and socioeconomic diversity, which may limit generalizability. Lastly, while standardized methods were used for MRI analysis, technical variability in imaging or segmentation could have affected volume estimates, particularly in the hippocampus.

Conclusion and Future Directions

This study reinforces the growing recognition that vascular health is critical in cognitive aging. The associations between endothelial dysfunction, subclinical atherosclerosis, and structural brain changes suggest that even modest vascular impairments may contribute to early neurodegenerative processes. From a public health standpoint, these findings support the importance of early identification and management of vascular risk factors, not only to prevent cardiovascular disease but also to protect long-term brain health. Incorporating vascular screening measures such as RHI and CIMT into midlife health assessments could help identify individuals at heightened risk for cognitive decline. Future research should focus on longitudinal, population-based studies to better understand the temporal relationship between vascular dysfunction and neurodegeneration and to evaluate whether interventions targeting vascular health can mitigate cognitive decline. Addressing vascular risk through lifestyle modification, equitable access to preventive care, and targeted intervention may offer scalable strategies to reduce the burden of dementia in aging populations.

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Table 1. Demographic and Clinical Characteristics by Cognitive Status

Characteristic	Overall N = 127 [1]	Normal Cognition N = 88 [1]	Mild Cognitive Impairment N = 39 [1]	p-value [2]
Age, years, median (IQR)	63 (58, 69)	64 (58, 69)	63 (59, 73)	0.4
Sex, n (%)				0.3
Female	84 / 127 (66%)	61 / 88 (69%)	23 / 39 (59%)	
Male	43 / 127 (34%)	27 / 88 (31%)	16 / 39 (41%)	
Race, n(%)				**0.001**
African American	76 / 127 (60%)	61 / 88 (69%)	15 / 39 (38%)	
White	51 / 127 (40%)	27 / 88 (31%)	24 / 39 (62%)	
Marital Status, n(%)				0.9
Married	50 / 126 (40%)	37 / 88 (42%)	13 / 38 (34%)	
Divorced/Separated	37 / 126 (29%)	25 / 88 (28%)	12 / 38 (32%)	
Widowed	15 / 126 (12%)	10 / 88 (11%)	5 / 38 (13%)	
Single/Never Married	24 / 126 (19%)	16 / 88 (18%)	8 / 38 (21%)	
Education, years, median (IQR)	16 (14, 18)	16 (14, 18)	16(14, 16)	**0.037**
Employed, n(%)				0.12
No	82 / 127 (65%)	53 / 88 (60%)	29 / 39 (74%)	
Yes	45 / 127 (35%)	35 / 88 (40%)	10 / 39 (26%)	

Salary, n(%)				0.13
< $25,000	40 / 110 (36%)	23 / 78 (29%)	17 / 32 (53%)	
$25,001-$50,000	24 / 110 (22%)	18 / 78 (23%)	6 / 32 (19%)	
$50,001-$80,000	25 / 110 (23%)	20 / 78 (26%)	5 / 32 (16%)	
> $80,001	21 / 110 (19%)	17 / 78 (22%)	4 / 32 (13%)	
BMI, n (%)				**0.018**
Underweight	1 / 127 (0.8%)	1 / 88 (1.1%)	0 / 39 (0%)	
Healthy weight	49 / 127 (39%)	36 / 88 (41%)	13 / 39 (33%)	
Overweight	38 / 127 (30%)	31 / 88 (35%)	7 / 39 (18%)	
Obesity	39 / 127 (31%)	20 / 88 (23%)	19 / 39 (49%)	
Hx of Hypertension, n(%)				0.6
No	61 / 127 (48%)	41 / 88 (47%)	20 / 39 (51%)	
Yes	66 / 127 (52%)	47 / 88 (53%)	19 / 39 (49%)	
Hx of Hyperlipidemia, n(%)				>0.9
No	65 / 127 (51%)	45 / 88 (51%)	20 / 39 (51%)	
Yes	62 / 127 (49%)	43 / 88 (49%)	19 / 39 (49%)	
Hx of Diabetes, n(%)				0.7
No	110 / 127 (87%)	77 / 88 (88%)	33 / 39 (85%)	
Yes	17 / 127 (13%)	11 / 88 (13%)	6 / 39 (15%)	
Hx of MI, n(%)				0.4
No	119 / 127 (94%)	81 / 88 (92%)	38 / 39 (97%)	
Yes	8 / 127 (6.3%)	7 / 88 (8.0%)	1 / 39 (2.6%)	

Hx of Stroke, n(%)				>0.9
No	125 / 127 (98%)	86 / 88 (98%)	39 / 39 (100%)	
Yes	2 / 127 (1.6%)	2 / 88 (2.3%)	0 / 39 (0%)	
Hx of Kidney Disease, n(%)				>0.9
No	120 / 127 (94%)	83 / 88 (94%)	37 / 39 (95%)	
Yes	7 / 127 (5.5%)	5 / 88 (5.7%)	2 / 39 (5.1%)	
MoCA, n(%)	25 (23, 28)	27.0 (25.0, 28.0)	23.0 (20.0, 24.0)	**<0.001**

[1] Median (Q1, Q3); n / N (%)

[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 2. Vascular and MRI Measures by Cognition Status

Characteristic	Overall N = 127 [1]	Normal Cognition N = 88 [1]	Mild Cognitive Impairment N = 39 [1]	p-value [2]
RHI	2.03 (1.61, 2.56)	2.17 (1.75, 2.78)	1.80 (1.53, 2.34)	**0.007**
Mean Right Carotid CIMT	0.73 (0.65, 0.84)	0.71 (0.62, 0.80)	0.76 (0.68, 0.88)	**0.032**
Mean Left Carotid CIMT	0.72 (0.65, 0.85)	0.72 (0.64, 0.82)	0.74 (0.69, 0.89)	0.095
Right Hippocampus Volume	3,760 (3,472, 4,099)	3,867 (3,624, 4,130)	3,528 (3,213, 4,031)	**0.013**
Left Hippocampus Volume	3,656 (3,401, 4,012)	3,740 (3,507, 4,029)	3,525 (3,314, 3,835)	**0.012**
WM Hypointensities	2,308 (1,532, 4,164)	2,220 (1,565, 3,529)	2,479 (1,319, 4,528)	0.9

[1] *Median (Q1, Q3)*

[2] *Wilcoxon rank sum test*

Table 3. Association of RHI and MRI Outcomes

MRI Outcome	Normal Cognition						Mild Cognitive Impairment					
	Unadjusted β	95% CI	P Value	Adjusted β	95% CI	P Value	Unadjusted β	95% CI	P Value	Adjusted β	95% CI	P Value
Left Hippocampus Volume	-42.8	-172.5, 86.9	0.51	-31.75	-159.3, 95.83	0.62	-67.26	-321.7, 187.2	0.6	-88.8	-366.7, 189.1	0.52
Right Hippocampus Volume	0.32	-142.8, 143.4	1	-6.6	-155.2, 142	0.93	-109.7	-397.6, 178.2	0.44	-99.37	-393.1, 194.4	0.49
Log WM hypointensities	-0.05	-0.24, 0.15	0.63	-0.02	-0.21, 0.18	0.87	0.04	-0.41, 0.49	0.85	-0.21	-0.73, 0.30	0.4

Table 4. Association of Mean Right Carotid CIMT and MRI Outcomes

MRI Outcome	Normal Cognition						Mild Cognitive Impairment					
	Unadjusted β	95% CI	P Value	Adjusted β	95% CI	P Value	Unadjusted β	95% CI	P Value	Adjusted β	95% CI	P Value
Left Hippocampus Volume	-44.55	-537.1, 448	0.86	387.3	-60.47, 835	0.09	-468.9	-1321, 382.9	0.27	-729.8	-1732, 272.4	0.15
Right Hippocampus Volume	-190.7	-731.4, 350.1	0.49	155.6	-374, 685.2	0.56	-504.4	-1474, 465	0.3	-414.6	-1505, 675.4	0.44
Log WM hypointensities	-0.04	-0.78, 0.70	0.92	-0.42	-1.11, 0.27	0.23	0.79	-0.71, 2.28	0.29	-0.44	-2.38, 1.49	0.64

Table 5. Association of Mean Left Carotid CIMT and MRI Outcomes

MRI Outcome	Normal Cognition						Mild Cognitive Impairment					
	Unadjusted β	95% CI	P Value	Adjusted β	95% CI	P Value	Unadjusted β	95% CI	P Value	Adjusted β	95% CI	P Value
Left Hippocampus Volume	-415	-947.3, 117.3	0.12	222.2	-341.1, 785.5	0.43	27.28	-531.4, 585.9	0.92	263.8	-424.7, 952.2	0.44
Right Hippocampus Volume	**-585.1**	-1166, -4.42	****0.05****	-49.8	-707.4, 607.8	0.88	-229.7	-859.8, 400.4	0.46	-84.74	-820.4, 651	0.82
Log WM hypointensities	0.32	-0.49, 1.13	0.44	-0.57	-1.42, 0.28	0.19	**0.98**	0.05, 1.90	****0.04****	0.6	-0.68, 1.87	0.35

Figure 1. Distribution of RHI by Cognition Status (p-value = 0.007)

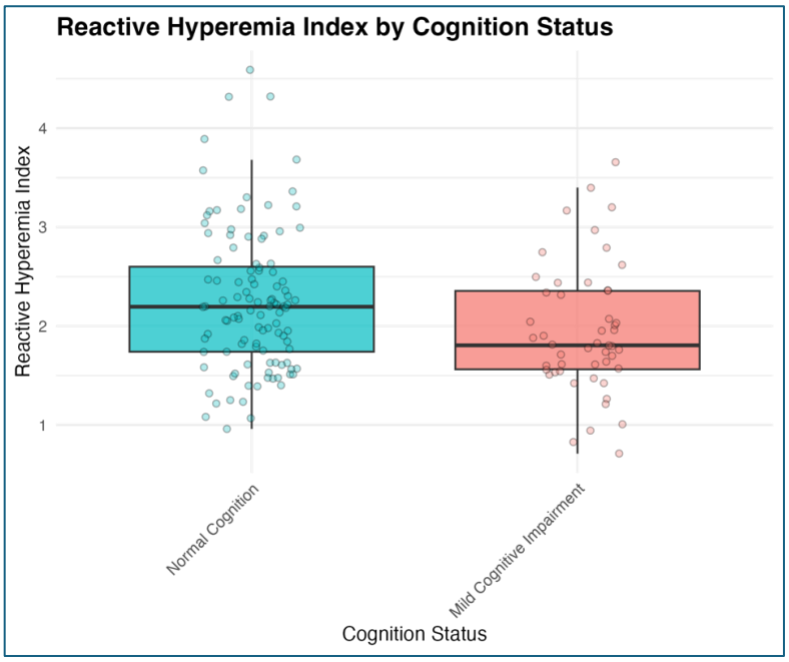

Figure 2. Distribution of Mean Right CIMT by Cognition Status (p-value = 0.032)

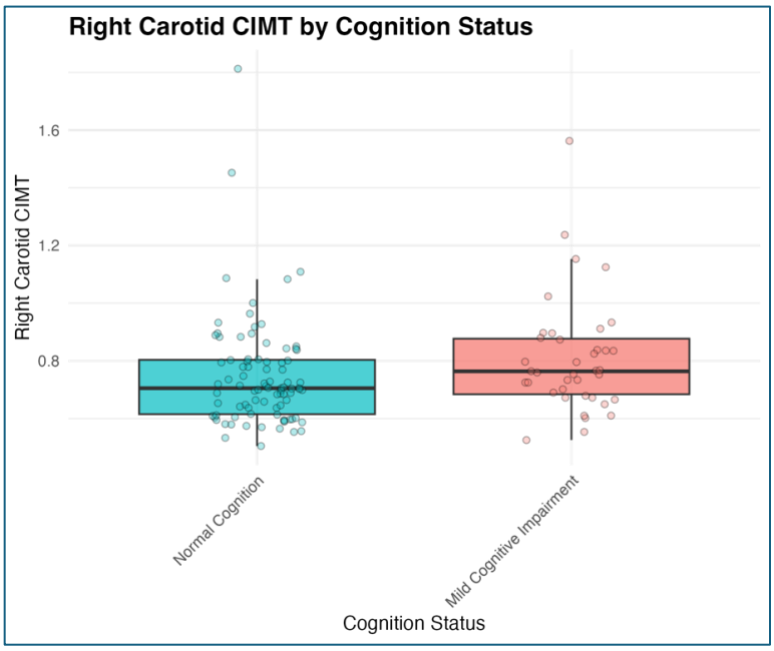

Figure 3. Distribution of Left CIMT by Cognition Status (p-value = 0.095)

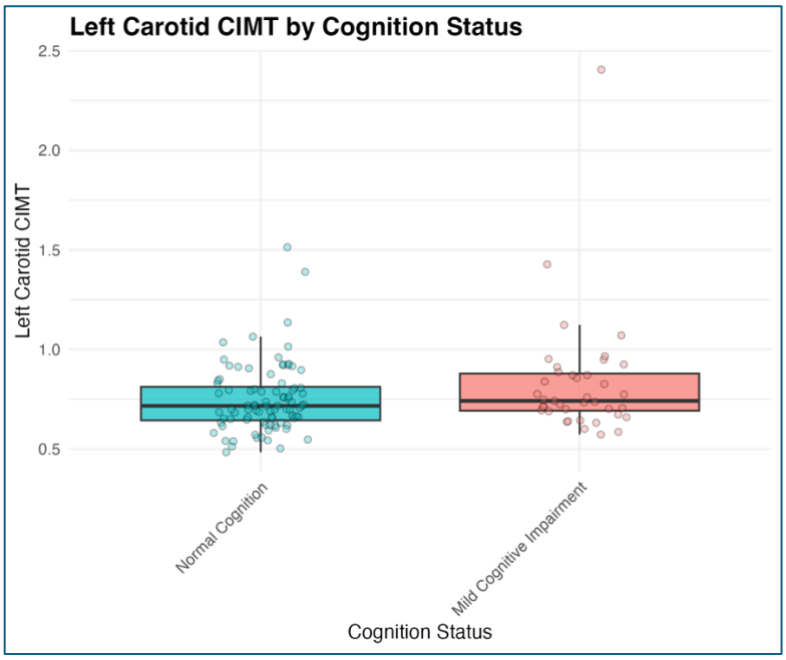

Figure 4. Distribution of Right Hippocampus Volume by Cognition Status (p-value =0.013)

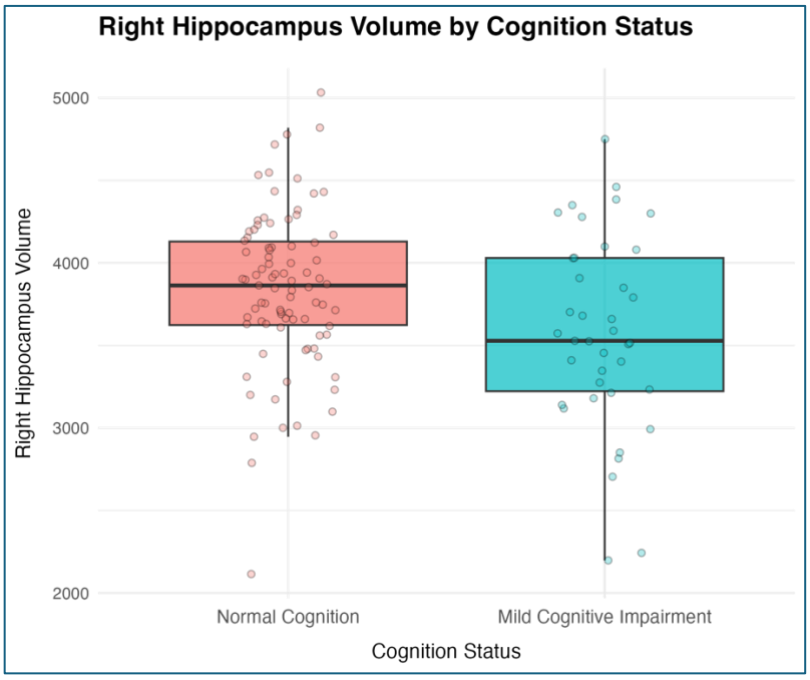

Figure 5. Distribution of Left Hippocampus Volume by Cognition Status (p-value =0.012)

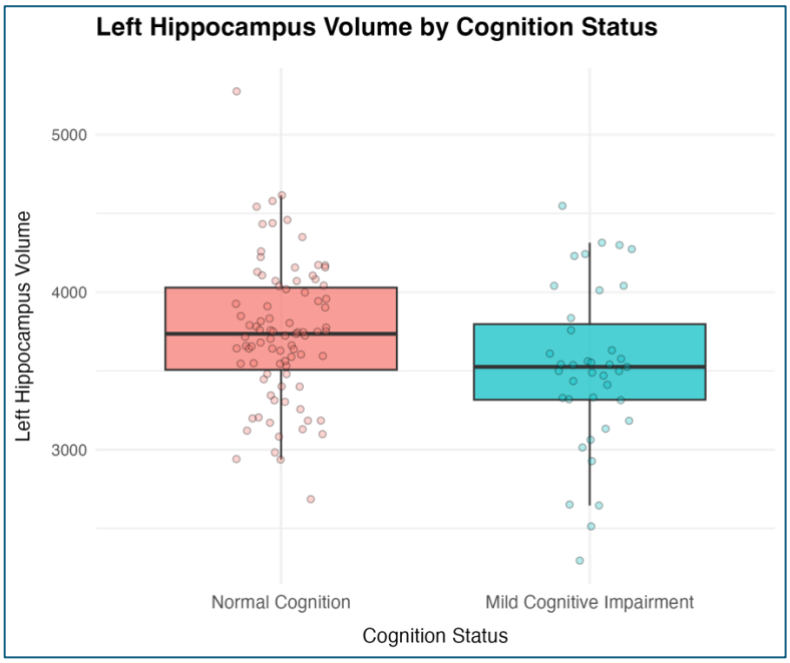

Figure 6. Distribution of White Matter Hypointensities by Cognition Status (p-value =0.9)

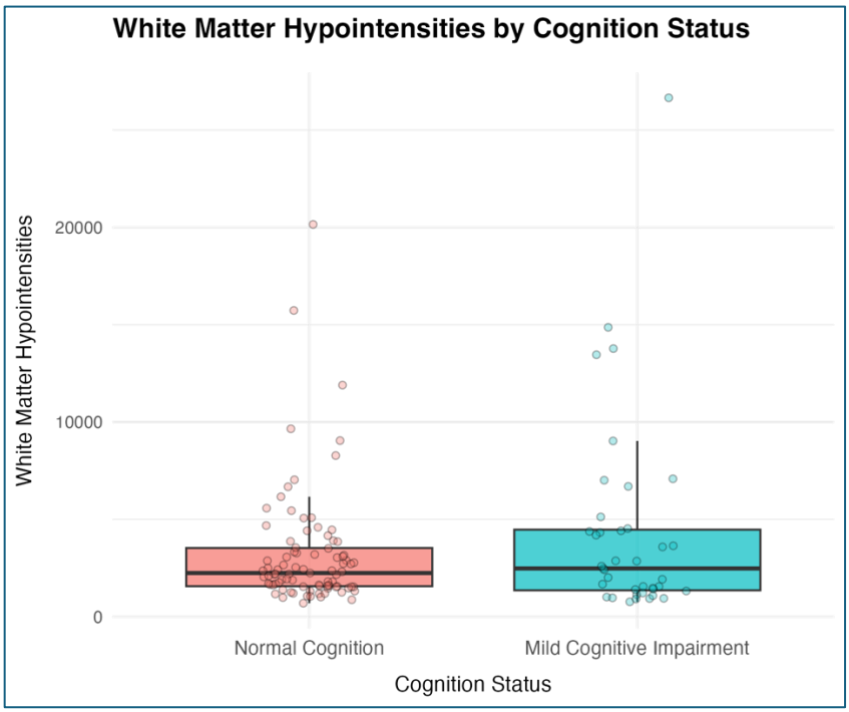

Figure 7. Spearman Correlation Heat Map (ρ)